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SYNTHETIC STUDIES ON PENTALENOLACTONES
AND
CERIUM ESTER ENOLATES IN ORGANIC SYNTHESIS

BY

© BING-YAN ZHU

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND

RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

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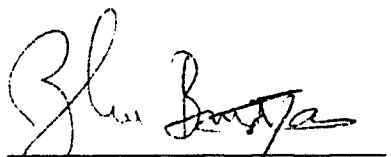

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SUBMITTED BY BING-YAN ZHU

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF THE DOCTOR OF PHILOSOPHY IN CHEMISTRY

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Date: June 15, 1990

Dedicated to my family and my late mother

ABSTRACT

The first chapter of this thesis describes the synthetic studies towards pentalenolactone (**3**) and pentalenolactones E (**6**), F (**8**), G (**9**) and H (**10**). The key intermediate bicyclo[3.2.0]heptane ring system **148** was prepared from 3,3–dimethylglutaric acid in nine steps. Acyloin reaction of diethyl 3,3–dimethylglutarate (**139**) induced by sodium in refluxing toluene followed by treatment with chlorotrimethylsilane afforded the cyclopentene derivative **140** in quantitative yield. Hydrolysis and subsequent dehydration of compound **140** with 85% H_3PO_4 gave enone **134** in excellent yield. Aldol reaction of cerium(III) ester enolate **142** with enone **134** at -78°C provided the β–hydroxy ester **133** in quantitative yield. Treatment of this tertiary allylic alcohol with PCC furnished the desired enone ester **132**. Intermolecular photocycloaddition of enone **132** with 1,1–dimethoxyethylene (**143**) afforded the bicyclic ring system **144**. The ketone unit in **144** was reduced by $NaBH_4$ and the resulting alcohol **146** was protected as its *t*–butyldiphenylsilyl ether **147**. The dimethyl ketal unit in **147** was hydrolyzed to give the four–membered ring ketone **148** as the key intermediate in quantitative yield. Expansion of the four–membered ring to a functionalized five–membered ring is under current investigation.

In the second and third chapters, some applications of cerium(III) ester enolates in organic synthesis are described. Cerium ester enolates were demonstrated to be superior nucleophilic reagents with lower basicity and greater nucleophilicity than the corresponding lithium enolates.

Chapter II discusses the addition of cerium ester enolates to carbonyl compounds. Cerium ester enolates were found to react readily with ketones including those which are highly enolizable and sterically hindered. Cerium enolates were also shown to undergo facile 1,2–addition with α,β–unsaturated ketones to afford the corresponding tertiary allylic alcohols in excellent yields. When the resulting γ,δ–unsaturated β–hydroxy esters were treated with PCC, β–carboalkoxymethyl α,β–unsaturated ketones were produced in 53–93% yields *via* an oxidative 1,3–carbonyl transposition process.

In Chapter III, an efficient synthetic approach to β–lactams is reported. Cerium ester enolates were found to condense readily with imines and related compounds under mild conditions to afford 2–azetidinones (β–lactams) directly in excellent yields. Where applicable, a high degree of stereoselectivity was observed.

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my sincere gratitude to my research director Professor H. J. Liu for his outstanding guidance, support and constant encouragement during my Ph. D. program. His patience, wisdom and humor all helped to pave the way. His invaluable assistance and interest in the preparation of this thesis is also greatly appreciated.

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My high school teachers, Yang Song–Bo, Ren Xin–Hua, Song Wen–Hua and the late Yang Gen–Guang deserve special mention for their excellent teaching, help and inspiration. Without their enlightenment, it would have been impossible for me to start my academic career in chemistry.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	Acetyl [$CH_3C(O)$–]
APT	Attached Proton Test
Ar	Aryl
Bn	Benzyl ($PhCH_2$–)
Boc	*t*–Butoxycarbonyl (*t*–BuOOC–)
Bu	Butyl
Bz	Benzoyl [$PhC(O)$–]
CI	Chemical ionization
Cp	Cyclopentadiene
m–CPBA	*m*–Chloroperoxybenzoic acid
DBU	1,8–Diazabicyclo[5.4.0]undec–7–ene
DCC	1,3–Dicyclohexylcarbodiimide ($C_6H_{11}N=C=NC_6H_{11}$)
de	Diastereoisomeric excess
decalin	Decahydronaphthalene
DIBAL–H	Diisobutylaluminium hydride (*i*–Bu_2AlH)
DME	1,2–Dimethoxyethane
DMF	*N*,*N*–Dimethylformamide ($HCONMe_2$)
DMSO	Dimethylsulfoxide ($Me_2S=O$)
ee	Enantiomeric excess
EE	Ethoxyethyl (–CHMeOEt)

Eq	Equation
Et_2O	Diethyl ether
FAB	Fast atom bombardment
FPP	Farnesyl pyrophosphate
HMPA	Hexamethylphosphoramide [$(Me_2N)_3P(O)$]
HRMS	High resolution mass spectrum
KHMDS	Potassium hexamethyldisilazide [$KN(SiMe_3)_2$]
LDA	Lithium diisopropylamide (*i*–Pr_2NLi)
LDMAN	Lithium 1–(dimethylamino)–naphthalenide
LHMDS	Lithium hexamethyldisilazide [$LiN(SiMe_3)_2$]
MMC	Methyl methoxymagnesiumcarbonate (MeOMgOCOOMe)
MOM	Methoxymethyl (–CH_2OMe)
MPM	*p*–Methoxyphenylmethyl (–CH_2PhOMe–*p*)
MS	Mass spectrometry
NBS	*N*–Bromosuccinimide
NOE	Nuclear overhauser effect
PCC	Pyridinium chlorochromate ($Py{\bullet}H^+ CrO_3^- Cl$)
PDC	Pyridinium dichromate [$(Py{\bullet}H)_2^{2+} Cr_2O_7^{2-}$]
Py	Pyridine
RT	Room temperature
SAMP	(*S*)–1–Amino–2–methoxypyrrolidine

L–Selectride	Lithium tri–*sec*–butylborohydride [$LiB(CHMeEt)_3H$]
TBDMS	*t*–Butyldimethylsilyl (*t*–$BuMe_2Si$–)
TBDPS	*t*–Butyldiphenylsilyl (*t*–$BuPh_2Si$–)
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'–Tetramethylethylenediamine ($Me_2NCH_2CH_2NMe_2$)
TMS	Trimethylsilyl (Me_3Si–)
Tf	Triflate (CF_3SO_2–)
Tr	Trityl (–CPh_3)
Ts	Tosyl (*p*–Toluenesulfonyl) (*p*–$MePhSO_2$–)
TsN_3	Tosyl azide (*p*–$MePhSO_2N_3$)
p–TsOH	*p*–Toluenesulfonic acid (*p*–$MePhSO_2OH$)

CHAPTER I

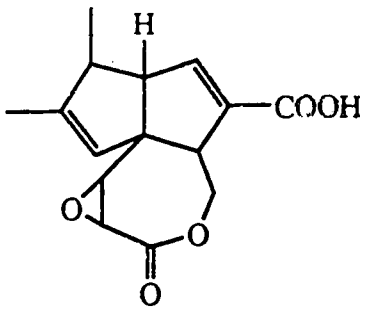
SYNTHETIC STUDIES ON PENTALENOLACTONES

INTRODUCTION

In 1957, during the course of an antibiotic screening program to search for agents effective against some of the plant fungal pathogens by Pfizer Co., a new acidic antibiotic named PA 132[1, 2] was isolated from the acidified fermentation broth culture of *Streptomyces*. This antibiotic showed excellent biological activity against gram–positive and gram–negative bacteria, as well as against pathogenic and saprophytic fungi.

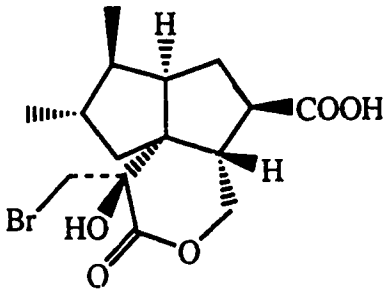
The antibiotic was unstable as the free lactonic acid or sodium salt but could be handled conveniently as the stable, crystalline monobenzylamine salt. The purified PA 132 free acid was initially a colorless, amorphous powder which darkened on standing. Solutions of the antibiotic and its benzylamine salt were strongly levorotatory, $[\alpha]_D^{22} = -161°$ and $[\alpha]_D^{22} = -130°$ (c = 1 in methanol) respectively. Mass spectrum suggested the molecular formula to be $C_{15}H_{16}O_5$ (m/e 276). Elemental analysis showed: C, 64.67; H, 6.29; N, 0.00. The infrared absorption at 1765 cm^{-1} indicated the presence of lactone ring system.

In 1969, Takeuchi *et al.*[3] also isolated the acidic lipophilic antibiotic from the fermented broth of the *Streptomyces* sp. No. 8403–MC which was confirmed by direct comparison to be identical in all respects with PA 132. Preliminary chemical examinations (PA 132 was converted to its tetrahydro derivative which was then transformed into the bromohydrin derivative) and detailed spectroscopic studies on PA 132 led Takeuchi *et al.* to propose the structure **1** for the antibiotic PA 132 and they suggested the name **pentalenolactone** for PA 132.



1

Subsequently in 1970, a group of chemists[4] in the Upjohn group, using antitumor assays, also isolated an acidic lipophilic antibiotic from the fermentation broth of *Streptomyces* UC 5319 which was shown to be identical with PA 132 by direct comparison. They found that the structure **1** proposed by Takeuchi *et al.* was incorrect on the basis of the structure of the bromohydrin derived from tetrahydropentalenolactone. The structure and absolute configuration of the crystalline bromohydrin of the tetrahydropentalenolactone was firmly established by X–ray diffraction analysis as structure **2**.



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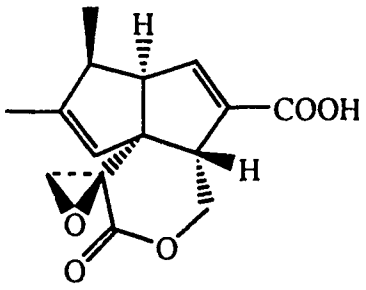
The structure of the bromohydrin of the tetrahydropentalenolactone, coupled with the work of Takeuchi *et al.*, established that pentalenolactone had the structure **3** with the absolute configuration as shown.



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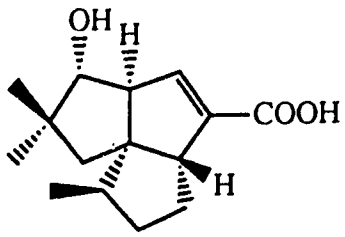
Due to the strong antibiotic activities of pentalenolactone, a great deal of effort has been focused on the biosynthetic pathway of this compound in the past few years. During the course of the biosynthetic studies, a series of structurally novel sesquiterpenes, namely tricyclic pentalenoic acid (**4**),[5] pentalenene (**5**)[6] and pentalenolactones E (**6**),[7] F (**7**),[8] G (**9**)[9, 10] and H (**10**)[5] were isolated from various pentalenolactone–producing fermentation broth cultures of *Streptomyces*. Besides their novel structural features, these compounds are all potential intermediates or shunt metabolites in the biosynthesis of pentalenolactone.

It is interesting to note that the structure of the pentalenolactone F was originally assigned as **7** by Cane *et al.*[8] primarily on the basis of the ^{1}H and ^{13}C NMR analyses. The configuration of the epoxide ring in pentalenolactone F was assumed to be the same as that of pentalenolactone. In 1988, Cane *et al.*[10] revised the structure of pentalenolactone F as **8** according to the X-ray crystal structure of its methyl ester. As a result, the epoxide ring in pentalenolactone F had the opposite stereochemistry to that of pentalenolactone and pentalenolactones G and H. This result suggested that pentalenolactone F might be a shunt metabolite in the biosynthesis of pentalenolactone.



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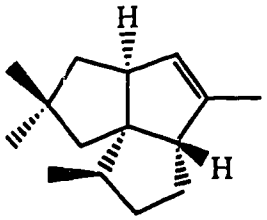

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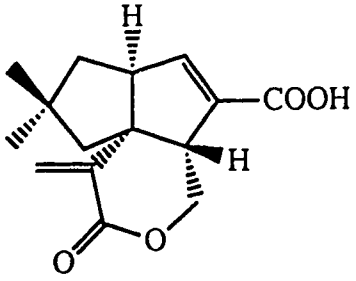

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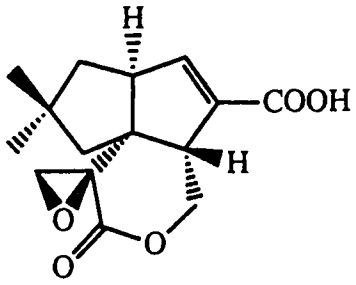

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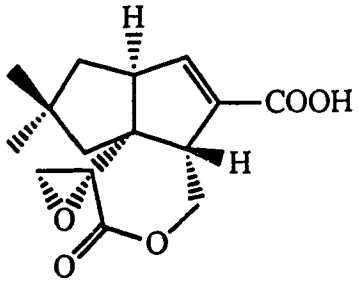

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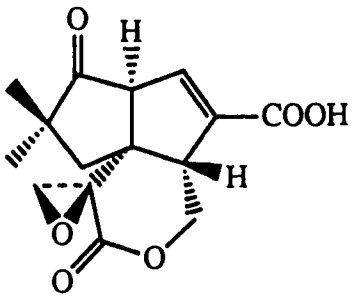

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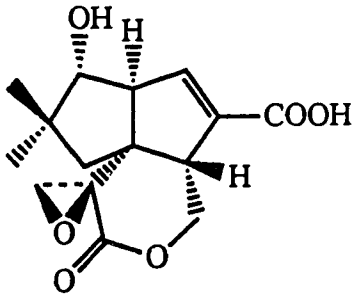
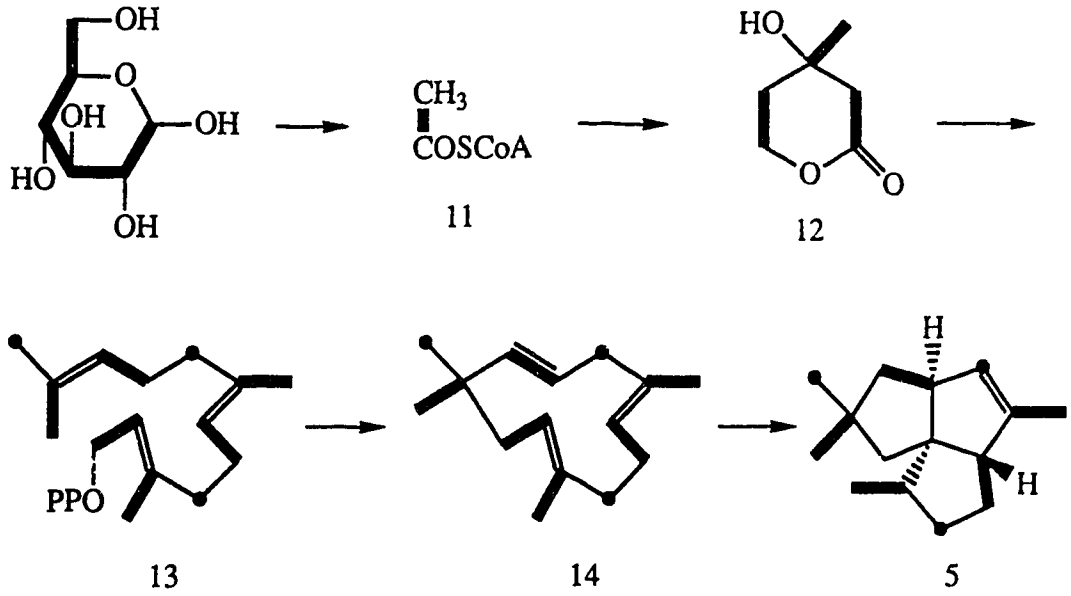


10

As a sesquiterpene, pentalenolactone is biosynthetically derived from *trans*, *trans*–farnesyl pyrophosphate (FPP) (**13**).[11] Farnesyl pyrophosphate serves as a biosynthetic precursor of cyclic sesquiterpenes by the use of cell–free enzymes to catalyze the cyclization of farnesyl pyrophosphate to humulene (**14**). Further cyclization of humulene yields a tricyclic intermediate pentalenene (**5**) which is the parent hydrocarbon of the pentalenolactone family of sesquiterpene antibiotics.

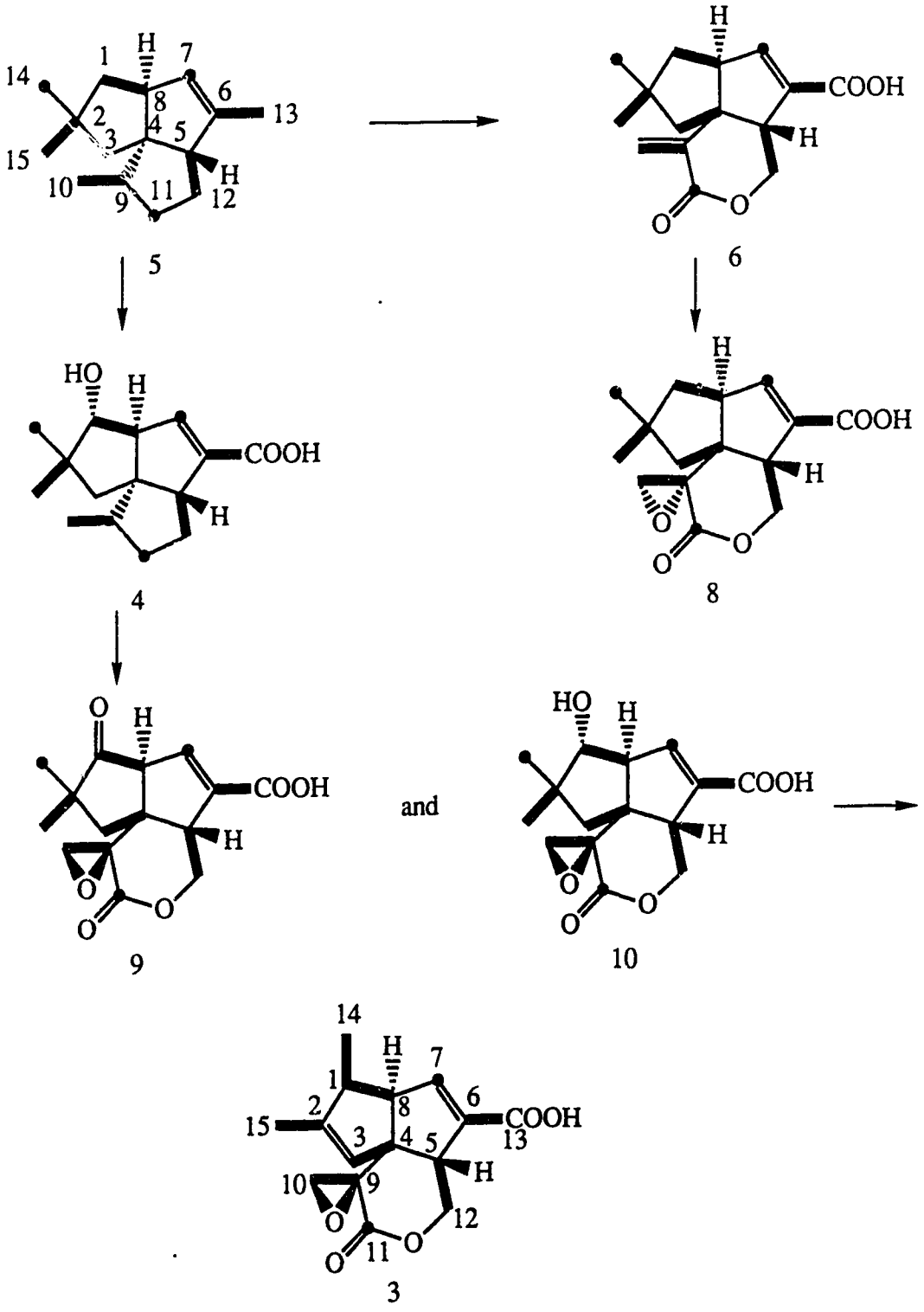
The complete biosynthetic pathway of pentalenolactone is illustrated in Scheme I–1. Pentalenolactone, pentalenoic acid and pentalenolactones E, F, G, and H are biosynthetically derived from pentalenene. Enzymatic oxidation of pentalenene gives pentalenoic acid from which pentalenolactone H can be derived by subsequent oxidative lactone formation across the C–11,12 bond of ring C. Wagner–Meerwein rearrangement of the β–C–14 methyl carbon from C–2 to C–1 of pentalenolactone H yields pentalenolactone. This biosynthetic pathway has been proven by Cane *et al.* by feeding [U–$^{13}C_6$]–glucose as an *in vivo* precursor of [1,2–$^{13}C_2$]–acetyl–CoA to the pentalenolactone–producing cultures. The ^{13}C NMR spectra of the derived pentalenoic acid and pentalenolactone methyl ester are completely consistent with the biosynthetic pathway illustrated in Scheme I–1.

Scheme I–1. Biosynthetic Pathway of Pentalenolactone



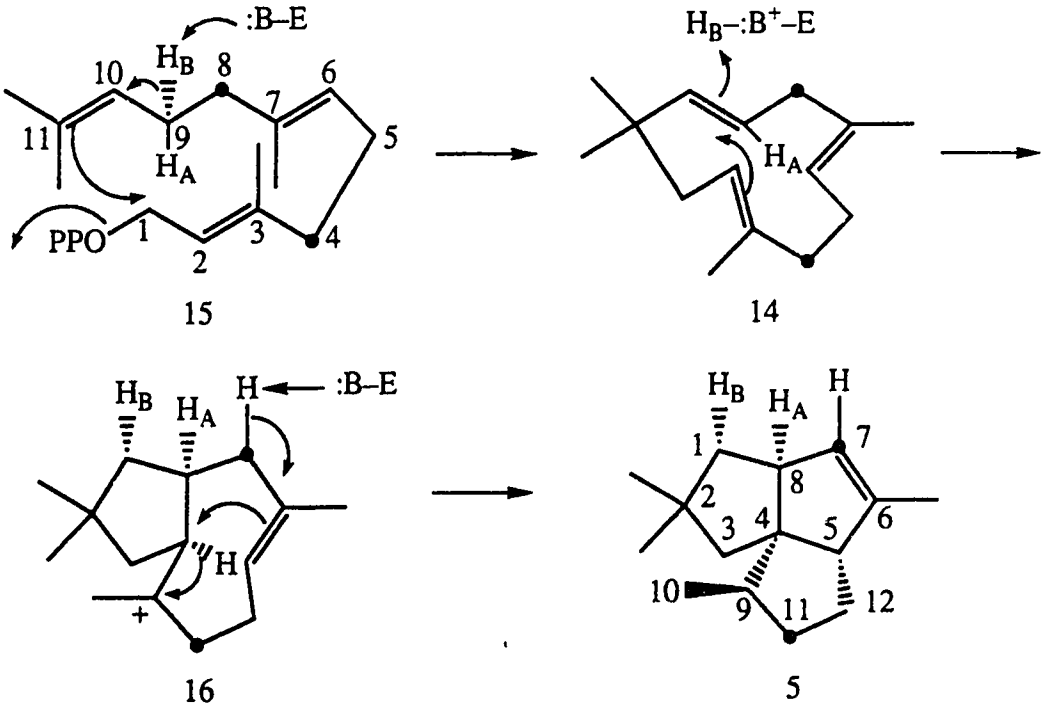
11 12 13 14 5

Scheme I–1 (continued)

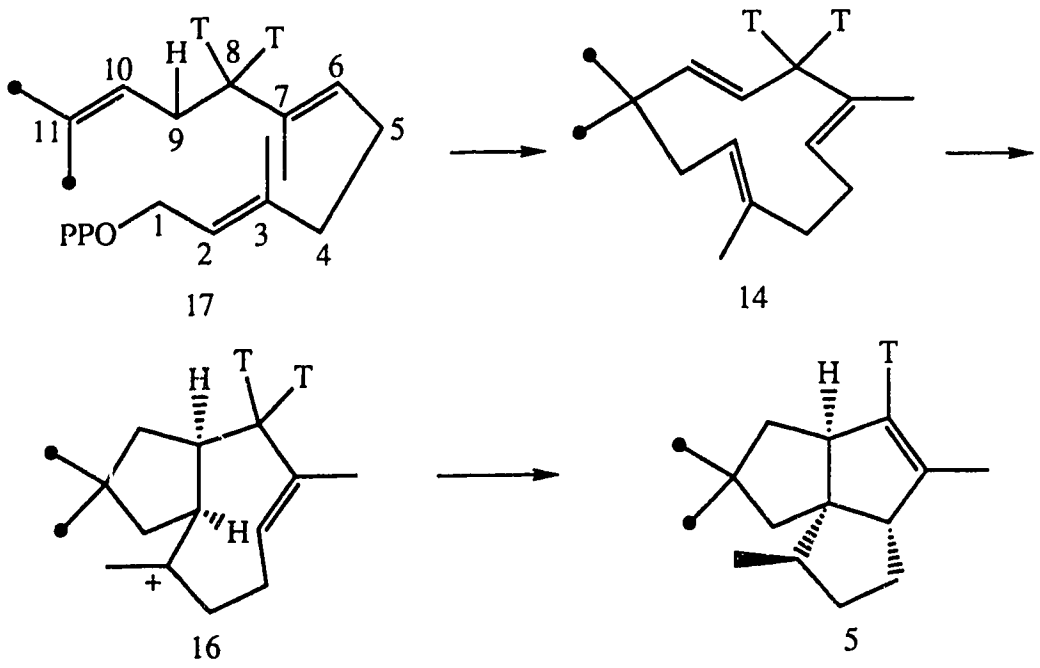


The biosynthetic mechanism of pentalenene[12, 13] involves the ionization and cyclization of farnesyl pyrophosphate to generate humulene (**14**) by electrophilic attack on the *si*–face of C–11 and deprotonation at C–9 of farnesyl pyrophosphate. Reprotonation of humulene at C–10 and attack on the C–2,3 double bond generates the cation **16**. Subsequent hydride migration and cyclization involving the C–6,7 double bond with loss of one of the H–8 protons of the farnesyl precursor yields pentalenene. The net results of this enzymatic cyclization are: H–9*re* of FPP becomes H–8 of pentalenene, while H–9*si* undergoes net intramolecular transfer to H–1α of pentalenene (**5**). This was fully supported by incubation experiments of (9*R*)– and (9*S*)–[9–^{3}H, 4,8–^{14}C]FPP (**15**) and [8–^{3}H, 12,13–^{14}C]FPP (**17**) with crude pentalenene synthetase to generate the labelled pentalenenes (Scheme I–2 and Scheme I–3).

Scheme I–2



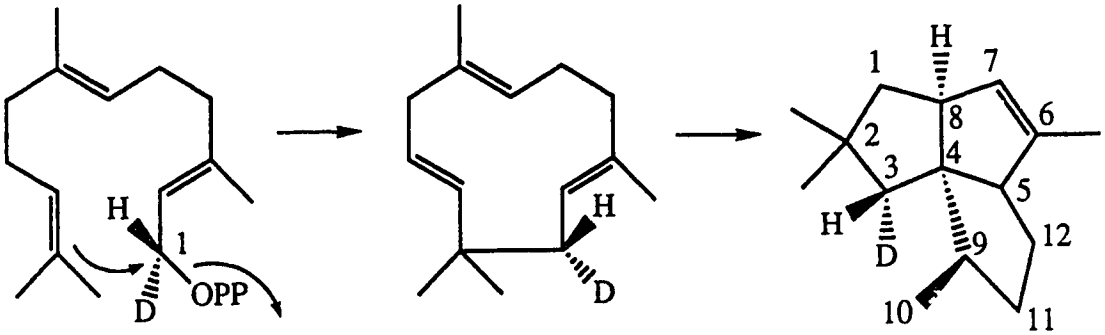
Scheme I–3



17 14 16 5

The inversion of the configuration at C–1 of FPP occurred (Scheme I–4) during cyclization of farnesyl pyrophosphate to pentalenene and was proven by incorporation experiments with both (1*S*)– and (1*R*)–[1–^{2}H]FPP (**18**).[14]

Scheme I–4



18 14 5

The unique structure of pentalenolactone with a tetracyclic δ–lactone ring system, five asymmetric carbons and several quaternary centers provides a challenge to synthetic organic chemists. To this date, there have been three total syntheses of (±)–pentalenolactone. The key features in all syntheses of pentalenolactone are the stereospecific construction of the tricyclic δ–lactone ring system and the control of the stereochemistry, particularly at the C–1 methyl and C–9 epoxide formation steps.

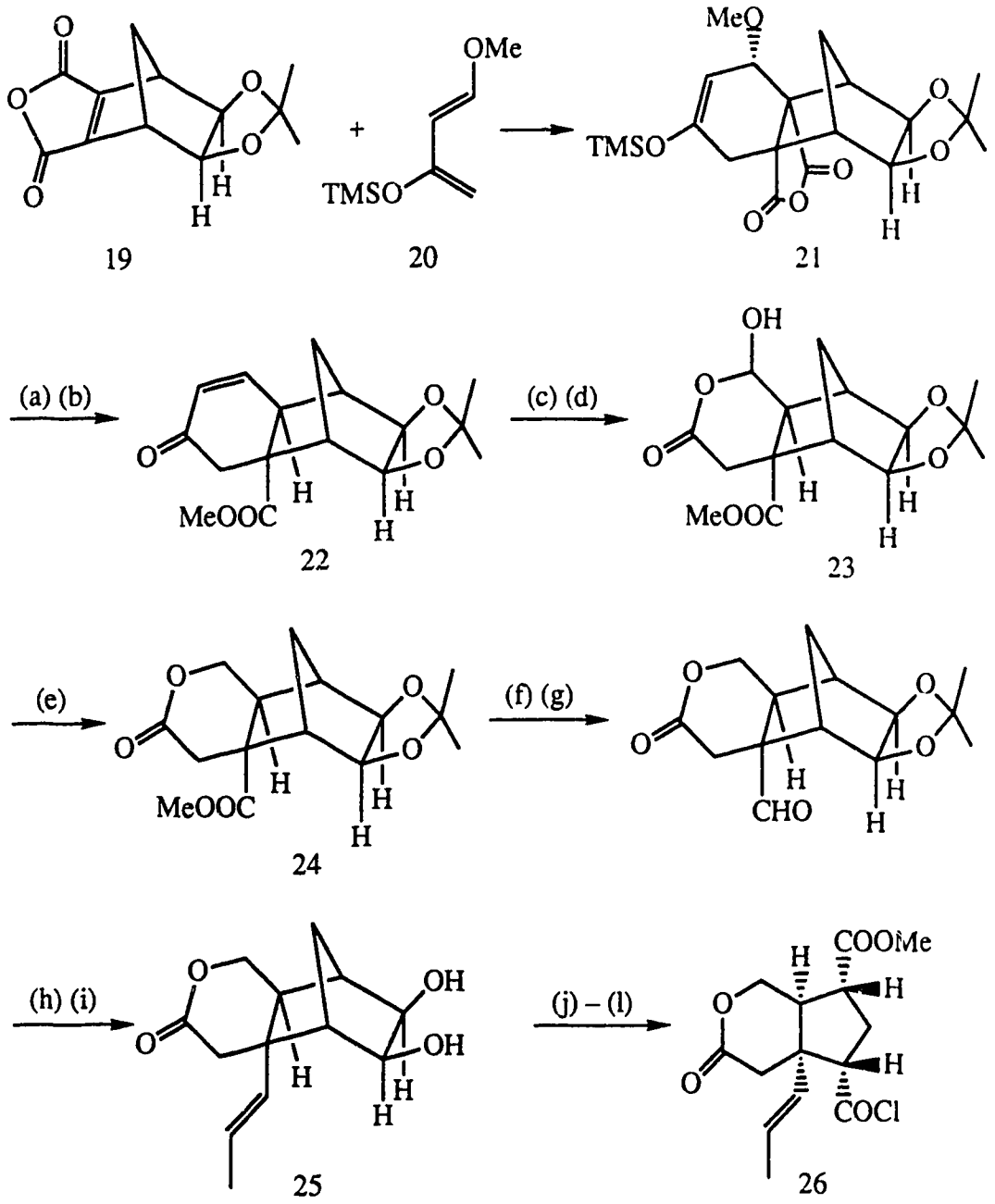
In 1978, Danishefsky *et al.*[15, 16] reported the first stereospecific synthesis of (±)–pentalenolactone (Scheme I–5). The key operations in this synthesis are as follows: (1) A Diels–Alder reaction between **19** and **20** to construct the 5–acylcyclohexenone **22** which was subsequently degraded by oxidation to the δ–lactone ring. This methodology served as the key step for the control of several important stereocenters and the elaboration of the δ–lactone ring system. (2) An intramolecular Darzens acylation reaction of compound **26** to build the A ring system of the target molecule. (3) The stereospecific formation of an epoxymethylenelactone *via* Sharpless oxidation of allylic lactol **31**.

The stereospecific Diels–Alder reaction of **19** and **20** gave **21** in nearly quantitative yield after refluxing in benzene for 2 h. Treatment of **21** with barium hydroxide followed by MeI afforded the *cis*–fused, bridged hydrindenone **22**. Oxidative degradation of **22** with OsO_4 and $Pb(OAc)_4$ produced the pseudolactone **23** which was reduced with $NaBH_4$ to afford the *cis*–fused δ–lactone system **24**. Cleavage of the *cis* diol **25** with Jones reagent provided the *cis*–fused bicyclic δ–lactone ring system required for the natural product.

The A ring system was introduced by an intramolecular Darzens–type acylation of compound **26** with $AlCl_3$, furnishing the construction of tricyclic δ–lactone ring system for pentalenolactone. Stereoselective hydrogenation, with Wilkinson catalyst, of the methylenecyclopentene, derived from **27** by Wittig olefination, gave the dihydro compound **28** as the only detectable product.

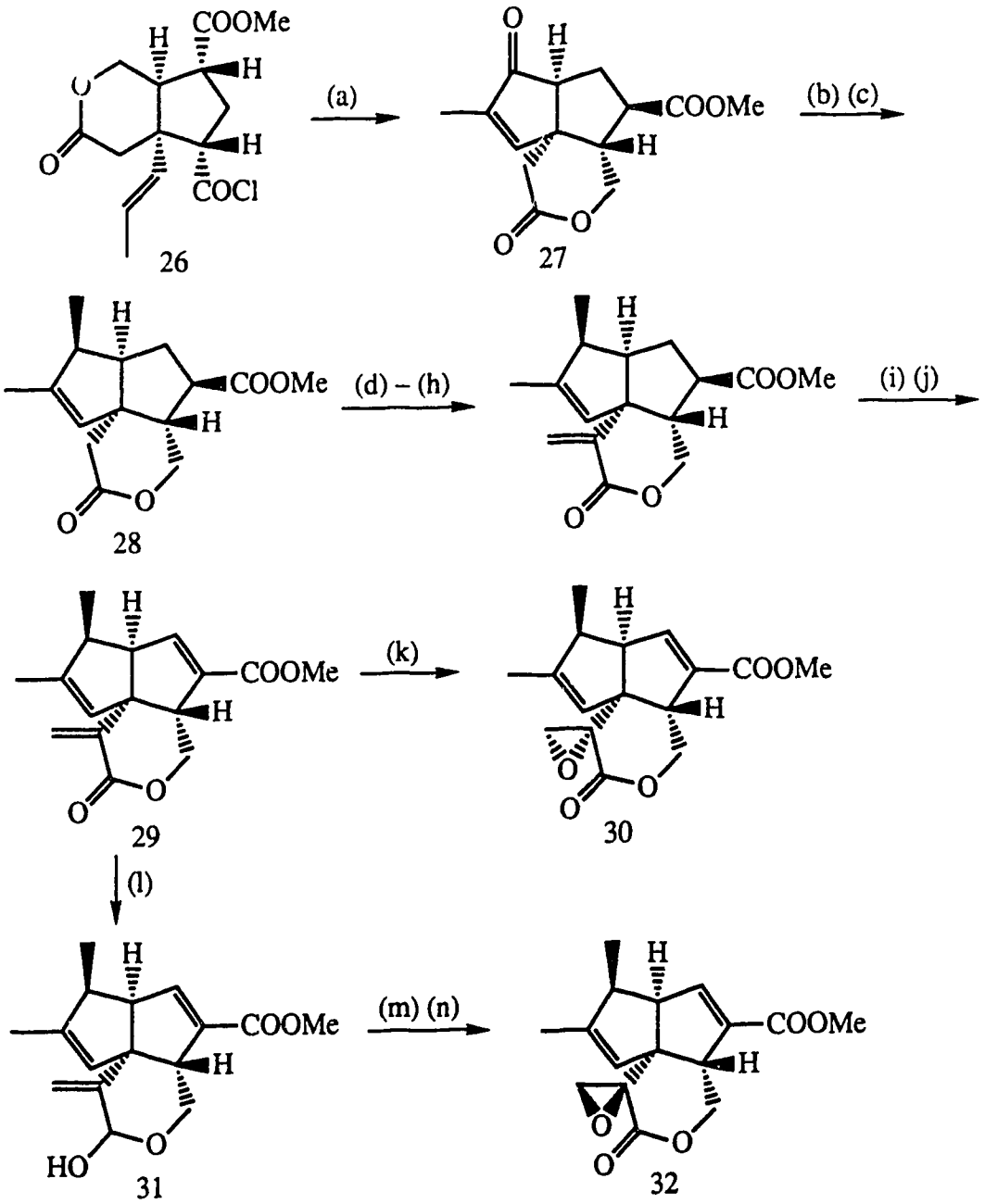
The last step in this synthesis was to convert the exocyclic methylene unit to a spiroepoxide with stereochemical control. Disappointingly, direct epoxidation of compound **29** with alkaline hydrogen peroxide afforded only 10% of pentalenolactone methyl ester **32** and the major product was the undesired epimeric α–epoxide **30**. However, it was reasoned that an axially oriented anomeric hydroxy group of a hemiacetal **31** derived from **29** might be disposed toward the β configuration wherein it resides on the convex surface of the oxahydrindan system. So stationed, this hydroxy, which would also be allylic to the exocyclic methylene group, might provide the required guidance for the β–epoxidation. Indeed epoxidation of allylic hemiacetal **31** using the Sharpless procedure (*t*–BuOOH, $VO(acac)_2$) followed by Jones oxidation yielded the pentalenolactone methyl ester **32** as the predominant product. Hydrolysis of the lactone methyl ester **32** with aqueous KOH in THF yielded the natural product pentalenolactone (**3**).

Scheme I–5



(a) $Ba(OH)_2$; (b) MeI, $NaHCO_3$; (c) OsO_4; (d) $Pb(OAc)_4$; (e) $NaBH_4$, aq. NaOH; H^+; (f) NaOH; H^+; (g) $SOCl_2$, PhH; H_2, $Pd/BaSO_4$, $PhCH_3$, reflux; (h) $Ph_3P{=}CHCH_3$, DME; (i) HCl, DME, reflux; (j) Jones; (k) MeOH, H_2SO_4; (l) $SOCl_2$.

Scheme I–5 (continued)



(a) $AlCl_3$, CH_2Cl_2; (b) $Ph_3P{=}CH_2$; (c) $(Ph_3P)_3RhCl$, H_2; (d) $(Me_2N)_2CH(OBu\text{–}t)$; (e) SiO_2; (f) $NaBH_4$; (g) $MeSO_2Cl$, Py., CH_2Cl_2; (h) DBU; (i) LDA, -78°C; PhSeCl, -78°C; (j) $NaIO_4$, MeOH; (k) NaOH, H_2O_2; (l) DIBAL-H; (m) *t*–BuOOH, $VO(acac)_2$; (n) Jones.

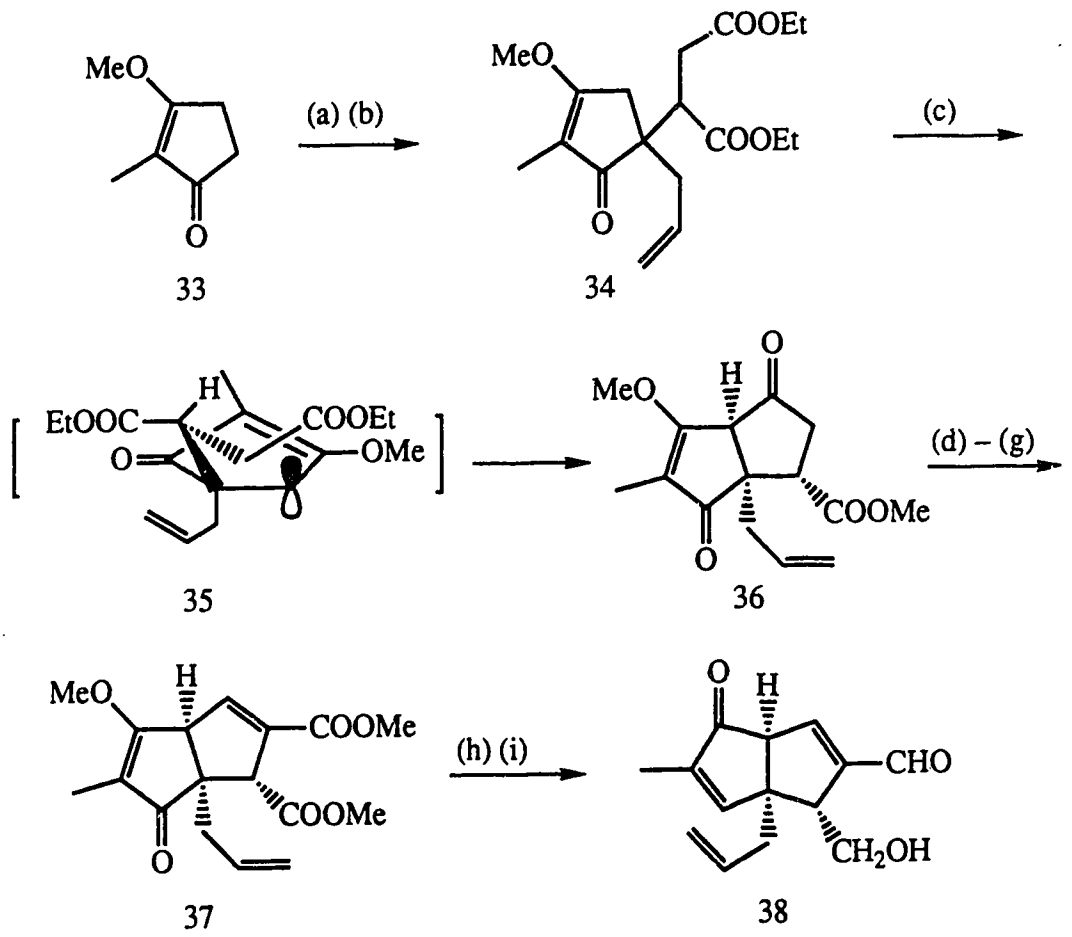
An alternative synthesis (Scheme I–6) of pentalenolactone was achieved by Schlessinger[17] who relied on the efficient formation of the pentalene system **36** by selective acylation and alkylation of the enolate ions. This was followed by an interlude of functional group reorganization and the introduction of carbons 14 and 10.

The pentalene system **36** was conveniently constructed by an intramolecular Claisen cyclization of **34**. Molecular models suggested that only anion **35** would undergo Claisen cyclization to provide the *cis*–fused pentalene system **36**. Compound **36** is a bicyclo[3.3.0]octane derivative possessing the desired AB ring system with a *cis* relationship between the allyl group and the carboxylate residue at C–5. Compound **36** is also appropriately functionalized for introduction of the required δ–lactone ring. The C–13 carboxyl residue present in the natural product was then introduced by carbonation (CO_2) of the cyclopentanone *via* the enolate. Acidification of the reaction mixture and esterification with diazomethane at -78°C gave the corresponding diester. Reduction with methanolic sodium borohydride followed by mesylation of the resulting β–hydroxy ester and elimination of methanesulfonic acid afforded the acrylate ester **37**.

The required tricyclic δ–lactone system was assembled from the aldehyde cyclopentenone **38**, which was ozonolyzed in CH_2Cl_2 containing a small amount of pyridine. Under the reaction conditions, the resulting hydroxy aldehyde **39** immediately cyclized to provide the lactol **40**. Oxidation of the bisacetal **41** with Jones reagent produced the desired tricyclic δ–lactone ring system. Further functional group manipulation furnished the α–methylene lactone **29**

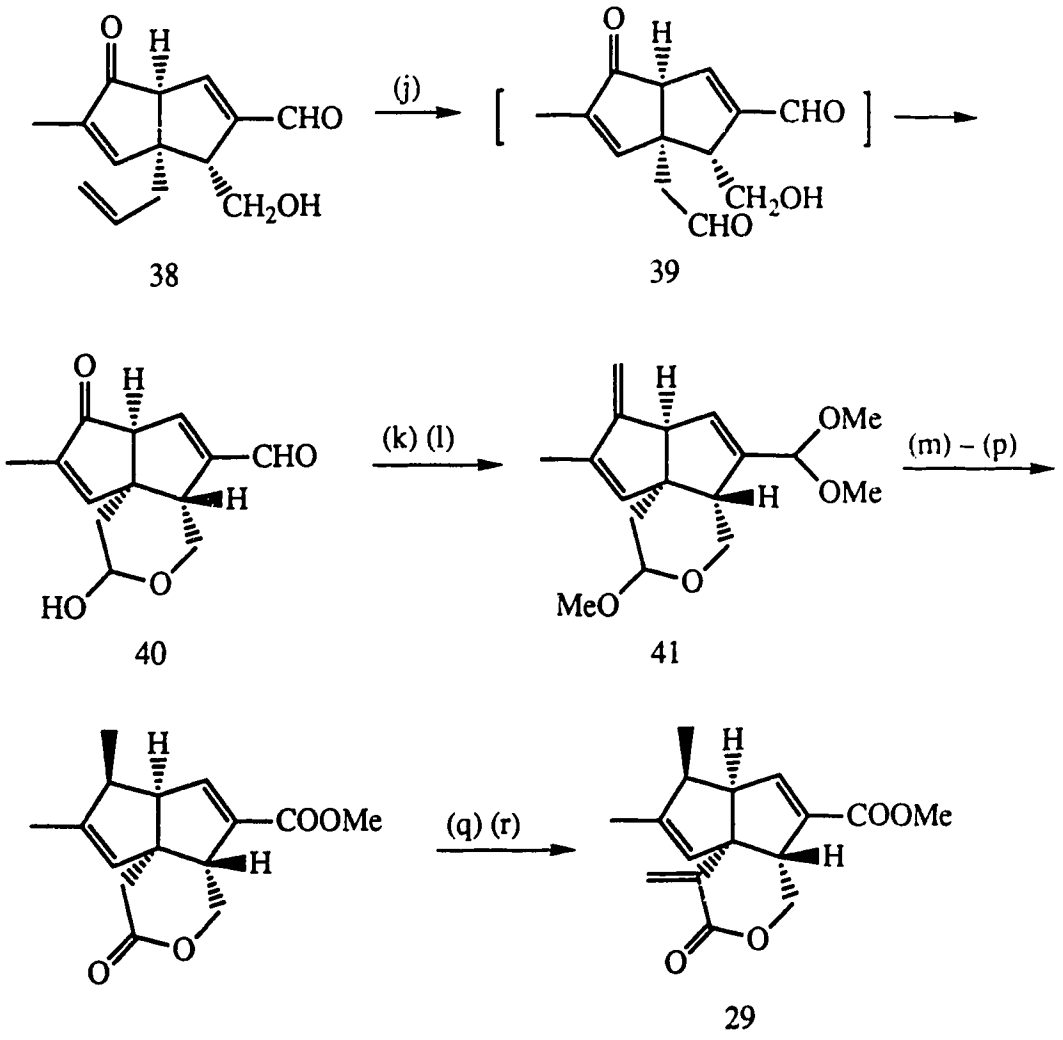
which had been previously converted to pentalenolactone by Danishefsky and coworkers.[15, 16] Thus, a formal synthesis of pentalenolactone (3) was completed.

Scheme I-6



(a) LDA, THF; CH_2=CH–CH_2Br, -78°C; (b) LDA, THF; EtO_2CCH=$CHCO_2Et$, -78°C; (c) NaH, $OC(OMe)_2$, 0°C; (d) $KN(SiMe_3)_2$, THF, -78°C; CO_2, -78°C → 0°C; 3% HCl, -15°C; CH_2N_2, CH_2Cl_2, -78°C; (e) $NaBH_4$, MeOH, -20°C; (f) $MeSO_2Cl$, Et_3N, THF; (g) 2,4,6-collidine, 180°C; (h) DIBAL-H, $PhCH_3$, 0°C; 6N HCl; (i) MnO_2, PhH.

Scheme I–6 (continued)



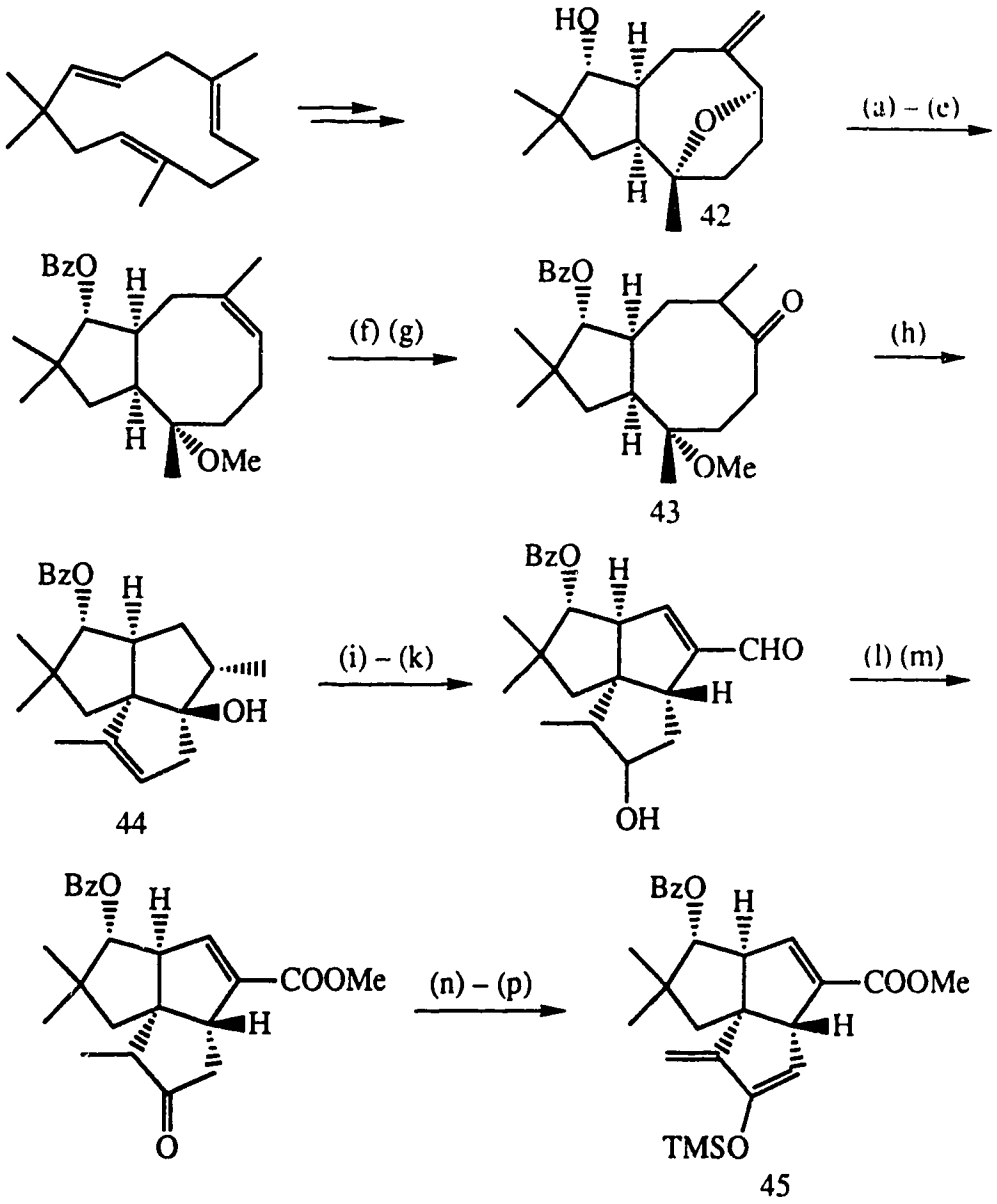
(j) O_3, CH_2Cl_2, pyridine, -78°C; Me_2S; (k) MeOH, $CH(OMe)_3$, HCl, 0°C; (l) $Ph_3P{=}CH_2$, THF; (m) H_2, $(Ph_3P)_3RhCl$, PhH; (n) 10% H_2SO_4, CH_3COCH_3, H_2O, 40°C; (o) Jones; (p) CH_2N_2, Et_2O; (q) MeOMgOCOOMe (MMC), 180°C; 3% HCl, CH_2Cl_2, -20°C; (r) 30% CH_2O, Et_2NH, 40°C.

As discussed in the biosynthetic studies, pentalenolactone was biosynthetically derived from humulene through several intermediates, pentalenene, pentalenolactones E, F, G and H as well as pentalenoic acid. These biosynthetic results prompted Matsumoto and his collaborators[18] to carry out the *in vitro* studies on the biomimetic humulene cyclization to the pentalenolactone family of sesquiterpene antibiotics. These studies have resulted in the total synthesis of pentalenolactone and pentalenolactones G and H (Scheme I–7).

Humulene was readily converted to bicyclo[6.3.0]undecanol **42** by employing oxymercuration as a key step. Transannular cyclization of methoxy ketone **43** was effected by treatment with formic acid at 45°C, giving the desired tricyclic pentalenane ring system **44**.

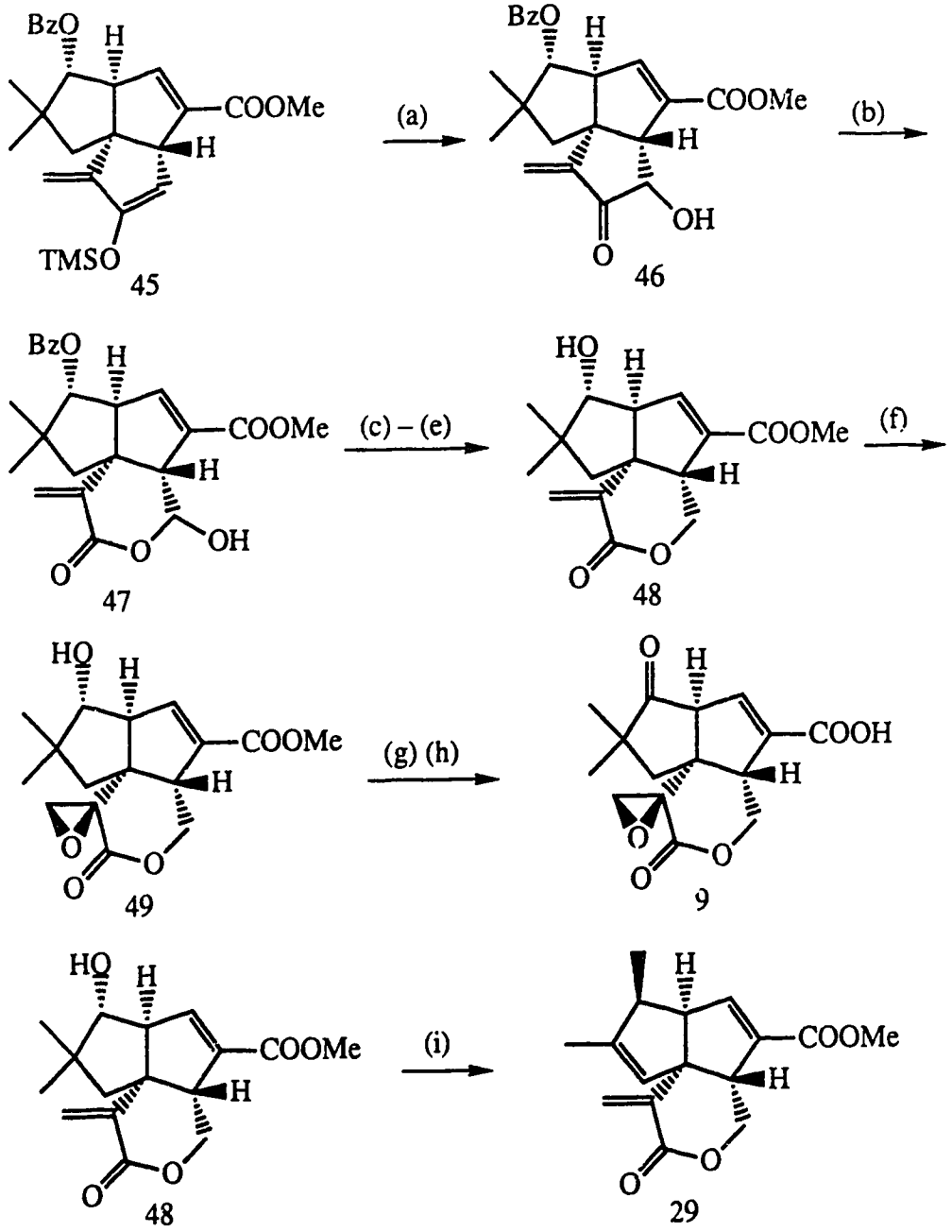
The δ–lactone ring system was constructed from the silyl enol ether **45** which was oxidized with *m*–CPBA to give the α–hydroxy ketone **46**. Further oxidation of the α–hydroxy ketone **46** with $NaIO_4$ in *t*–BuOH yielded the pseudolactone **47**. Reduction of **47** using $NaBH_4$ gave the desired tricyclic δ–lactone **48** with a methylene unit α to the lactone carbonyl group. The epoxide ring in the pentalenolactone H methyl ester (**49**) was introduced by the direct epoxidation of the α–methylene lactone **48** with H_2O_2 and $NaHCO_3$ in aqueous MeOH. Oxidation of the hydroxy group in compound **49** followed by the hydrolysis of the ester moiety gave rise to pentalenolactone G (**9**). Treatment of **48** with carbon tetrabromide in the presence of Ph_3P afforded the known compound **29** in low yield. Since compound **29** had been previously used by Danishefsky *et al.*[15, 16] to prepare pentalenolactone, a formal synthesis of natural product was completed.

Scheme I–7



(a) TMSCl, Et_3N; (b) Li, $EtNH_2$, THF, -78°C; (c) NaH, MeI; (d) HCl, MeOH; (e) BzCl, Py.; (f) B_2H_6, THF, 0°C; H_2O_2, NaOH; (g) Jones; (h) HCOOH; aq. Na_2CO_3, MeOH; (i) B_2H_6, THF; H_2O_2, NaOH; (j) HCOOH; (k) SeO_2, EtOH; (l) MnO_2, NaCN, AcOH, MeOH; (m) Jones; (n) TMSOTf, Et_3N; (o) NBS, THF; (p) TMSOTf, Et_3N, $NaHCO_3$.

Scheme I–7 (continued)

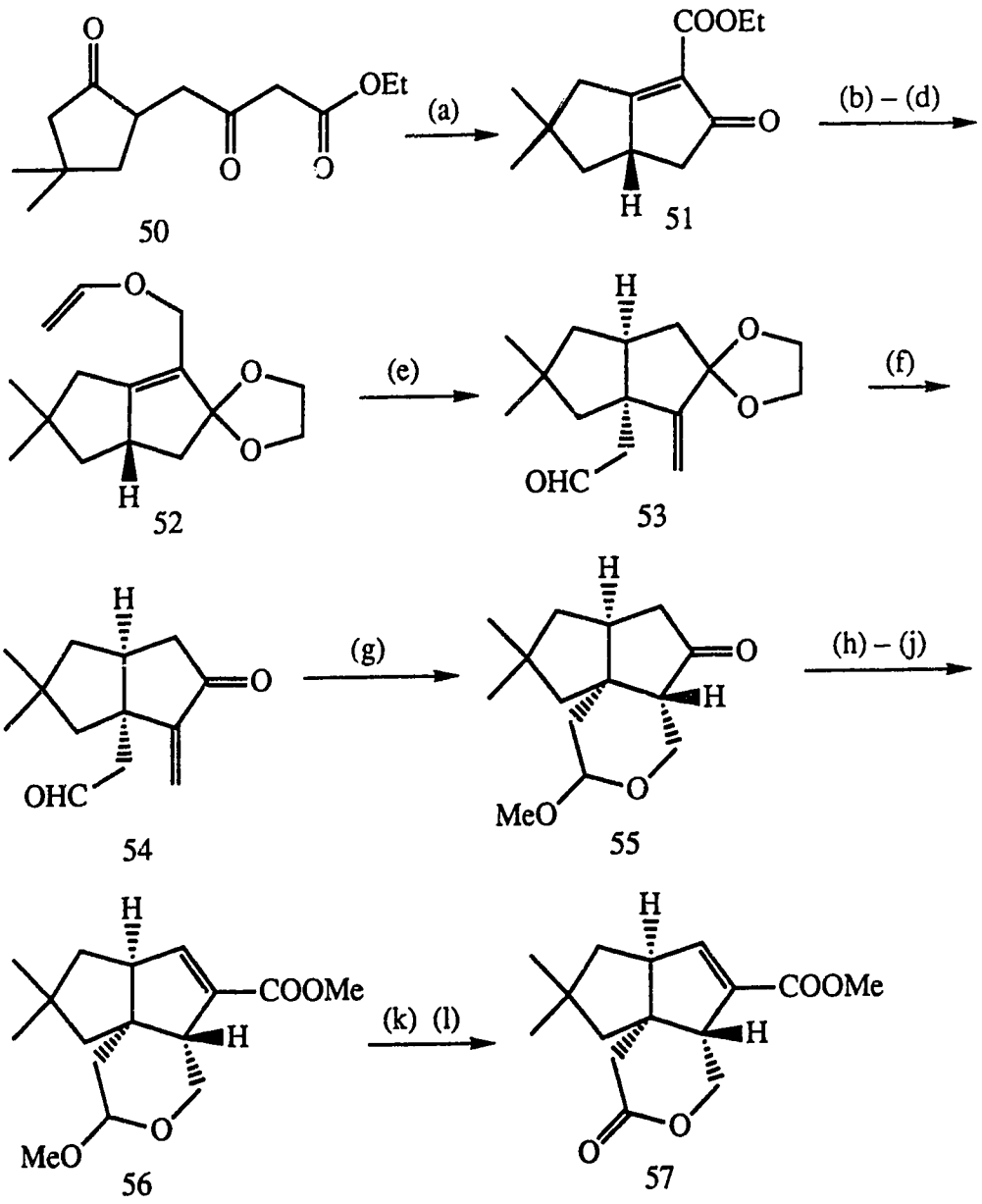


(a) *m*–CPBA, hexane; (b) $NaIO_4$, *t*–BuOH, H_2O; (c) $NaBH_4$, EtOH; (d) LiOH, THF, H_2O; HCl; (e) CH_2N_2, Et_2O; (f) H_2O_2, $NaHCO_3$, MeOH, H_2O; (g) Jones; (h) LiOH, THF, H_2O; HCl; (i) CBr_4, Ph_3P, PhH, reflux.

The synthetic challenges presented by the novel polyquinane systems of pentalenolactones E, F, G, and H have also inspired a number of interesting synthetic approaches. Up to now, there have been ten published total syntheses for pentalenolactones E and F including an enantioselective synthesis of optically active pentalenolactone E. Two total syntheses for pentalenolactone G and one for pentalenolactone H have also been reported. Similar to the synthesis of pentalenolactone, the crucial steps in the syntheses of pentalenolactones E, F, G, and H are the construction of the tricyclic δ–lactone ring system with the desired functionalities at C–1 and C–6 and the installation of the proper chiral centers.

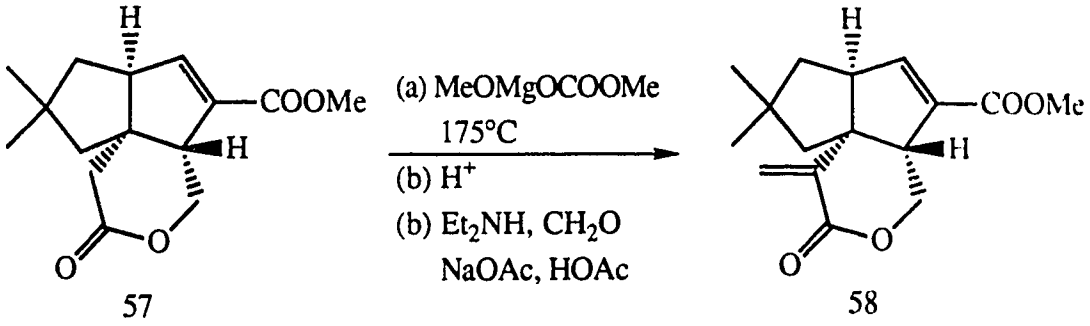
In 1982, Paquette *et al.*[19] reported the first total synthesis of pentalenolactone E methyl ester (Scheme I–8). Several salient features are as follows. (1) The bicyclic enone carbon framework **51** was efficiently established *via* an aldol reaction of diketo ester **50**. (2) Claisen rearrangement of allyl enol ether **52** generated a suitably functionalized *cis*–locked bicyclo[3.3.0]octane system **53** with an acetaldehyde side chain at the angular site (C–4) and a methylene group at C–5. (3) Chemospecific (kinetically controlled) nucleophilic attack at the aldehyde carbonyl group of **54** by sodium methoxide followed by intramolecular Michael addition of the resulting alkoxide to the proximally positioned α, β–unsaturated ketone delivered the expected tricyclic keto acetal **55** as a single stereoisomer. (4) After the ketone unit in **55** was converted to the α, β–unsaturated ester functionality, the acetal was subjected to acidic hydrolysis and Jones oxidation, resulting in efficient unmasking of the lactone functionality and formation of tricyclic δ–lactone **57**. The last step in this synthesis was the introduction of a methylene group α to the lactone carbonyl.

Scheme I–8



(a) NaOEt, EtOH; (b) $HOCH_2CH_2OH$, *p*–TsOH, PhH; (c) DIBAL–H, Et_2O, -116°C; (d) CH_2=CHOEt, $Hg(OAc)_2$; (e) decalin, 145–150°C; (f) Py•HOTs, Me_2CO, H_2O; (g) NaOMe (catalytic amount), MeOH; (h) NH_2NH_2–H_2O, Et_3N, EtOH; (i) I_2, Me_3N, THF, 0°C; (j) $Ni(CO)_4$, NaOMe, MeOH; (k) H^+, CH_3COCH_3, H_2O; (l) Jones.

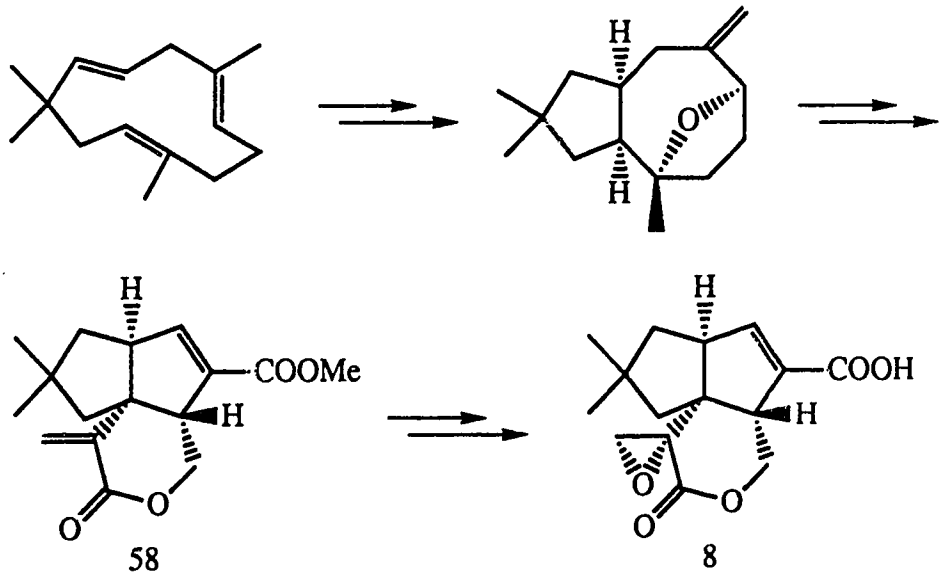
Scheme I–8 (continued)



57 58

Matsumoto *et al.*[20] also accomplished the total synthesis of pentalenolactones E and F in 1983, while carrying out *in vitro* studies on the cyclization of humulene to the pentalenane family of antibiotics. As shown in Scheme I–9, the synthetic approach followed closely that used in their synthesis of pentalenolactones G and H described earlier.[18]

Scheme I–9



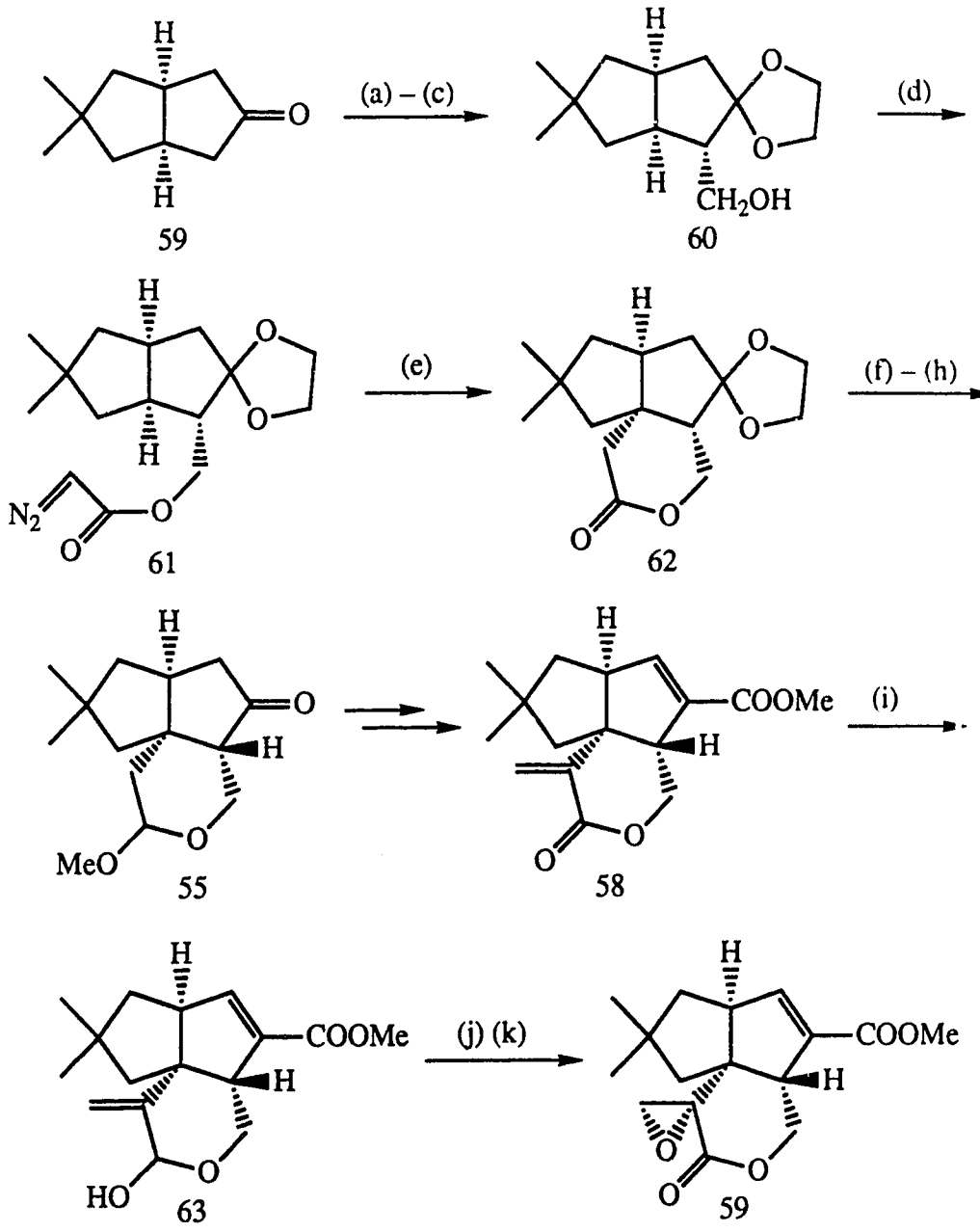
58 8

A quite different approach to pentalenolactones E and F methyl esters[21] (Scheme I–10) appeared in 1984. Here the intramolecular insertion reaction of an α–acylcarbene into an unactivated 3° C–H bond was utilized to effect the formation of the key fused tricyclic δ–lactone ring system with high stereo– and regioselectivity.

The requisite (diazoacetoxy)methyl side chain was appended to **59** by a sequence of carbomethoxylation, ketalization, and reduction followed by acylation of the resulting hydroxy ketal **60** with glyoxalyl chloride tosylhydrazone and base catalyzed elimination of *p*–toluenesulfinate. Treatment of diazo acetate **61** with $Rh_2(OAc)_4$ catalyst in Freon TF readily effected the desired intramolecular carbene insertion at the unactivated C–1 bridgehead C–H bond to generate the tricyclic δ–lactone **62**. The competing carbene insertion at C–2 to generate the γ–lactone ring was expected to be disfavored due to steric hinderance by the adjacent ethylene ketal, while the insertion reaction at C–4, C–5, or the ketal methylene carbon would lead to a 7 or 8–membered ring. Lactone reduction, deketalization, and selective acetalization of the derived lactol provided keto acetal **55**. Using the method described by Paquette,[19] **55** was converted to pentalenolactone E methyl ester (**58**).

Pentalenolactone F methyl ester was synthesized from pentalenolactone E methyl ester by stereospecific epoxidation of the exocyclic double bond, using the method reported by Danishefsky[15, 16] for the synthesis of pentalenolactone. It is interesting to note that the opposite stereochemistry was achieved by means of the same procedure even though pentalenolactone and pentalenolatone F have opposite stereochemistry.

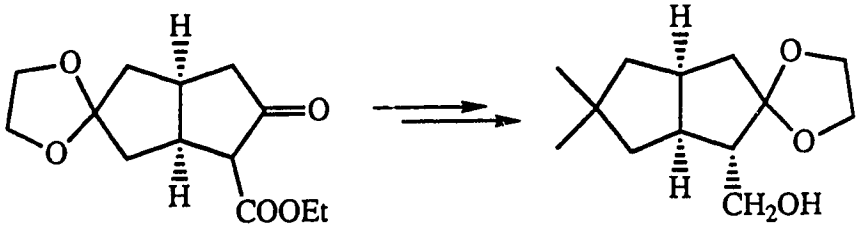
Scheme I–10



(a) NaH, $CO(OMe)_2$; (b) 2–methyl–1,3–dioxolane, $BF_3 \cdot OEt_2$; (c) $LiAlH_4$; (d) TsNHN=CHCOCl, AgCN; Et_3N; (e) $Rh_2(OAc)_4$, Freon TF; (f) DIBAL–H; (g) Me_2CO, $BF_3 \cdot OEt_2$, H_2O; (h) MeOH, HCl; (i) DIBAL–H; (j) *t*–BuOOH, $VO(acac)_2$; (k) Jones.

In 1988 Mori[22] completed the first enantioselective total synthesis of (–)–pentalenolactone E methyl ester by following Cane's[21] synthesis starting with the enantiomerically pure (+)–**60**. Optically active (+)–**60** was prepared from (+)–2–ethoxycarbonyl–7,7–ethylenedioxybicyclo[3.3.0]octan–3–one (**64**) (Scheme I–11).

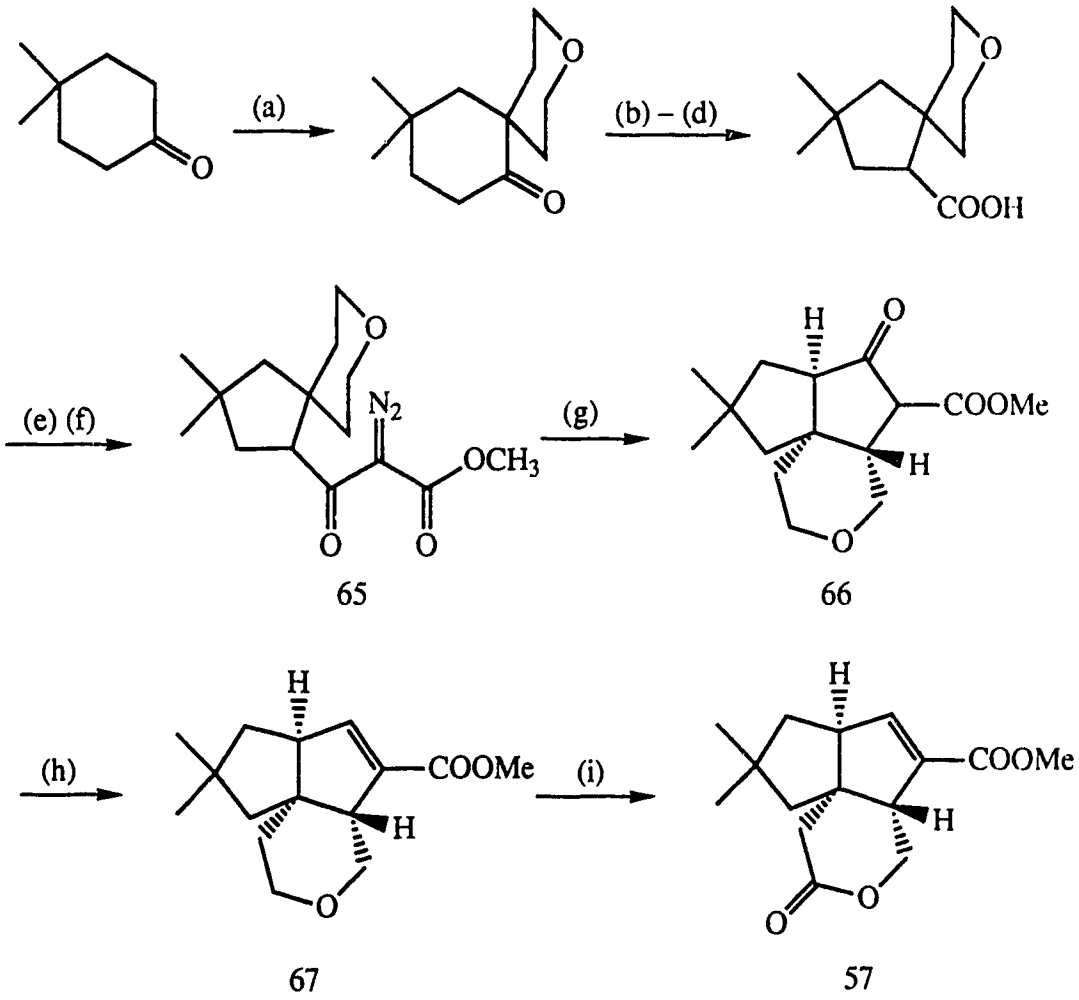
Scheme I–11



(+)–64 (+)–60

Similar to Cane's approach,[21] Taber[23, 24] also utilized the rhodium mediated intramolecular C–H insertion reaction as the key step in the synthesis of pentalenolactone E methyl ester (Scheme I–12). The intramolecular C–H insertion reaction was smoothly effected by exposure of α–diazo–β–ketoester **65** to a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2. The desired tricyclic ether **66** was obtained as a single product in excellent yield. Reduction of the tricyclic β–keto ester **66** followed by dehydration gave the α,β–unsaturated ester **67**. Oxidation of its tetrahydropyran moiety to the required δ–lactone **57** was best effected with CrO_3, resulting in preferential oxidation at the desired, less hindered methylene position (C–10). Lactone **57** thus obtained was identical with authentic material and its conversion to pentalenolactone E methyl ester had been previously demonstrated by Paquette.[19]

Scheme I–12

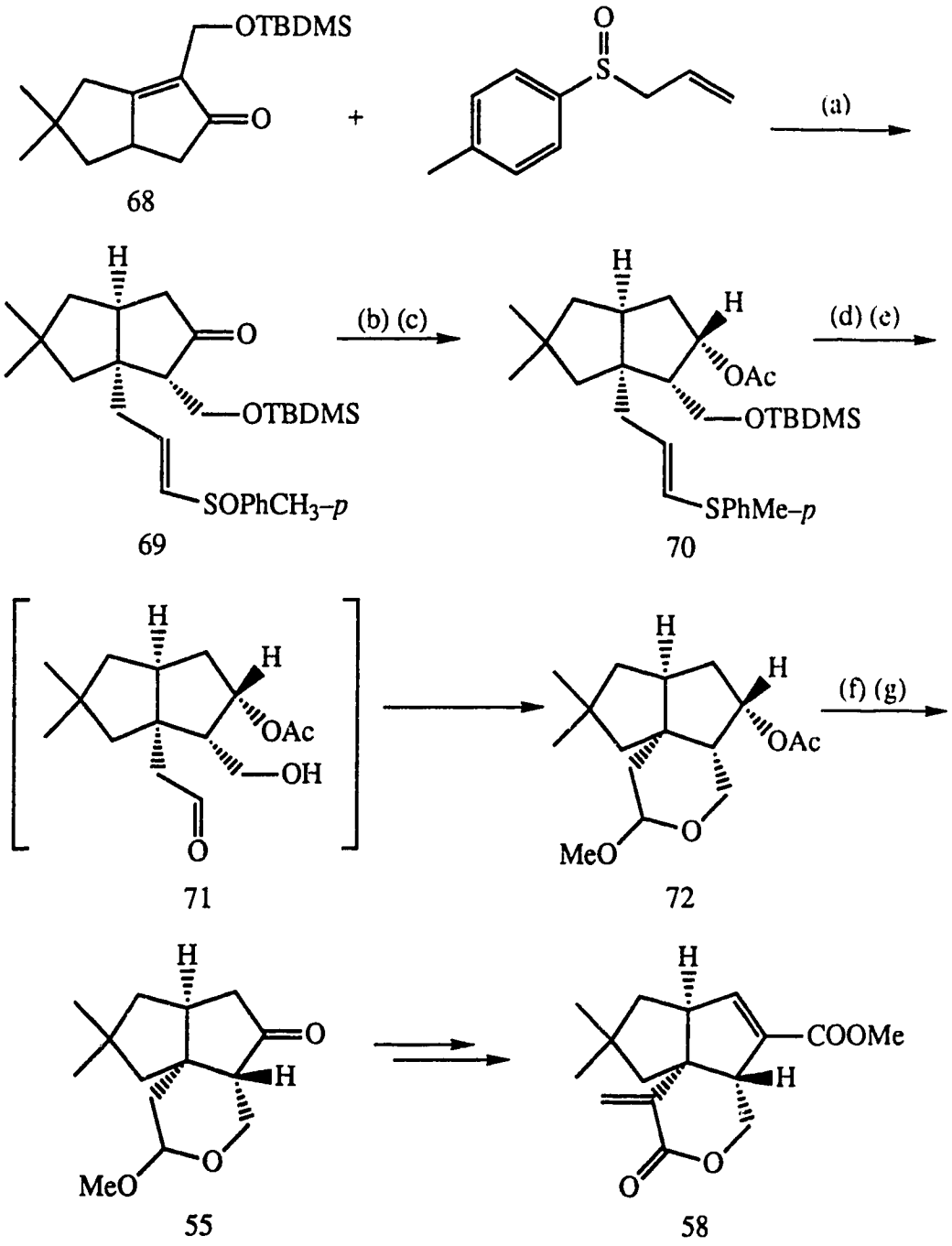


(a) NaH, $(ICH_2CH_2)_2O$, THF; (b) 2,4,6–triisopropylphenylsulonyl azide, 18–Crown–6, $(n\text{–}Bu)_4N^+Br^-$, aq. KOH, PhMe, 40°C; (c) hv, Pyrex, MeOH; (d) LiOH, DME, reflux; 6N HCl; (e) $(COCl)_2$, 0°C → 25°C; $LiCH_2COOMe$, THF, -60°C; (f) TsN_3, CH_3CN, Et_3N; (g) $Rh_2(OAc)_4$, CH_2Cl_2, 25°C; (h) $NaBH_4$, MeOH, 0°C; DCC, Cu_2Cl_2, THF, reflux; (i) CrO_3, HOAc, CH_2Cl_2, 25°C.

In 1987, Hua *et al.*[25] reported a quite different route for the synthesis of (±)–pentalenolactone E methyl ester (Scheme I–13). In this synthetic approach, stereospecific 1,4–addition of the sulfinylallyl anion to enone **68**, providing the corresponding 1,4–adduct **69** as a single isomer with the desired *cis* ring junction, was utilized as a strategy for the elaboration of functionalized tricyclic ring system.

Reduction of the ketone **69** with $NaBH_4$ gave the corresponding sulfoxide alcohol which was treated with acetyl chloride and excess pyridine at 0°C to provide the sulfide **70**. Apparently, acetylation of the hydroxy group and reduction of the sulfoxide group took place under these mild and basic conditions. The desired C ring lactol was assembled in a two–step sequence: (1) ozonolysis of sulfide **70** in CH_2Cl_2 and MeOH to yield the aldehyde intermediate; (2) desilylation with 48% HF in MeOH to give the hydroxy aldehyde **71** which underwent spontaneous lactolization and acetal formation to provide the desired tricyclic acetate **72**. Transformation of acetate **72** to the known ketone **55** was effected by deacetylation with K_2CO_3 in MeOH followed by oxidation of the resulting alcohol with PCC in CH_2Cl_2. Since ketone **55** had previously been converted to pentalenolactone E methyl ester (**58**) by other investigators,[19, 21] a formal synthesis of pentalenolactone E methyl ester was completed.

Scheme I-13

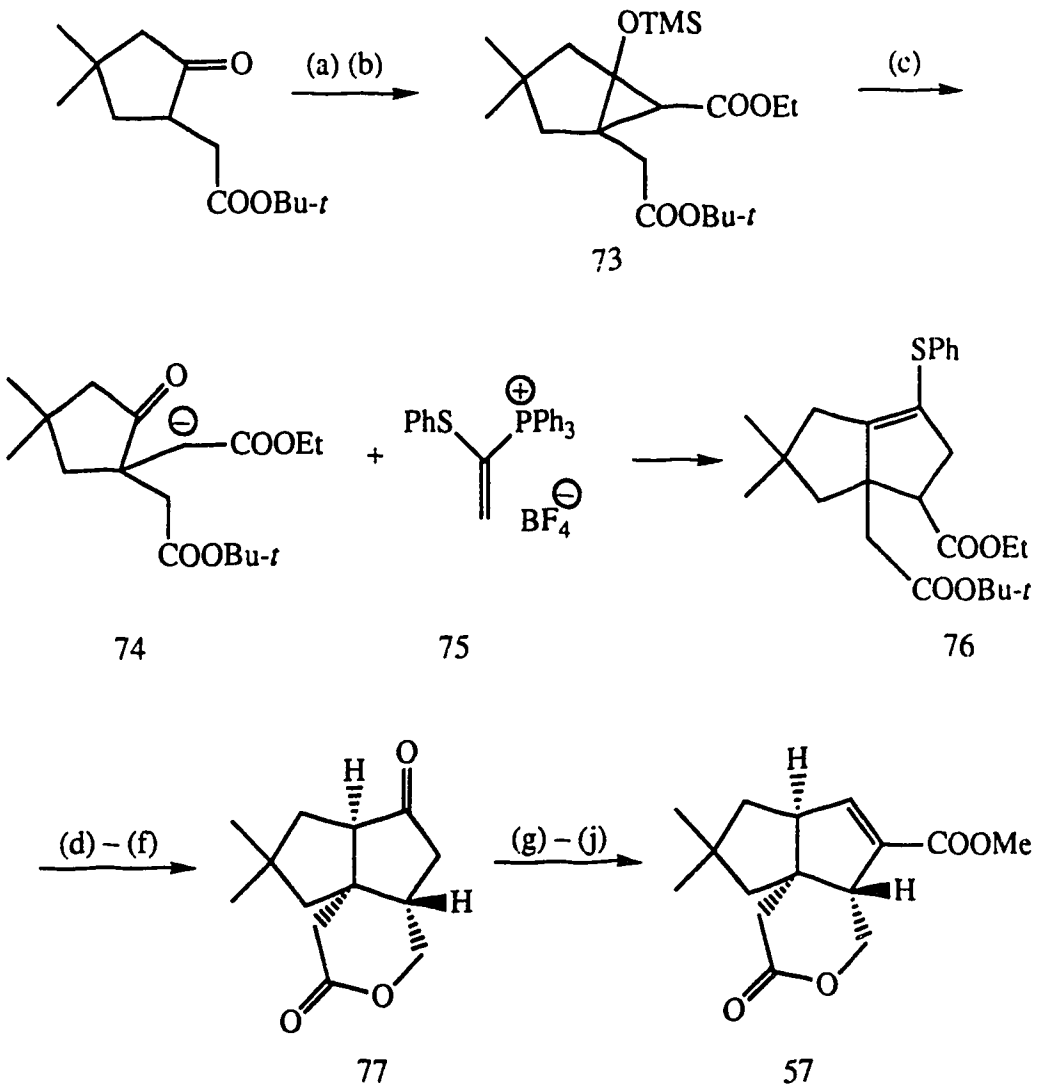


(a) LDA, THF, -78°C; (b) $NaBH_4$, MeOH; (c) AcCl, pyridine, CH_2Cl_2, 0°C; (d) O_3, CH_2Cl_2, MeOH, -78°C; (e) 48% HF, MeOH; (f) K_2CO_3, MeOH; (g) PCC, CH_2Cl_2.

In 1987, Marino[26] developed a stepwise [3+2] annulation strategy to construct the five–membered ring system, through which a total synthesis of pentalenolactone E methyl ester has been achieved.

This strategy relies on the *in situ* generation of a γ–oxo ester enolate **74** from β–(silyloxy)cyclopropyl ester **73** by treatment with potassium fluoride and 18–Crown–6. The requisite β–(siloxy)cyclopropane **73** was readily prepared by the cyclopropanation reaction of the trimethylsilyl enol ether of the starting cyclopentanone derivative with ethyl diazoacetate. The 1,3–bifunctional system **74**, when combined with a two–carbon Michael acceptor, [α–(phenylthio)vinyl]triphenylphosphonium tetrafluoroborate **75**, led to the bicyclo[3.3.0]octene system **76** in 95% yield as a 1:1 mixture of *cis/trans* stereoisomers. Chemoselective hydrolysis of the ethyl ester in methanolic hydroxide yielded a *cis/trans* mixture of the carboxylic acid. Reduction of the *cis* carboxylic acid was effected with $NaBH_4$ *via* its mixed anhydride. Treatment of the resulting alcohol with CF_3COOH in $CHCl_3$ gave rise to the crystalline keto lactone **77**. Apparently, under the reaction conditions, CF_3COOH converted the vinyl sulfide to the ketone, hydrolyzed the *t*–butyl ester and catalyzed the lactonization to form compound **77**. Conversion of the ketone unit in **77** to the α,β–unsaturated methyl ester afforded the key precursor **57** which had previously been prepared by Paquette[19] in his synthesis of pentalenolactone E methyl ester.

Scheme I-14



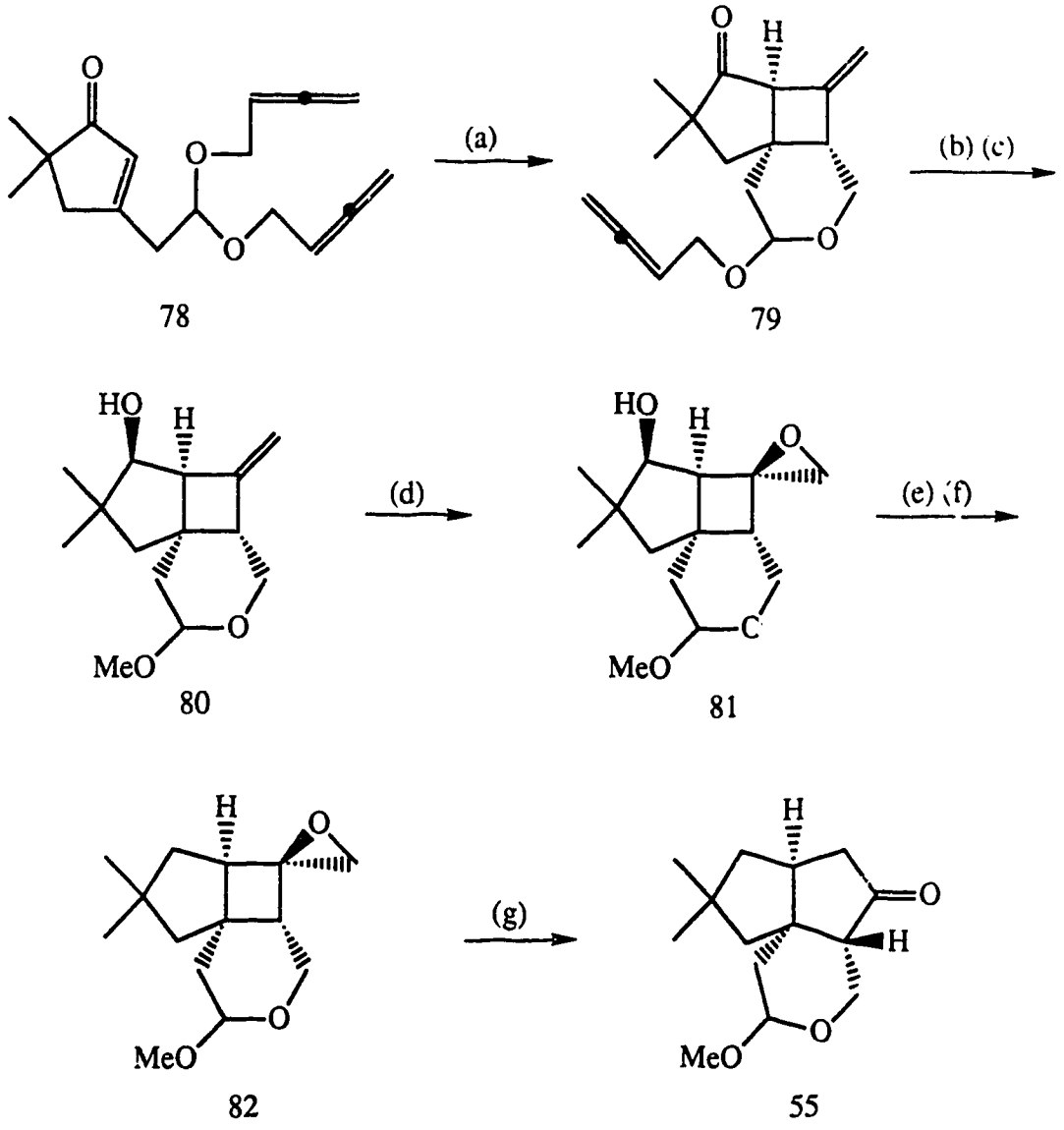
(a) Me_3SiCl, Et_3N, DMF, 135°C; (b) $N_2CHCOOEt$ (4 equiv.), $CuSO_4$, PhH; (c) **75**, KF, 18–Crown–6, MeCN, 82°C; (d) NaOH, H_2O, MeOH, THF, 60°C; (e) ClCOOEt, Et_3N, THF; $NaBH_4$, THF, H_2O; (f) CF_3COOH, $CHCl_3$; (g) C_4H_9N, *p*–TsOH, PhH, 80°C; (h) ClCOOMe (10 equiv.), PhH, 80°C; (i) $NaCNBH_3$ (3 equiv.), MeOH; HCl, 25°C; (j) *m*–CPBA, CH_2Cl_2; K_2CO_3, THF, 25°C.

Despite a decade of synthetic work involving a number of groups, it was not until 1988 that a general synthetic approach[27] to pentalenolactones E, F, G and H emerged in which an intramolecular [2 + 2] photocycloaddition of enone acetal **78** was the key step for the construction of the tricyclic δ–lactone ring system (Scheme I–15).

Irradiation of enone acetal **78** gave the tricyclic acetal **79** in 70% yield as a diastereoisomeric mixture with the desired *cis*–fused ring junctures. In this photocycloaddition process, only head–to–head addition to the allene unit was observed. Reduction of the ketone **79** with L–Selectride followed by transacetalization yielded a single *endo* alcohol **80**. Subsequently, the alcohol–directed epoxidation, according to the Sharpless protocol, delivered exclusively the *syn* epoxy alcohol **81**. The hydroxy group in **81** was removed using Barton's method and the resulting epoxide **82** was subjected to ring expansion with LiBr and HMPA in refluxing benzene to provide the desired ring expansion product **55**. Compound **55** proved to be identical with one of the acetal isomers prepared by Cane[21] during the course of his synthesis of pentalenolactones E and F methyl esters, thus completing a formal synthesis of these natural products.

Towards the syntheses of pentalenolactones G and H (Scheme I–16), the epoxy alcohol **81** was oxidized with PCC to give the epoxy ketone **83**. When treated with LiBr and HMPA, this compound underwent an exceptionally facile ring expansion reaction to produce the tricyclic diketo acetal **84** in 95% yield.

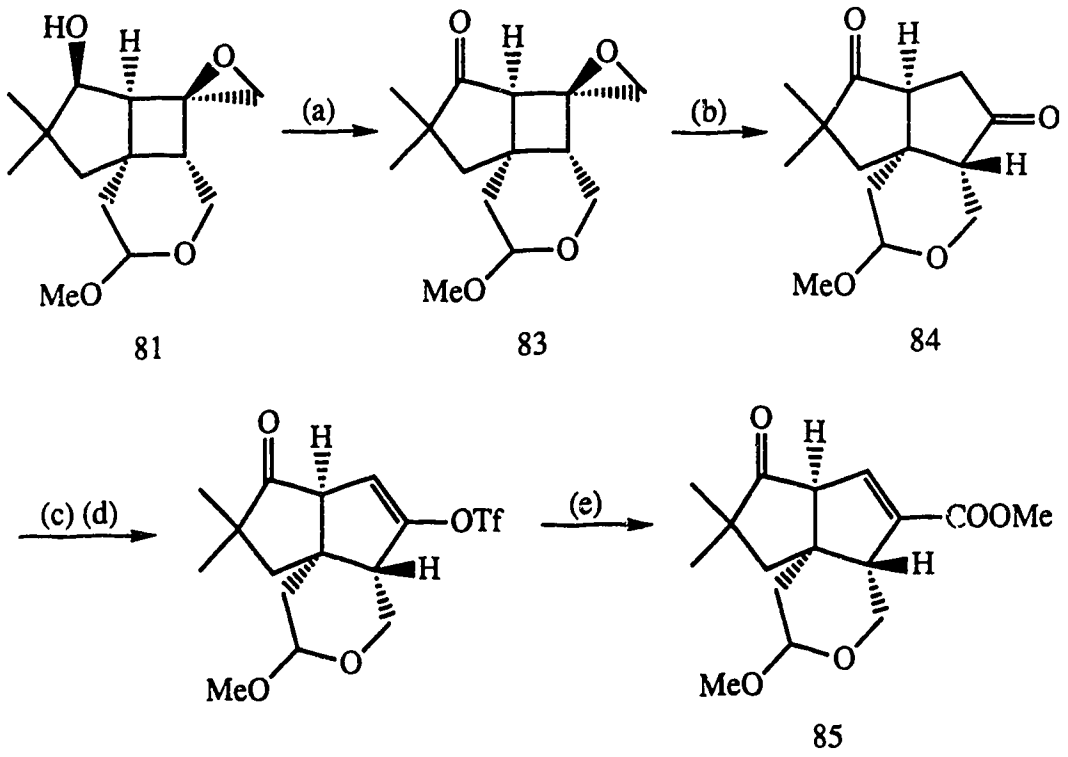
Scheme I–15



(a) hν, Pyrex filter, 450 W medium pressure Hg lamp; (b) L–Selectride; (c) MeOH, H^+; (d) $VO(acac)_2$, *t*–BuOOH, PhH; (e) NaH, CS_2; MeI, THF; (f) Bu_3SnH, PhMe, reflux; (g) LiBr, HMPA, PhH, reflux.

The ketone moiety at C–6 in compound **84** was then converted to the α,β–unsaturated ester unit by the palladium catalyzed coupling of vinyl triflate with CO in THF/MeOH. Treatment of the resulting keto ester **85** with Jones reagent followed by ketalization afforded the δ–lactone **86**. Finally, introduction of a methylene unit α to the δ–lactone carbonyl, deketalization and epoxidation of the methylene group of compound **87** completed the total synthesis of pentalenolactone G methyl ester (**88**). This compound was readily converted to pentalenolactone H methyl ester (**49**)[5] by sodium borohydride reduction.

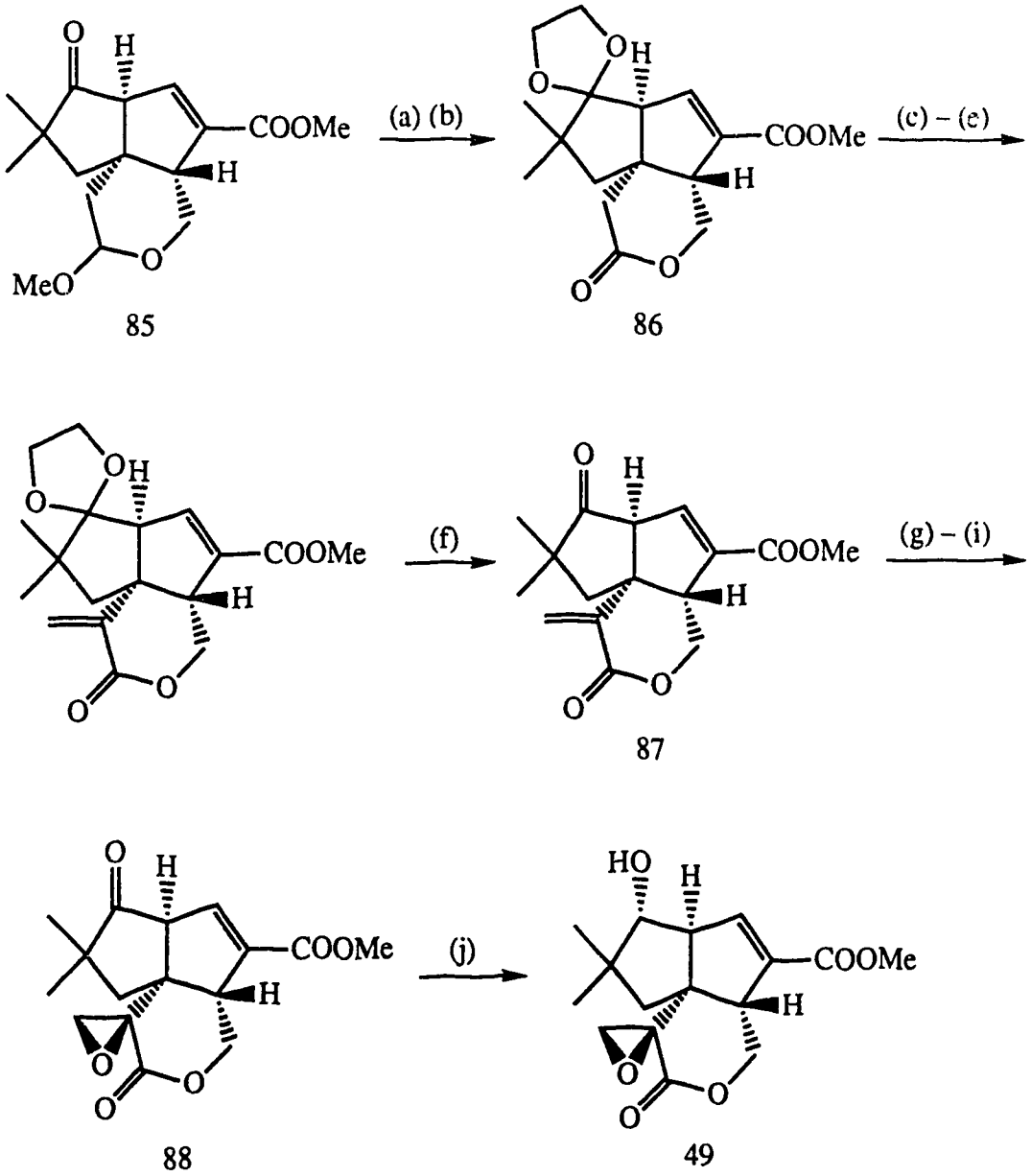
Scheme I–16



81 83 84 85

(a) PCC, CH_2Cl_2; (b) LiBr, HMPA, PhH, 25°C; (c) LDA; (d) $(CF_3SO_2)_2NPh$; (e) CO, MeOH, K_2CO_3, $PdCl_2(Ph_3P)_2$, THF.

Scheme I–16 (continued)



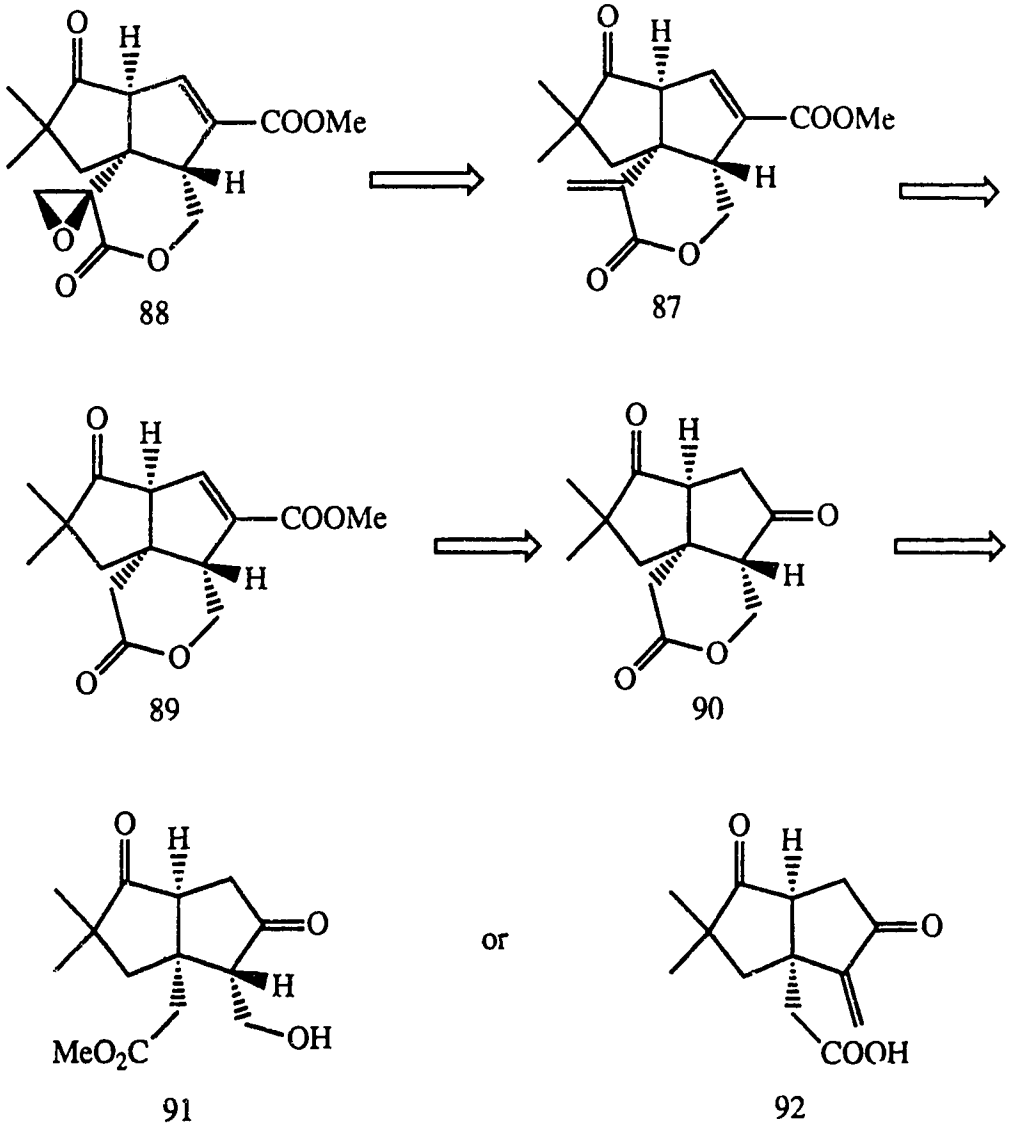
(a) Jones; (b) $HOCH_2CH_2OH$, *p*–TsOH; (c) LDA; $CH_2=N^+(Me)_2I^-$, THF; (d) MeI, MeOH, THF; (e) DBU, THF; (f) HCl, THF, reflux; (g) DIBAL–H; (h) *t*–BuOOH, $VO(acac)_2$; (i) Jones; (j) $NaBH_4$.

We have also been intrigued by the unique structural features of the pentalenolactone family of sesquiterpenes. In spite of the fact that several syntheses of pentalenolactone and pentalenolactones E, F, G and H had appeared, there were no general synthetic approaches to these compounds available when we initiated this project. The main purpose of this synthetic project was to design a common route leading to pentalenolactone and its congeners.

These sesquiterpenoids have common structural features that might enable a general synthetic route to be established. Pentalenolactone G methyl ester **88** was selected as the immediate target molecule. The ketone unit required for this compound could, in principle, be deoxygenated to a methylene unit (for pentalenolactones E and F), reduced to a hydroxy group (for pentalenolactone H) and subsequently rearranged to provide the pentalenolactone skeleton.

The retrosynthetic analysis is shown in Scheme I–17 and Scheme I–18. Dissection of the epoxide ring at C–9 and C–10 in **88** would lead to the α–methylene lactone **87** which should be available from the tricyclic lactone **89**. The α,β–unsaturated ester functionality at C–7 in **89** was anticipated to arise from the ketone unit of diketone **90**. This compound could be assembled either *via* lactonization of hydroxy ester **91** or *via* enone acid **92**.

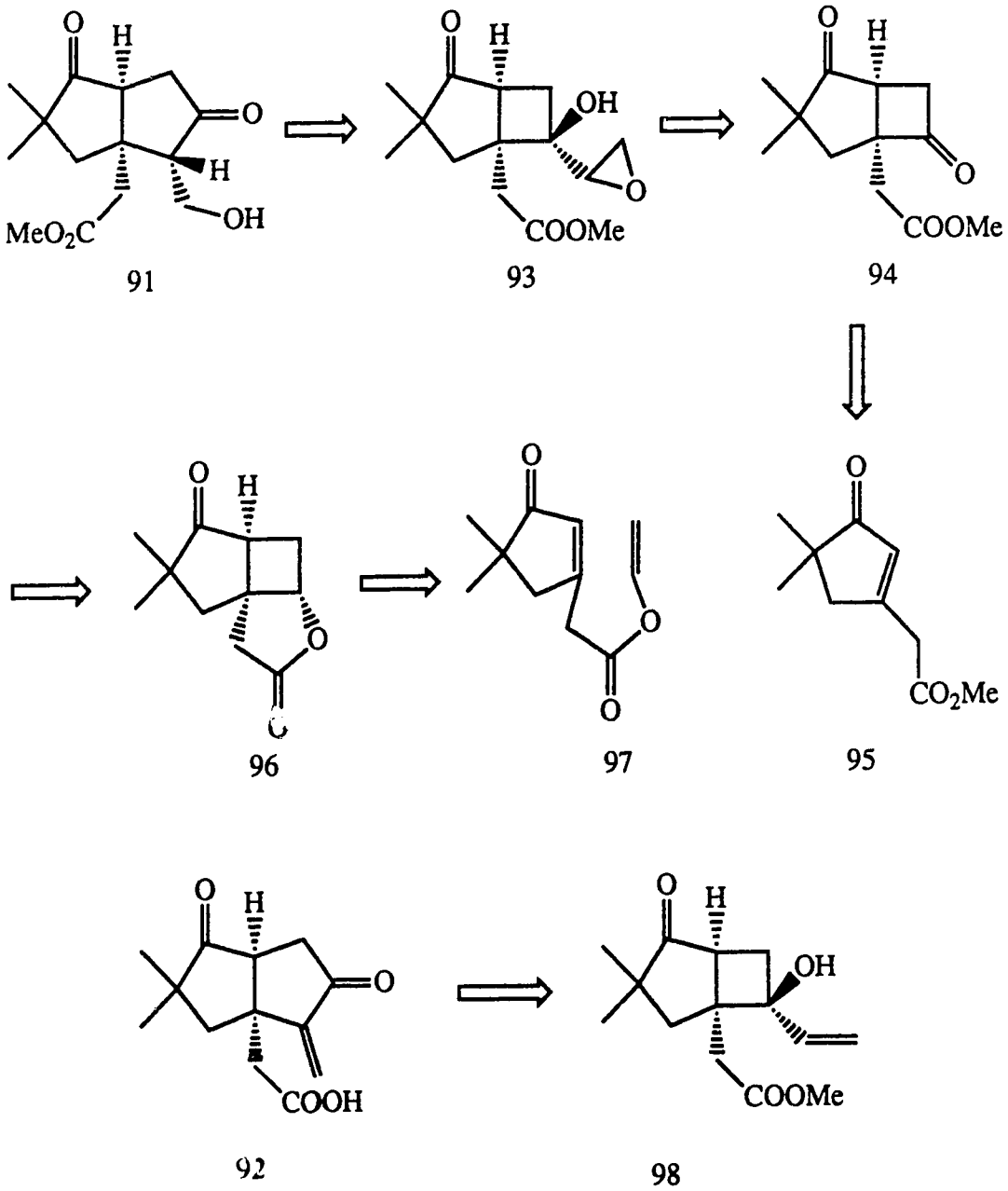
Scheme I-17



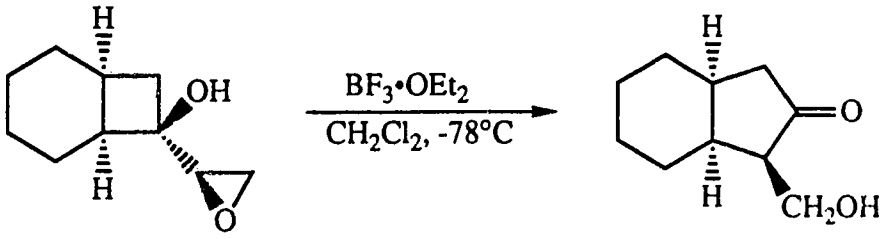
Hydroxy ester **91** could be derived from ring expansion of hydroxy epoxide **93**. This compound could be synthesized from cyclobutanone **94**. Compound **94** might be derived either from enone ester **95** *via* intermolecular photocycloaddition with 1,1-dimethoxyethylene[28, 29] or from vinyl ester **97** *via* an intramolecular photocycloaddition. The latter process should proceed in a highly regioselective manner to give tricyclic lactone **96** according to the "rule

of five".[30] In the case of enone acid **92**, we envisaged its formation by means of a ring expansion of cyclobutanol **98**, which could be prepared from cyclobutanone **14**.

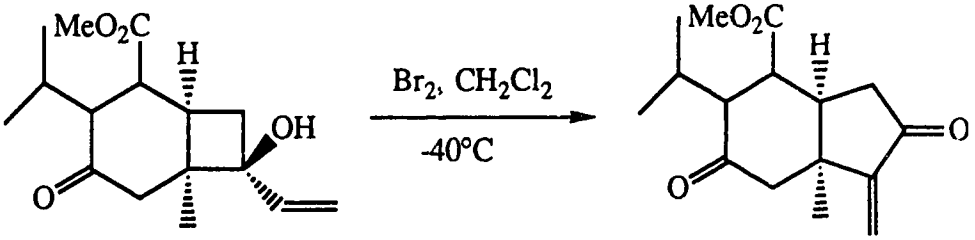
Scheme I-18



The key ring expansion reactions were proposed based on the following precedence. Exposure of epoxy alcohol **99** to a catalytic amount of boron trifluoride in dichloromethane at -78°C resulted in the regio– and stereoselective expansion of its cyclobutanol ring, giving the hydroxymethyl ketone in good yield.[31] Similarly, treatment of compound **100** with bromine in CH_2Cl_2 at -40°C gave rise to the ring expansion product in satisfactory yield.[32]



99

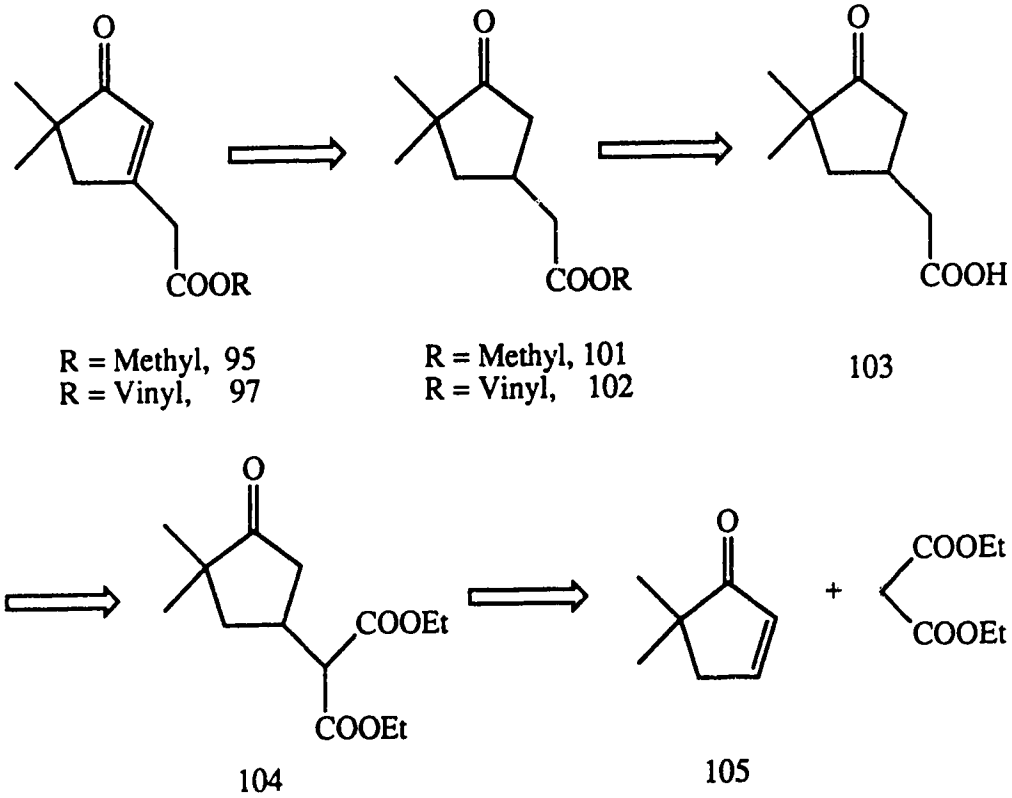


100

RESULTS and DISCUSSION

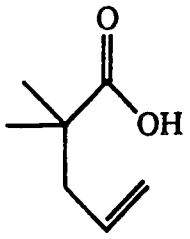
According to the retrosynthetic analysis, our immediate task was to prepare the enone ester **95** or **97**. To the best of our knowledge, there were no existing methods available for the preparation of this type of enone ester. A conceivable synthetic approach to **95** and **97** involves the introduction of a double bond to the corresponding keto esters **101** and **102** which should be readily available from keto acid **103**. The keto acid **103** could arise from keto diester **104** *via* decarboxylation. The latter compound, in turn, could be formed by Michael addition of diethyl malonate to enone **105** (Scheme I–19).

Scheme I–19

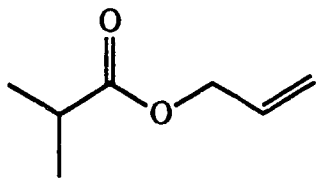


The known procedure for the preparation of enone **105**[33] was followed. Isobutyric acid was transformed to acid **106** in multigram quantities either by direct alkylation of the dianion of isobutyric acid[34] or by a two–step process involving the Claisen rearrangement of the enolate of allyl isobutyrate (**107**).[35] Treatment of isobutyric acid with two equivalents of LDA at 0°C followed by alkylation with allyl bromide provided acid **106** in about 60% yield. In the mass spectrum, the molecular ion peak of compound **106** was observed at m/e 128.0840, in agreement with the molecular formula $C_7H_{12}O_2$. This compound displayed a carboxylic acid absorption at 3200 cm^{-1} and a carbonyl band at 1702 cm^{-1} in the IR spectrum. A broad singlet at δ 11.8 in the ^1H NMR spectrum was assigned to the proton of the carboxyl group. The methylene protons appeared at δ 2.30 as a doublet of triplets (J = 7 and 1 Hz). Its ^{13}C NMR spectrum indicated the presence of carbonyl group displaying a singlet at δ 184.53. A doublet at δ 133.94 and a triplet at δ 118.25 were observed for the vinylic carbons.

In practice, the direct alkylation method was not suitable for the preparation of large quantities of acid **106**, since a large amount of *n*–BuLi must be used. An alternative method for the preparation of acid **106** made use of Claisen rearrangement of the enolate of allyl isobutyrate (**107**).[35] This methodology proved to be more useful for the preparation of large amounts of acid **106**.



106



107

For the preparation of allyl isobutyrate (**107**), a mixture of isobutyric acid and thionyl chloride was refluxed for 2 h and the derived acyl chloride was then subjected to treatment with allylic alcohol in the presence of pyridine. Allyl isobutyrate (**107**) was isolated in 95% yield as a clear oil after fractional distillation.

This ester showed, in the IR spectrum, an absorption at 1738 cm^{-1} due to the ester carbonyl group. The molecular ion peak was observed in the high resolution mass spectrum at m/e 128.0836, consistent with the molecular formula $C_7H_{12}O_2$. The complete ^1H NMR and ^{13}C NMR assignments are compiled in Table I–1 and Table I–2.

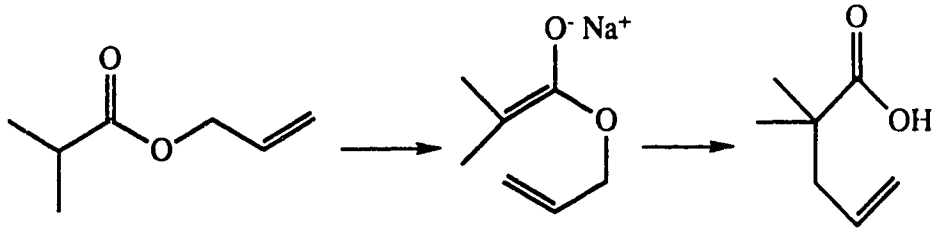
Table I–1. 300 MHz ^1H NMR Spectral Data for Allyl Ester **107**

Proton	Chemical Shift (δ)	Multiplicity (*J* in Hz)
$CH{=}CH_2$	5.92	ddt (17, 10, 5.5)
trans CHH=CH	5.32	ddt (17, 1.5, 1.5)
cis CHH=CH	5.22	ddt (10, 1.5, 1.5)
OCH_2	4.58	dt (5.5, 1.5)
$CH(CH_3)_2$	2.59	septet (7)
$CH(CH_3)_2$	1.20	d (7)

Table I–2. 75 MHz ^{13}C NMR Spectral Data for Allyl Ester **107**

Carbon	Chemical Shift (δ)	Multiplicity
C=O	176.75	s
CH=CH_2	132.45	d
CH_2=CH	117.82	t
CH_2O	64.87	t
$CH(CH_3)_2$	34.00	d
$CH(CH_3)_2$	18.98	q

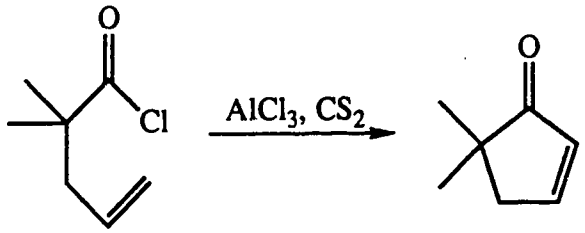
Treatment of allyl isobutyrate (**107**) with sodium hydride in refluxing toluene generated the corresponding ester enolate which then underwent Claisen rearrangement to afford acid **106** in 68% yield.



107 106

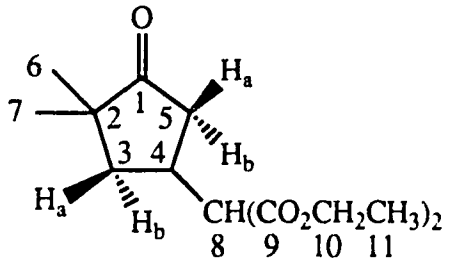
Enone **105** was prepared *via* Friedel–Crafts acylation from acid chloride **108** in about 50% yield. Thus, a mixture of acid **106** and thionyl chloride was refluxed for 1 h. The crude acyl chloride in carbon disulfide was added dropwise to $AlCl_3$ in CS_2 and the resulting mixture was heated at reflux for 2 h. Enone **105** was best isolated by fractional distillation *via* a vigreux column.

It exhibited a strong absorption at 1708 cm^{-1} in the IR spectrum, indicating the presence of the α,β–unsaturated ketone. A molecular ion peak at m/e 110.0731 was observed in the mass spectrum, in agreement with the molecular formula $C_7H_{10}O$. The doublets of triplets at δ 7.64 (J = 5.8 and 2.5 Hz) and 6.14 (J = 5.8 and 2 Hz) in the ^1H NMR spectrum were assigned respectively to the β proton and α proton of the enone. The structure of **105** was also evident from the ^{13}C NMR spectrum which showed signals at δ 214.79 (s) for the carbonyl carbon and at δ 161.76 (d) and 131.85 (d) for the doubly bonded carbons.



108 105

Keto diester **104** was conveniently prepared in 82% yield through the Michael addition[36] of diethyl malonate to enone **105** in the presence of sodium ethoxide. In the IR spectrum, a strong band at 1734 cm^{-1} was due to the carbonyl groups. The mass spectrum showed the molecular ion peak at m/e 270.1469 for the molecular formula $C_{14}H_{22}O_5$. In order to assign the ^1H NMR signals, the proton decoupling experiments were carried out. On the basis of the results outlined in Table I–4, it was possible to assign all the protons present in the molecule. These assignments are compiled in Table I–3, which also summarizes the ^{13}C NMR spectral data of **104**.



104

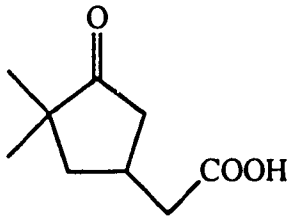
Table I–3. ^{1}H NMR and ^{13}C NMR (APT) Data for Keto–Diester **104**

Carbon	δ (Multiplicity)	Proton	Chemical Shift (δ)	Multiplicity (*J* in Hz)
C–1	220.72 (s)	H–10	4.22	m
C–9	168.13 (s)	H–8	3.27	d (9.5)
C–10	61.62 (t)	H–4	2.88	m
C–8	57.05 (d)	H–5b	2.64	ddd (18.5, 10, 2)
C–2	46.02 (s)	H–5a	2.06	dd (18.5, 11)
C–5	42.99 (t)	H–3b	2.05	ddd (12.5, 6.5, 2)
C–3	41.95 (t)	H–3a	1.54	dd (12.5, 12)
C–4	32.41 (d)	H–11	1.29	t (7)
C–6	24.13 (q)	OCH_2CH_3	1.28	t (7)
C–7	23.99 (q)	H–6	1.10	s
C–11	14.12 (q)	H–7	1.08	s

Table I–4. Spin Decoupling Data for Compound **104**

Signal Irradiated (δ)	Signal Changed (δ)
3.27 (d), H–8	2.88
2.88 (m), H–4	3.27 (d→s); 2.64 (ddd→dd); 2.06 (dd→d); 1.54 (dd→d)
2.64 (ddd), H–5b	2.06; 2.05; 2.88
2.06 (dd), H–5a	2.88
2.05 (ddd), H–3b	2.64 (ddd→dd); 1.54
1.54 (dd), H–3a	2.88; 2.05

In order to prepare keto acid **103**, diester **104** was treated with aqueous 3N HCl in refluxing ethanol. Under these conditions, the resulting keto diacid intermediate underwent a remarkably clean decarboxylation[36] to afford the desired keto acid **103** in 94% yield. The keto acid showed absorptions in its IR spectrum at 3200, 1740 and 1709 cm^{-1} respectively for the hydroxy and carbonyl groups of the acid and the ketone carbonyl. A molecular ion peak at m/e 170.0944 was observed for the molecular formula $C_9H_{14}O_3$ which was also confirmed by the elemental analysis. Interestingly, the proton of the carboxylic acid unit was not observed in the ^1H NMR spectrum. In the ^{13}C NMR APT spectrum, two singlets at δ 221.70 and 177.98 were assigned to the carbons of the ketone and carboxyl carbonyl groups respectively.

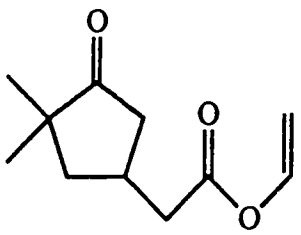


103

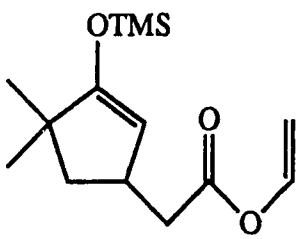
With the desired keto acid **103** in hand, we then directed our efforts to the preparation of vinyl ester **102**. This compound was obtained in 94% yield by the ester exchange reaction of acid **1** [illegible]nyl acetate[37, 38] in the presence of mercury acetate and a catalytic am[illegible]oncentrated sulfuric acid. The ester exchange reaction was found to g[illegible]e best results when carried out at room temperature. Vinyl ester **102** displayed an absorption at 1742 cm^{-1} in its IR spectrum for the carbonyl groups. In its high resolution mass spectrum, a molecular ion peak was shown at m/e 196.1103, in agreement with the molecular formula $C_{11}H_{16}O_3$ which was also substantiated by the elemental analysis. In the ^1H NMR spectrum, a doublet of doublets at δ 7.28 (J_{trans} = 14 and J_{cis} = 6 Hz) was assigned to the vinylic proton adjacent to the oxygen. A doublet of doublets at δ 4.91 (J_{trans} = 14 Hz, J_{gem} = 2 Hz) was assigned to the *trans* proton of $CH{=}CH_2$. Similarly, a doublet of doublets at δ 4.59 (J_{cis} = 6 Hz and J_{gem} = 2 Hz) was assigned to the *cis* proton of $CH{=}CH_2$. In the ^{13}C NMR spectrum, four low–field signals were observed at δ 221.36 (s), 169.25 (s), 141.01 (d) and 98.07 (t). The former two were assigned to the carbonyl carbons and the latter two were due to the vinylic carbons.

At this stage, it was set to prepare the desired enone **97**. Unfortunately, all attempts to convert the ketone **102** to the enone **97** failed. The first method examined was chemoselective deprotonation of the keto–ester **102** with LDA in

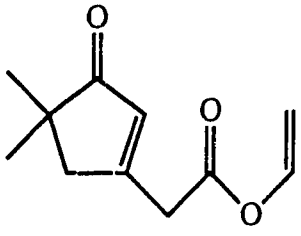
tetrahydrofuran at -78°C followed by selenenylation with phenylselenenyl bromide.[39, 40] In this case, the vinyl group was found to undergo facile addition with phenylselenenyl bromide. We also attempted the preparation of the enone **97** by oxidation of the silyl enol ether **109** with palladium acetate.[41] The required silyl enol ether[42] was easily prepared from **102** by selective deprotonation with LDA in tetrahydrofuran at -78°C, followed by silylation using chlorotrimethylsilane. The ^{1}H NMR spectrum of **109** showed a doublet at δ 4.43 (J = 2 Hz), indicating the formation of the silyl enol ether. Quite disappointingly, oxidation of the resulting silyl enol ether **109** with one equivalent of palladium acetate failed to afford the desired enone **97**.



102



109

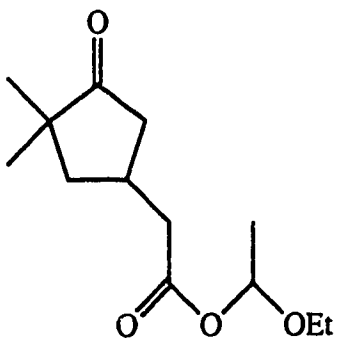


97

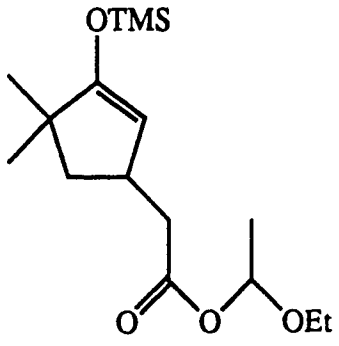
In light of the above results, we turned our attention to a different route to prepare the desired enone ester **97**. We anticipated that the carboxyl group of the acid **103** could be first protected and the saturated ketone subsequently transformed to the required enone group. The protected carboxyl was then to be converted to a vinyl ester. Towards this end, the acid **103** was converted to the corresponding ethoxy ethyl ester (OEE) **110** essentially in quantitative yield as a mixture of diastereoisomers in a ratio of 1:1. This was carried out simply by exposure of the acid **103** to ethyl vinyl ether in the presence of a catalytic amount of *p*–toluenesulfonic acid at 0°C. The ethoxy ethyl ester **110** displayed an absorption at 1739 cm^{-1} in its IR spectrum for both the ketone and ester

carbonyl groups. A molecular ion peak at m/e 242.1519 was observed for the molecular formula $C_{13}H_{22}O_4$ which was further supported by the elemental analysis. The ^{13}C NMR signals at δ 221.64 (s) and 171.91 (s) corresponded to the carbons of the ketone and ester carbonyl groups.

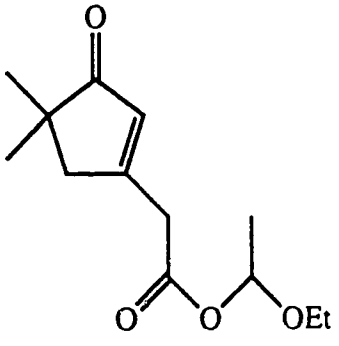
The keto ester **110** was chemoselectively deprotonated with LDA at -78°C. This was followed by trapping of the enolate ion thus produced with phenylselenenyl bromide to give a mixture of diastereoisomers. Unfortunately, all attempts to oxidatively eliminate the α–phenylseleno group failed to produce the desired enone. It seemed that highly volatile products were produced, since even careful evaporation of the solvent on a rotatory evaporator left no detectable products. On the other hand, oxidation of the silyl enol ether **111** with palladium acetate afforded mainly the starting keto ester **110**. Only a trace amount of enone ester **112** was detected by the ^1H NMR analysis which showed a broad singlet at δ 6.09 for the vinylic proton and a broad doublet at δ 3.46 for the methylene protons adjacent to the ester carbonyl.



110



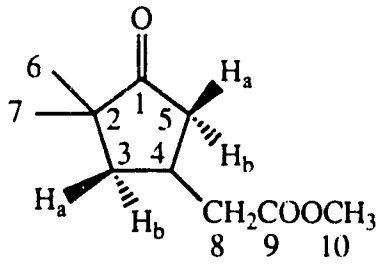
111



112

Due to the unsuccessful attempts to prepare the enone **97**, we decided to focus our efforts on the stable keto ester **101** which was readily obtainable by

refluxing a methanolic solution of the keto acid **103** in the presence of sulfuric acid. The IR spectrum of **101** exhibited a carbonyl band at 1739 cm^{-1} for the ketone and ester carbonyl groups. The high resolution mass spectrum confirmed the molecular formula of $C_{10}H_{16}O_3$ with a molecular ion peak at m/e 184.1098. The presence of the methyl ester was also evident from the singlet at δ 3.70 in the ^1H NMR spectrum and from the methoxy carbon resonance at δ 51.61 (q) in its ^{13}C NMR spectrum. To assign all the protons and to examine the coupling patterns in the ^1H NMR spectrum, a series of the spin decoupling experiments were carried out (Table I–6). Several interesting coupling features were drawn from these experiments. First, three AB types of geminal couplings were observed for the methylene protons at C–3, C–5 and C–8 with coupling constants of 12, 18 and 15 Hz respectively. Secondly, the H–3b proton and H–5b proton were shown to couple with each other across four single bonds which could exist in a planar zig–zag configuration (W–coupling). The detailed ^1H and ^{13}C NMR analyses are to be found in Table I–5.



101

Table I–5. ^{13}C NMR (APT) and ^{1}H NMR Spectral Data for Keto Ester **101**

Carbon	δ (Multiplicity)	Proton	Chemical Shift (δ)	Multiplicity (*J* in Hz)
C–1	221.66 (s)	H–10	3.70	s
C–9	172.59 (s)	H–4, H–5b	2.62	m
C–10	51.61 (q)	H–8a	2.44	dd (15, 6)
C–2	46.23 (s)	H–8b	2.43	dd (15, 7)
C–5	44.95 (t)	H–3b	2.08	ddd (12, 6, 2)
C–8	43.62 (t)	H–5a	1.89	dd (18, 12)
C–3	39.91 (t)	H–3a	1.42	dd (12, 11)
C–4	29.34 (d)	H–6	1.08	s
C–6	24.17 (q)	H–7	1.04	s
C–7	24.13 (q)			

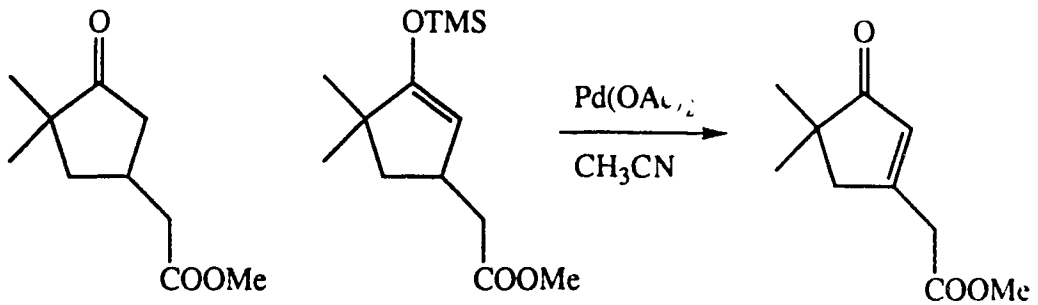
Table I–6. Spin Decoupling Data for Methyl Ester **101**

Signal Irradiated (δ)	Signal Changed (δ, *J* in Hz)
2.62, H–4, H–5b	2.44, H–8a (dd→d, 15); 2.43, H–8b (dd→d, 15) 1.89, H–5a (dd→s); 2.08, H–3b (ddd→d, 12); 1.42, H–3a (dd→d, 12)
2.44 and 2.43, H–8	2.62, H–4
2.08, H–3b	2.62, H–5b and H–4; 1.42, H–3a (dd→d, 12)
1.89, H–5a	2.62, H–5b
1.42, H–3a	2.62, H–4; 2.08, H–3b (ddd→dd, 12, 6.5)

To incorporate a double bond into keto ester **101**, the procedure involving phenylselenenylation and oxidative elimination[39, 40] was initially investigated. This method met with little success. In several attempts, a severe loss of material occurred without apparent production of the desired enone ester **95.**

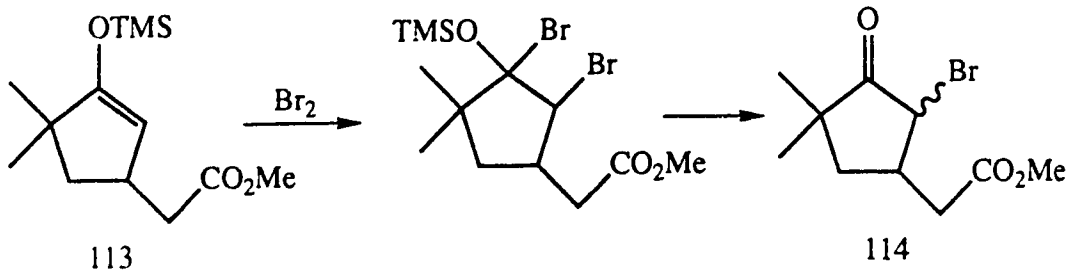
In another approach, direct oxidation of the corresponding silyl enol ether **113** with palladium acetate in acetonitrile was carried out. In this case, the desired enone ester **95** was formed, but in poor yield. The major product was shown to be the keto ester **101**. The IR spectrum of the enone ester **95** showed absorptions at 1743 and 1707 cm^{-1}, indicating the presence of ester and enone carbonyl groups. The formation of the enone system was further confirmed by the 300 MHz ^1H NMR spectrum in which a multiplet at δ 6.04 was observed for the α proton of the enone. The resonance signals in its ^{13}C NMR spectrum at δ

169.07 (s, C–3) and 129.92 (d, C–2) also revealed the existence of the enone double bond in the molecule. Its high resolution mass spectrum displayed a molecular ion peak at m/e 182.0944, in agreement with the molecular formula $C_{10}H_{14}O_3$ which was verified by the elemental analysis.



101 113 95

The consistently low yield of the desired enone ester prompted us to search for another approach for its preparation. In principle, enone **95** could be formed by dehydrobromination of the α-bromo ketones **114**. Initially, direct bromination of the keto ester **101** was attempted for the preparation of **114**. Treatment of ketone **101** with pyridinium bromide perbromide[43] in acetic acid and dichloromethane led to a mixture of the monobromo ketones **114** (mixture of diastereoisomers) and the undesired dibromo ketone **116** in a ratio of *ca.* 2:1 as determined by the relative intensities of the methoxy signals in the ^1H NMR spectrum. The methoxy groups of the diastereoisomeric monobromo ketones **114** appeared at δ 3.73 and 3.72 as singlets, whereas the methoxy group of the dibromo ketone **116** displayed a singlet at δ 3.76. Attempts to effect the product ratio by changing the reaction temperature did not lead to substantial improvement.



113 114

An alternative route to α–bromo ketones **114** was exploited. In 1974, Hassner[44] reported a methodology for regiospecific halogenation of carbonyl compounds *via* the corresponding silyl enol ethers. This procedure was successfully applied. The desired silyl enol ether **113** was easily prepared using conditions previously described for the transformation **102** to **109**. The reaction of the silyl enol ether **113** with one equivalent of bromine in carbon tetrachloride took place instantaneously at -20°C and an inseparable mixture of diastereoisomeric monobromo ketones **114** was produced in an overall yield of 64% from ketone **101**. In this case, the dibromo ketone **116** was not observed. The infrared spectrum of **114** displayed a band at 1738 cm^{-1} for the carbonyl groups. The high resolution mass spectrum showed two molecular ion peaks at m/e 264.0178 and 262.0177, consistent with the molecular formula $C_{10}H_{15}O_3Br$. In the ^1H NMR spectrum, the proton adjacent to the bromine atom appeared at δ 4.50 as a doublet of doublets with J = 4.5 and 1.5 Hz (W–coupling) for one isomer and at δ 4.16 as a doublet with a coupling constant of 11 Hz for the other.

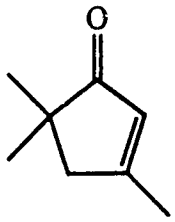
Several bases and various reaction conditions were explored to induce the dehydrobromination of α–bromo ketones **114**. Treatment of **114** with triethyl amine at reflux temperature did not effect any reaction. With DBU in refluxing benzene, the starting material underwent extensive decomposition

without producing the desired enone. The use of pyridine as a base proved to be more fruitful. When a solution of α–bromo ketones **114** in pyridine was heated at 80°C for 30 min, the enone **95** was formed albeit in low yield (20–30%). Attempted dehydrobromination at room temperature resulted in the recovery of the starting material. The low yield of enone **95** was probably due to its subsequent decarbomethoxylation, initiated by the attack of the methyl ester by bromide ion, to give the volatile enone **115**.

To prove this assumption, the dibromo ketone **116** was prepared in 94% yield by direct bromination of ketone **101** with two equivalents of pyridinium bromide perbromide in CH_2Cl_2. Its high resolution mass spectrum showed three molecular ion peaks at m/e 343.9281, 341.9304 and 339.9321, corresponding to the molecular formula $C_{10}H_{14}O_3Br_2$ which was also supported by the elemental analysis. The IR spectrum showed carbonyl absorptions at 1761 and 1740 cm^{-1} for the ketone and ester carbonyl groups respectively. In the ^1H NMR spectrum, the methoxy singlet shifted downfield to δ 3.76 from δ 3.70 observed for that of the starting material **101**. The methylene protons adjacent to the ester group also displayed two distinct signals at δ 3.05 (dd, J = 16, 3 Hz) and 2.55 (dd, J = 16, 9.6 Hz) with the geminal coupling constant of 16 Hz. The proton at C–3 resonated at δ 2.82 as a doublet of doublets of doublets with coupling constants of 12, 9.6, 6 and 3 Hz. The methylene protons at C–4 appeared as two mutually coupled signals at δ 2.10 (dd, J = 12.5, 12 Hz) and 1.70 (dd, J = 12.5, 6 Hz) with a geminal coupling constant of 12.5 Hz. In the ^{13}C NMR spectrum, the ketone and ester carbonyl carbons resonated at δ 206.40 (s) and 171.56 (s) respectively. The carbon bearing the bromine atoms was also observed as a singlet at δ 69.54.

The methoxy carbon displayed a quartet at δ 52.01 and the C–3 carbon resonated as a doublet at δ 47.25.

Treatment of the dibromo keto ester **116** with pyridine at reflux temperature for 1.5 h cleanly produced the expected decarboxylated α–bromo enone **117** in 94%. The disappearance of the methyl ester unit was evident from both the ^{1}H and ^{13}C NMR spectra in which carbomethoxy resonances were absent. Furthermore, the ^{1}H NMR spectrum showed a broad quartet at δ 2.51 (J = 1 Hz) for the methylene protons and a broad triplet at δ 2.16 (J = 1 Hz) for the vinylic methyl group. In the ^{13}C NMR spectrum, the carbonyl carbon resonated at δ 206.09 as a singlet. Two other low–field singlets at δ 170.28 and 120.78 were assigned to the carbons of the double bond.



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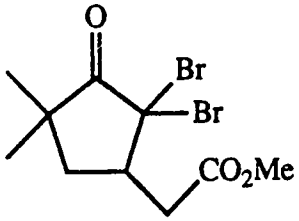
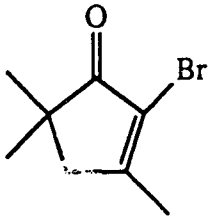


116



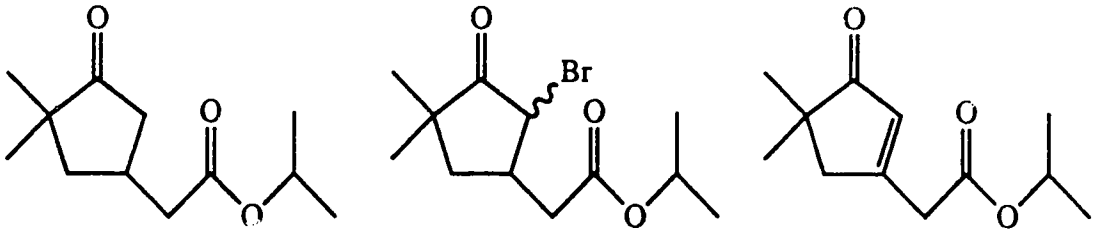
117

The above observation lent support to the assumption that the low yield of enone **95** obtained from the dehydrobromination of **114** was due to the formation of enone **115** *via* decarbomethoxylation. In order to improve the yield, it was necessary to suppress this side reaction. One conceivable approach was to replace the methyl ester in **114** with a larger ester group.

Towards this end, isopropyl ester **118** was prepared in quantitative yield by esterification of keto acid **103** in refluxing isopropanol under the catalysis of

sulfuric acid. Ester **118** displayed an absorption band at 1740 cm^{-1} in the IR spectrum for both the ketone and ester carbonyls. A molecular ion peak was observed at m/e 212.1411 corresponding to the molecular formula $C_{12}H_{20}O_3$. In its ^{13}C NMR APT spectrum, singlets at δ 221.85 and 171.71 were due to the ketone and ester carbonyl carbons respectively. The doublet at δ 67.91 was assigned to the isopropyl carbon directly attached to the oxygen atom.

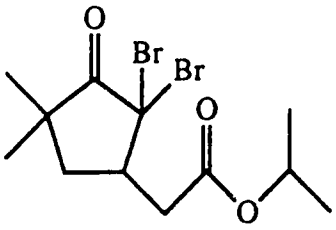
Conversion of the keto ester **118** to the α–bromo ketone **119** was readily achieved by treatment of the corresponding silyl enol ether with bromine. Disappointingly, dehydrobromination of the α–bromo ketone **119** with pyridine afforded the desired enone ester **120** in only 20% yield from ketone **118**.



118 119 120

The low yield of the desired enone **120** could also be attributed to its propensity to undergo decarboxylation. This rational was indirectly supported by the fact that heating dibromo keto ester **121** in pyridine at reflux for 20 min furnished mainly the decarboxylated enone **117** (56% yield), along with a small amount of bromo enone ester **122** (32% yield). The latter has a molecular formula $C_{12}H_{17}O_3Br$ as determined by the high resolution mass spectrum displaying the molecular ion peaks at m/e 290.0335 and 288.0355. Its IR spectrum showed absorptions at 1729 and 1620 cm^{-1} due to the ester and enone

carbonyl groups. When the dehydrobromination of **121** was carried out over an extended period of 1.5 h, the enone **117** was formed as the sole product in 92% yield.



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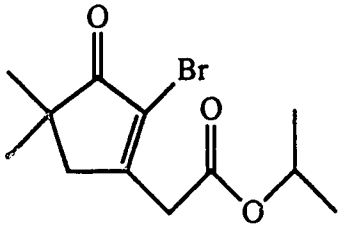
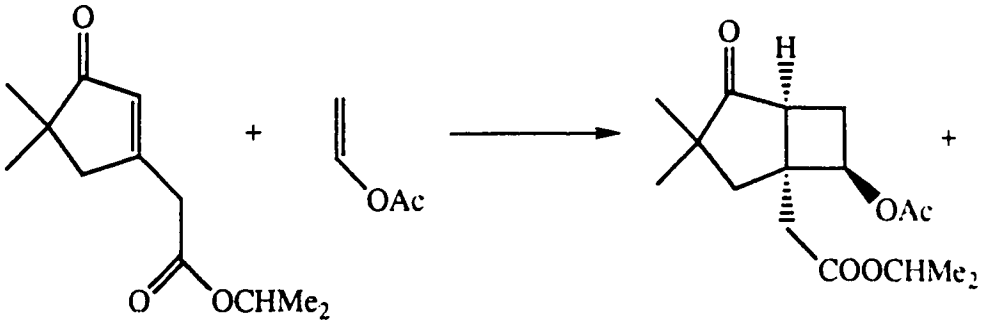
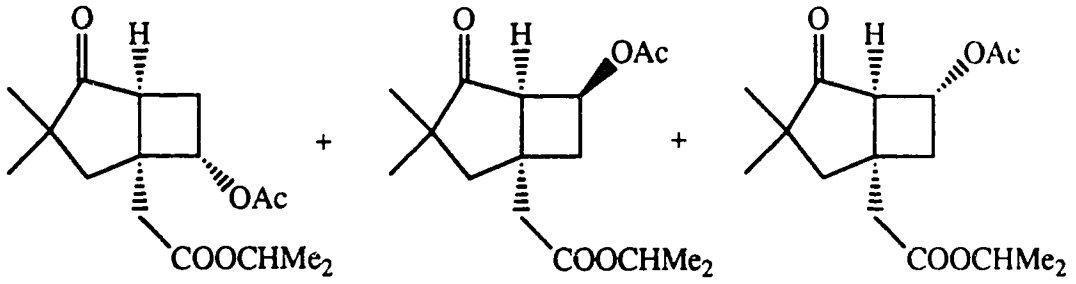


122

At this point, in spite of its unsatisfactory yield, gram quantities of enone ester **120** became available, so we decided to examine the feasibility of its intermolecular photocycloaddition reactions. Commercially available vinyl acetate was employed as the counterpart in the initial studies. Irradiation of a degassed solution of enone **120** and a large excess of vinyl acetate in benzene using a 450 W high pressure mercury lamp through a Pyrex filter at 0°C under an atmosphere of argon yielded an inseparable mixture of products. The expanded ^{1}H NMR spectrum showed the presence of at least four compounds displaying four acetyl singlets at δ 2.06–2.09. This observation could be accounted for by the formation of two diastereoisomers of both the head–to–tail (**123** and **124**) and the head–to–head (**125** and **126**) adducts.

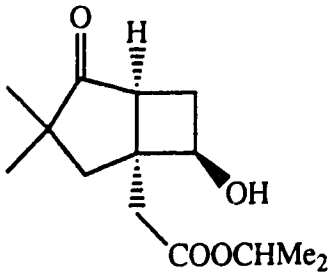


120 123



124 125 126

In order to remove the undesired regioisomers **125** and **126**, the mixture of the photoadducts was heated with DBU in refluxing benzene. This process, which was expected to facilitate selective elimination of acetic acid from **125** and **126**, had been successfully used previously in our laboratory in similar situations. In the present case, however, extensive decomposition of the desired head–to–tail adducts **123** and **124** also took place. An alternative method for separation of these photoadducts could be *via* hydrolysis. In principle, the alcohols **129** and **130** derived from the head–to–head photoadducts **125** and **126** could undergo retroaldol reaction, whereas those (**127** and **128**) from the head–to–tail isomers should remain intact.



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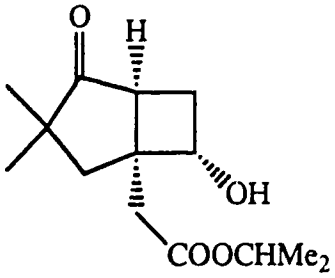

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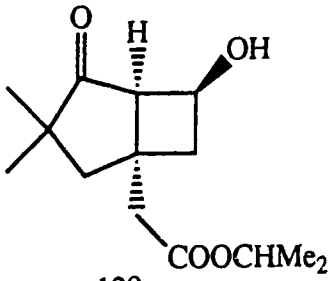

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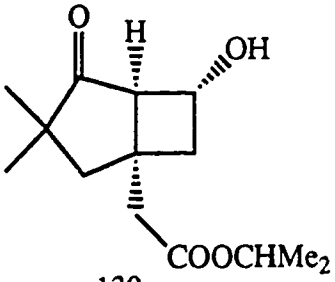


130

Thus, the crude mixture of photoadducts was treated with sodium isopropoxide in isopropanol at 25°C. A rather complex mixture was formed. However, the presence of hydroxy groups in the product mixture was confirmed both by the IR spectrum which showed an absorption band at 3500 cm^{-1} and by the ^1H NMR spectrum in which the broad singlet at δ 4.55 disappeared upon addition of D_2O. To gain further evidence for the formation of **127** and **128**, the mixture was subjected to Swern oxidation.[45] The bicyclic diketone **131** was isolated in an overall yield of 30% in three steps from the enone **120**. The IR spectrum of diketone **131** displayed a strong absorption band at 1786 cm^{-1}, characteristic for the four–membered ring ketone. It also exhibited a band at 1730 cm^{-1} for the five–membered ring ketone and the ester carbonyl groups. A molecular ion peak at m/e 252.1362 in its high resolution mass spectrum was in agreement with the molecular formula $C_{14}H_{20}O_4$. The complete assignment

for the ^{1}H and ^{13}C NMR spectra (Table I–7) was made on the basis of the results of the detailed NMR analysis, spin decoupling experiments (Table I–8) and NOE measurements (Figure I–1).

Several interesting coupling patterns were observed from the results of spin decoupling and NOE experiments. The H–4α proton was found to be coupled with the H–7β proton through five single bonds with the long–range coupling constant of 1 Hz. Assignments for the α and β protons at C–4 and C–7 were made on the basis of the NOE experiments. It was found that the coupling constant of the *cis* vicinal protons (J_{cis} = 11 Hz) was larger than that of the *trans* vicinal protons (J_{trans} = 5 Hz) in the four–membered ring system.

As far as the ring junction stereochemistry is concerned, the *trans* fused bicyclo[3.2.0]heptane ring system is sterically forbidden. The *cis* fusion was further confirmed by the NOE experiment in which a *cis* relationship for the H–1 and H–10 protons was established.

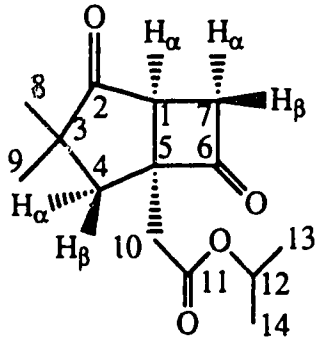
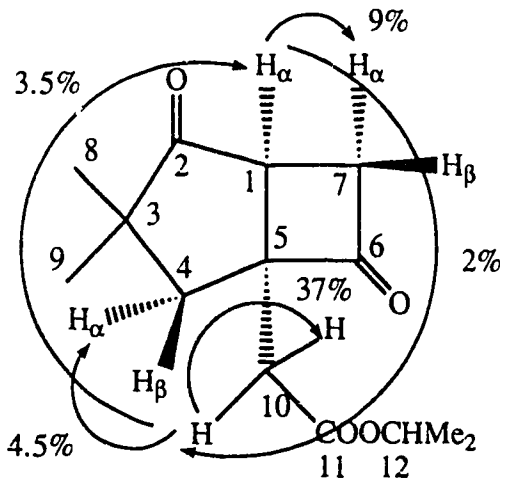


Table I–7. ^{13}C NMR and ^{1}H NMR Spectral Data for Keto Ester **131**

Carbon	δ (multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–2	221.00 (s)	H–12	5.00	septet (6)
C–6	208.90 (s)	H–7α	3.74	dd (18, 11)
C–11	169.86 (s)	H–1	3.20	dd (11, 5)
C–12	68.89 (d)	H–7β	3.04	ddd (18, 5, 1)
C–5	64.72 (s)	H–10a	2.94	d (17)
C–7	50.71 (t)	H–10b	2.63	d (17)
C–3	47.13 (s)	H–4β	2.22	d (14)
C–10	44.11 (t)	H–4α	1.81	br d (14)
C–1	42.32 (d)	H–13	1.24	d (6)
C–4	39.20 (t)	H–14	1.23	d (6)
C–8	26.20 (q)	H–8	1.16	s
C–9	26.07 (q)	H–9	1.14	s
C–13, C–14	21.80 (q)			



131

Figure I-1. NOE Data for Compound **131**

Table I-8. Spin Decoupling Data for Compound **131**

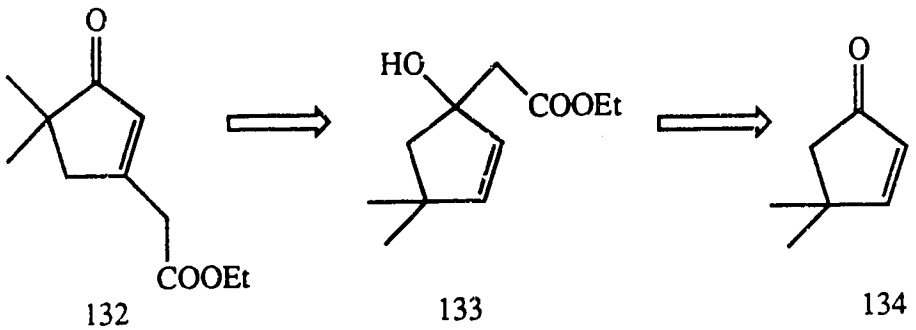
Signal Irradiated (δ)	Signal Changed (δ, *J* in Hz)
1.81, H–4α	3.04, H–7β (ddd → dd, 18, 5); 2.22, H–4β (d → s)
3.20, H–1	3.74, H–7α (dd → d, 18); 3.04, H–7β (dd → d, 18)

From the above preliminary results, it was realized that intermolecular photocycloaddition was a feasible process for the construction of the key bicyclio[3.2.0]heptane ring system. However, two problems remained to be solved in order to prepare the desired bicyclic intermediate with high efficiency. First, a more efficient route to enone esters **95** and **120** types of compounds had to be developed. Secondly, the intermolecular

photocycloaddition process should also be improved so that a high yield of head–to–tail adduct could be obtained.

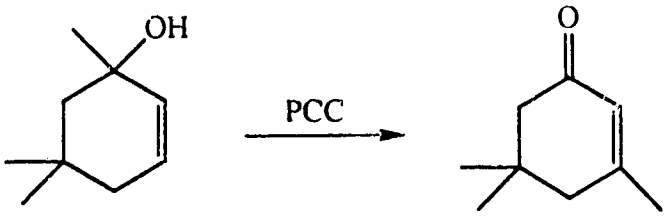
To improve the yield of the desired enone ester, an alternative route was proposed (Scheme I–20). Enone ester **132** was envisioned to be derived from oxidation of tertiary allylic alcohol **133** *via* 1,3–carbonyl transposition. Compound **133**, in principle, could be prepared by the aldol reaction of enone **134** with lithium enolate of ethyl acetate.

Scheme I–20



132 133 134

The 1,3–carbonyl transposition by means of oxidation of tertiary allylic alcohols with pyridinium chlorochromate (PCC)[46], pyridinium dichromate (PDC) [47] or Jones reagent[48] to afford transposed 3–alkyl α,β–unsaturated ketones was well documented. For example, direct oxidation of 1,5,5–trimethyl–2–cyclohexen–1–ol (**135**) with PCC in dichloromethane at room temperature afforded isophorone (**136**) in 96% yield.[46]

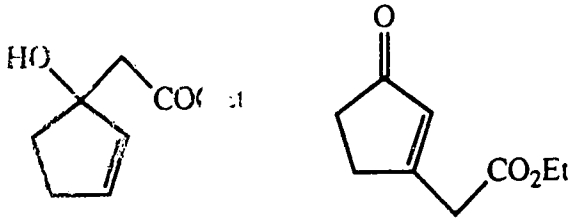


135 136

Due to the unavailability of enone **134**, model studies were carried out first using the commercially available 2–cyclopentenone as a substrate. Aldol reaction of 2–cyclopentenone with the lithium enolate of ethyl acetate at -78°C in tetrahydrofuran gave the desired β–hydroxy ester **137** in 76% yield. This alcohol dispiayed, in the IR spectrum, absorption bands at 3400 cm^{-1} for the hydroxy group and 1730 cm^{-1} for the ester carbonyl. A molecular ion peak was observed at m/e 170.0786, in accordance with the molecular formula $C_9H_{14}O_3$. In the ^1H NMR spectrum, signals at δ 5.91 and 5.79 (each as a doublet of triplets, J = 5.5 and 2 Hz) were assigned to the vinylic protons. The singlet at δ 3.61 was assigned to the hydroxy proton. Two methylene protons adjacent to the ester unit appeared at δ 2.66 and 2.62 as a pair of doublets with J_{gem} = 15 Hz.

Upon oxidation of the alcohol **137** with PCC at room temperature in CH_2Cl_2, the desired enone ester **138** was formed in 74% yield. The presence of the enone ester moiety in the molecule was indicated by the IR absorption bands at 1735 and 1713 cm^{-1} respectively for the ester and enone carbonyl groups. The mass spectrum exhibited a molecular ion peak at m/e 168.0787 suggesting the molecular formula of $C_9H_{12}O_3$. A multiplet at δ 6.12 in its ^1H NMR spectrum was assigned to the vinylic proton. A broad singlet at δ 3.74 was attributed to the methylene protons adjacent to the ester carbonyl group. In the ^{13}C NMR

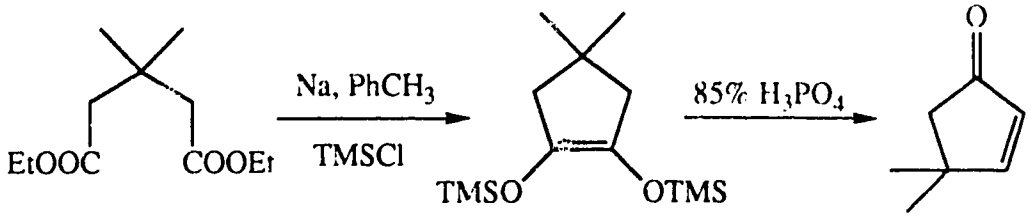
spectrum, ketone and ester carbonyl carbons appeared at δ 209.02 and 172.55 (each as a singlet). The vinylic carbons resonated at δ 168.59 (s) and 132.23 (d).



137 138

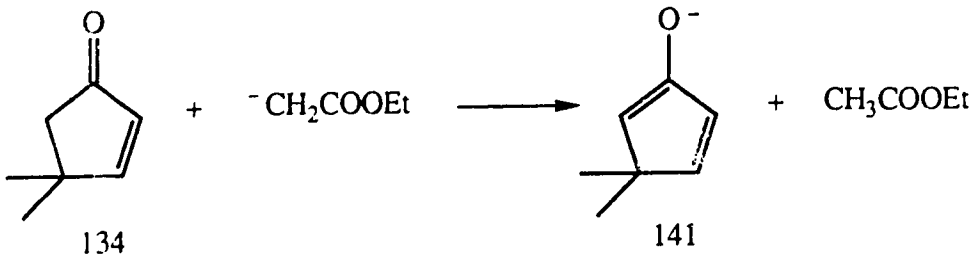
The encouraging results of the model studies promoted us to proceed with the preparation of the enone ester **132**. Of the several methods available for the synthesis of the required precursor 4,4–dimethyl–2–cyclopentenone (**134**), Holder's[49] procedure was selected for its simplicity. The preparation began with the commercially available 3,3–dimethylglutaric acid. Its esterification with ethanol in the presence of a catalytic amount of sulfuric acid yielded the diester **139** in nearly quantitative yield. Acyloin condensation of **139** induced by sodium in refluxing toluene followed by trapping of the resulting salt with chlorotrimethylsilane produced the crude cyclopentene product **140** in excellent yield. This compound was subsequently hydrolyzed and dehydrated with 85% phosphorous acid to furnish the desired enone **134** in 94% yield over two steps. Its IR spectrum displayed a strong absorption band at 1710 cm^{-1} for the enone carbonyl. The presence of the enone moiety was also verified by the ^{13}C NMR spectrum which displayed a singlet at δ 210.07 for the carbonyl carbon and two doublets at δ 173.91 and 131.11 for the vinylic carbons. The required formula of $C_7H_{10}O$ was determined by the high resolution mass spectrum displaying the molecular ion peak at m/e 110.0733. Additional evidence was provided by the

^{1}H NMR spectrum which showed a pair of mutually coupled doublets (J = 5.5 Hz each) at δ 7.46 and 6.00 for the vinylic protons.



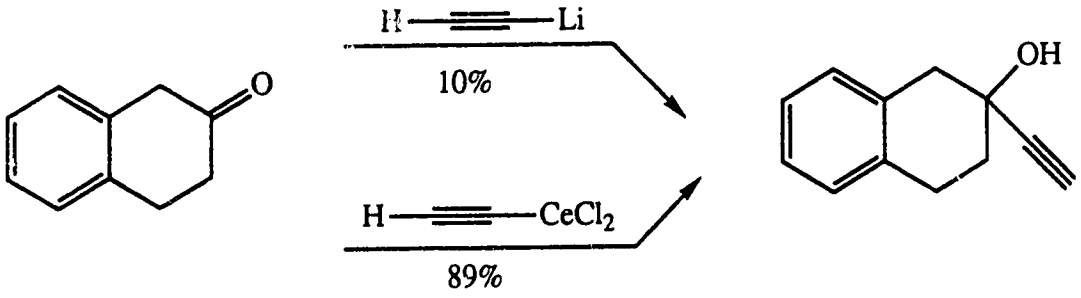
139 140 134

With the desired enone **134** in hand, the required 1,2–addition of the lithio ethyl acetate was examined. Initial attempts to make the β-hydroxy ester **133** by the classical aldol reaction between one equivalent of the lithium enolate derived from ethyl acetate and LDA, and the enone **134** in THF at -78°C provided quite disappointing results. Only a low yield (50%) of the hydroxy ester **133** was formed, accompanied by the unreacted enone **134** which was detected by the ^{1}H NMR analysis of the crude product. Attempts to improve the yield by employing two or three equivalents of lithium enolate were unsuccessful. In all the cases examined, the yield of hydroxy ester **133** remained approximately the same. These results could be explained by the competing acid–base reaction between enone **134** and the lithium enolate. In addition to the addition reaction with the enone **134**, the lithium enolate could also function as a base to deprotonate the ketone, forming the corresponding enolate **141**.



134 141

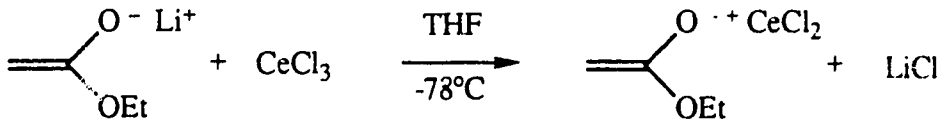
In order to improve the yields of β–hydroxy ester **133**, our efforts were then focused on exploring new ester enolate nucleophiles with low basicity, so that the addition would be more efficient. Of particular interest were those which could also add to enone exclusively in a 1,2–addition fashion, so that only the desired β–hydroxy ester would be formed. Of all the existing reagents documented, cerium mediated reagents seemed to be one of the best choices. It has been well demonstrated that cerium mediated reagents have low basicity and, at the same time, are stronger nucleophiles towards carbonyl compounds than the corresponding lithium reagents. Moreover, the cerium reagents have the advantage over the lithium reagents in that the former almost always give rise to the 1,2–addition products with conjugated enones.[50] An example is cited below.



During the recent years, much attention has been directed towards the development and synthetic applications of the cerium mediated reagents as a new class of nucleophiles. We also became interested in the cerium reagents,

especially those based on ester enolates. When this project was initiated, only one application dealing with the cerium ester enolate had been reported. Our detailed investigation on the synthetic applications of cerium ester enolate will be presented in next two chapters of this thesis.

The cerium ester enolate **142** was generated at -78°C over a 2 h period by direct transmetallation of the corresponding lithium enolate with anhydrous cerium chloride.

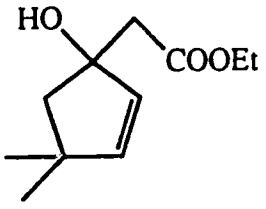


142

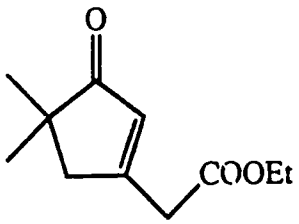
The enone **134** was then treated with the cerium ester enolate **142** at -78°C in tetrahydrofuran for 2 h. To our delight, the desired β-hydroxy ester **133** was isolated in excellent yield (98%). This product showed a hydroxy absorption at 3500 cm^{-1} and ester carbonyl band at 1733 cm^{-1} in the IR spectrum. A molecular ion peak at m/e 198.1249 was observed in the mass spectrum, corresponding to the molecular formula $C_{11}H_{18}O_3$. In the ^1H NMR spectrum, two vinylic protons appeared as a pair of doublets at δ 5.70 and 5.60 (J = 5.5 Hz each). The hydroxy proton was displayed at δ 3.63 as a singlet. The methylene protons next to the ester unit resonated at δ 2.68 and 2.64, each as a doublet with geminal coupling constant of 16 Hz. Similarly, the methylene protons attached to the ring were observed as a pair of doublets (J = 14 Hz each) at δ 1.92 and 1.81. The geminal dimethyl protons appeared at δ 1.19 and 1.09 as singlets. In the ^{13}C NMR spectrum, the ester carbonyl carbon

resonated at δ 172.81 as a singlet, while two doublets were observed at δ 144.97 and 131.70 for the vinylic carbons. The carbon bearing the hydroxy group resonated at δ 83.35 as a singlet.

The alcohol **133** was subsequently treated with PCC in dichloromethane at 25°C, giving the enone ester **132** in satisfactory yield (65%) after purification by column chromatography on silica gel. This enone ester displayed, in the IR spectrum, two carbonyl absorptions at 1739 and 1708 cm^{-1} respectively for the ester and enone groups. The formation of enone ester **132** was also supported by the ^{13}C NMR spectrum which displayed the enone and the ester carbonyl carbons respectively at δ 213.75 and 169.35 (each as a singlet). The vinylic carbons resonated at δ 168.82 as a singlet and 129.82 as a doublet for the β and α carbons of enone. Its molecular ion peak at m/e 196.1099 in the high resolution mass spectrum was consistent with the molecular formula $C_{11}H_{16}O_3$. A multiplet at δ 6.04 in the ^1H NMR spectrum was attributed to the vinylic proton. The methylene protons next to the ester unit resonated at δ 3.42 as a broad doublet (J = 1 Hz), whereas the methylene protons attached to the ring appeared at δ 2.56 as a multiplet.



133

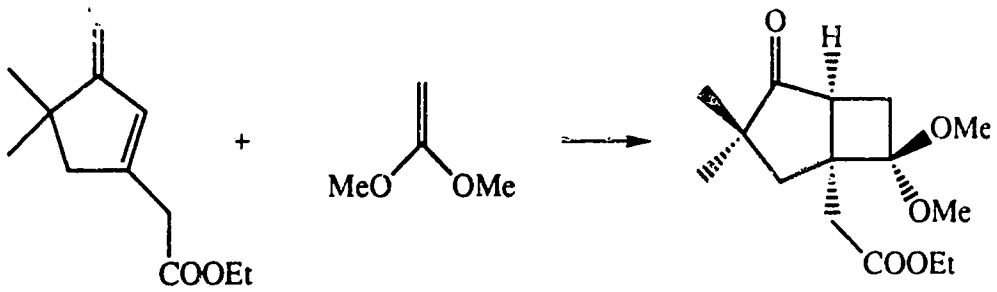


132

Having developed an efficient procedure for the preparation of the enone ester **132**, our immediate efforts were directed towards the improvement of the

photocycloaddition reaction. As described previously, the photocycloaddition of enone **120** and vinyl acetate proceeded with poor regioselectivity. The regioselectivity could conceivably be improved by replacing vinyl acetate with 1,1–dimethoxyethylene which had been demonstrated as a superior reagent for the formation of head–to–tail photoadducts with enones.[30]

1,1–Dimethoxyethylene (**143**) was readily prepared according to the procedure described by Corey *et al.*[28] Irradiation of a degassed solution of enone ester **132** and excess 1,1–dimethoxyethylene in pentane by means of 450 W high pressure mercury lamp through a Pyrex filter at 0°C under an atmosphere of argon for 3 h afforded the desired photocycloaddition product **144** in 81% yield after purification by flash column chromatography on silica gel.



132 143 144

Compound **144** showed an infrared absorption at 1733 cm^{-1} for the carbonyl groups. A molecular ion peak was observed at m/e 284.1622 in agreement with the molecular formula $C_{15}H_{24}O_5$. Elemental analysis also supported this chemical composition. The complete assignment for the ^1H NMR spectral data illustrated in Table I–9 was made on the basis of detailed analysis of the spectrum and NOE measurements (Table I–10). Several important assignments should be pointed out. The H–1 proton signal at δ 2.82 was split into a doublet

of doublets by the H–7α proton (J = 11 Hz) and the H–7β proton (J = 5 Hz). The assignments for the H–7 protons were made possible by the NOE experiments. Irradiation of the signals at δ 2.84 and 2.82 (signals for H–1 and H–12a protons) produced the enhancements of 6.5% and 25.4% respectively for the signals at δ 2.50 and 2.60 (H–12b). This indicated that H–1 was spatially close to H–7α and as a result the signal at δ 2.50 (dd, J = 13, 11 Hz) was assigned to H–7α. Accordingly, the signal at δ 2.10 (dd, J = 13, 5 Hz) was attributed to H–7β. The doublet at δ 1.84 (J = 14 Hz) was assigned to H–4α. This assignment was confirmed by the following observation. Upon irradiation of the doublet at δ 1.84, the signals at δ 2.84 (H–12a), 2.60 (H–12b) and 2.40 (H–4β) were enhanced by 3.2%, 5.9% and 34% respectively. These NOE results indicated that the doublet at δ 2.40 (J = 14 Hz) was due to the H–4β proton. The ^{13}C NMR spectrum was also found to be consistent with the structural assignment. Details are also outlined in Table I–9.

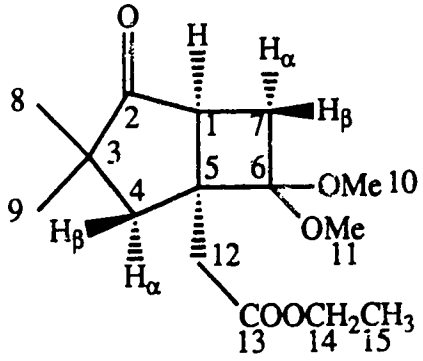


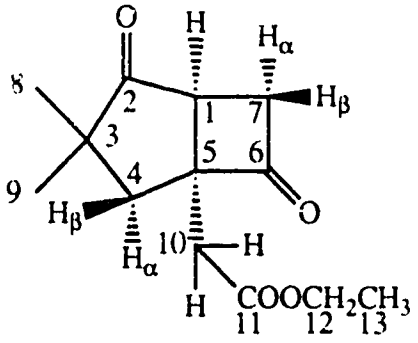
Table I–9. ^{13}C NMR and ^{1}H NMR Spectral Data for Compound **144**

Carbon	δ (Multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–2	223.06 (s)	H–14	4.12	m
C–13	172.00 (s)	H–10	3.18	s
C–6	102.00 (s)	H–11	3.14	s
C–14	60.39 (t)	H–12a	2.84	d (16)
C–5	50.79 (s)	H–1	2.82	dd (11, 5)
C–10	49.60 (q)	H–12b	2.60	d (16)
C–11	49.50 (q)	H–7α	2.50	dd (13, 11)
C–12	47.39 (t)	H–4β	2.40	d (14)
C–1	42.33 (d)	H–7β	2.10	dd (13, 5)
C–3	41.00 (s)	H–4α	1.84	d (14)
C–7	38.37 (t)	H–15	1.26	t (7)
C–4	32.83 (t)	H–8	1.20	s
C–8	27.67 (q)	H–9	1.08	s
C–9	25.89 (q)			
C–15	14.27 (q)			

Table I–10. ^{1}H Nuclear Overhauser Effect Data for Compound **144**

Irradiation (δ)	Response
H–4α (1.84)	H–4β (34%); H–12b (5.9 %) H–12a (3.2%)
H–1 and H–12a (2.84 and 2.82)	H–7α (6.5 %); H–12b (25.4%)

In order to ascertain its regiochemistry, the photoadduct **144** was transformed to the less polar diketone **145** in 86% yield by hydrolysis with 2N HCl in THF for one week at ambient temperature. The IR spectrum of diketone **145** displayed two distinct carbonyl absorptions, one at 1785 for the four–membered ketone and the other at 1733 cm^{-1} for the five–membered ketone and the ester groups. The high resolution mass spectrum revealed the molecular formula of $C_{13}H_{18}O_4$, displaying a molecular ion peak at m/e 238.1203. The ^{1}H and ^{13}C NMR assignments are summarized in Table I–11. In the ^{1}H NMR spectrum, the doublet of doublets at δ 3.74 was assigned to the H–7α proton which was coupled to H–7β (J = 18 Hz) and H–1 (J = 11 Hz). This assignment was further supported by the following NOE result. Irradiation of the doublet of doublets at δ 3.21 (H–1) resulted in the enhancements of 6.9% and 2.3% for the signals at δ 3.74 (H–7α) and 2.67 (H–10b) respectively. The signal at δ 3.04 (ddd) was assigned to the H–7β proton coupled to H–7α (J = 18 Hz), H–1 (J = 4.8 Hz) and H–4α (J = 1 Hz). The signals at δ 2.20 (d, J = 14 Hz) and 1.80 (br d, J = 14 Hz) were assigned to the H–4β and H–4α protons respectively.



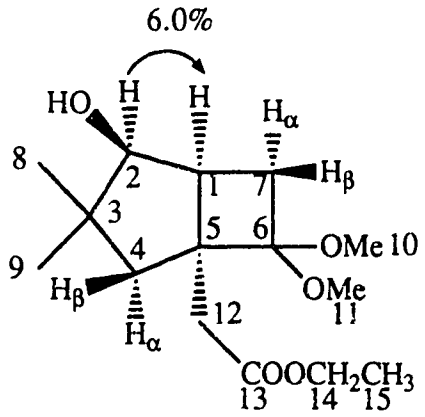
145

Table I–11. ^1H NMR and ^{13}C NMR Spectral Data for Diketone **145**

Carbon	δ (Multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–2	220.91 (s)	H–12	4.14	q (7)
C–6	208.86 (s)	H–7α	3.74	dd (18, 11)
C–11	170.38 (s)	H–1	3.21	dd (11, 4.8)
C–12	64.62 (t)	H–7β	3.04	ddd (18, 4.8, 1)
C–7	61.12 (t)	H–10a	2.97	d (17.6)
C–5	50.69 (s)	H–10b	2.67	d (17.6)
C–3	47.11 (s)	H–4β	2.22	d (14)
C–10	44.05 (t)	H–4α	1.82	br d (14)
C–1	42.29 (d)	H–13	1.26	t (7)
C–4	38.85 (t)	H–8	1.16	s
C–8	26.18 (q)	H–9	1.14	s
C–9	26.04 (q)			
C–13	14.13 (q)			

After an efficient approach was developed for the preparation of the projected key intermediate **144**, the synthetic studies proceeded as planned. The next major operation was to expand the four–membered ring to its homologue *via* the intermediary cyclobutanol. Prior to this operation, the existing ketone carbonyl was preferably protected. Thus, the keto ester **144** was subjected to reduction with excess $NaBH_4$, giving alcohol **146** as the only diastereoisomer in 98% yield after purification by column chromatography on silica gel. The hydroxy ester **146** displayed, in the FT–IR spectrum, a typical hydroxy absorption at 3490 cm^{-1} and an absorption at 1734 cm^{-1} for the ester carbonyl. The formation of alcohol **146** was evident from the absence of ketone carbonyl carbon resonance in the ^{13}C NMR spectrum. The carbon bearing the hydroxy group resonated at δ 81.20 as a doublet in the ^{13}C NMR spectrum. A molecular ion peak at m/e 286.1781 was in agreement with the molecular formula $C_{15}H_{26}O_5$ which was supported by the elemental analysis. The complete assignment of the ^{13}C and ^{1}H NMR spectral data (Table I–13) was made possible after a series of spin decoupling experiments illustrated in Table I–12 and an NOE experiment (Figure I–2). D_2O exchange showed that the hydroxy proton resonated at δ 2.54 which was eclipsed with other protons. The angular methine proton (H–1) resonated at δ 2.54 as a doublet of doublets of doublets (J = 9.5, 6.5 and 4.5 Hz). The assignments for the H–7α (δ 2.23, dd, J = 13.5, 9.5 Hz) and H–7β (δ 2.16, dd, J = 13.5, 4.5 Hz) protons were made on the basis of the coupling constants of vicinal protons in the four–membered ring system. The H–4α proton resonated δ 1.57 as a doublet of doublets (J = 14 and 1 Hz), coupled to the H–2 proton probably through the W configuration with a

coupling constant of 1 Hz. This assignment was confirmed by the spin decoupling experiment.



146

Figure I–2. NOE Data for Alcohol **146**

Table I–12. Spin Decoupling Data for Hydroxy Ester **146**

Signal Irradiated (δ)	Signal Changed (δ *J* in Hz)
3.61 (d), H–2	2.54 (ddd→dd, 9.5, 4.5); 1.57 (dd→d, 14)
2.64 [illegible]	2.55 (d→s)
2.23 (dd), H–7α	2.54 and 2.16
2.16 (dd), H–7β	2.54 and 2.23
1.57 (dd), H–4α	2.05 (d→s)

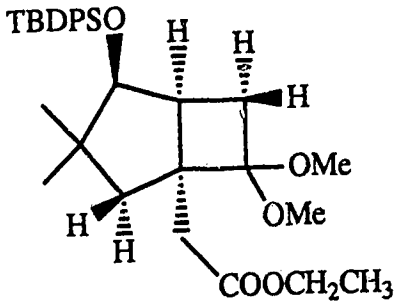
Table I–13. ^{13}C NMR and ^{1}H NMR Data for Alcohol **146**

Carbon	δ (Multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–13	172.73 (s)	H–14	4.10	m
C–6	103.69 (s)	H–2 (α)	3.61	br d (6)
C–2	81.20 (d)	H–10	3.22	s
C–14	60.12 (t)	H–11	3.14	s
C–5	56.16 (s)	H–12a	2.64	d (16)
C–10	50.54 (q)	H–12b	2.55	d (16)
C–11	49.74 (q)	OH	2.54	s
C–12	46.83 (t)	H–1	2.54	ddd (9.5, 6.5, 4.5)
C–1	41.24 (d)	H–7α	2.23	dd (13.5, 9.5)
C–3	41.24 (s)	H–7β	2.16	dd (13.5, 4.5)
C–7	41.00 (t)	H–4β	2.05	d (14)
C–8	28.51 (q)	H–4α	1.57	dd (14, 1)
C–4	27.85 (t)	H–15	1.25	t (7)
C–9	23.90 (q)	H–8	1.10	s
C–15	14.41 (q)	H–9	0.92	s

As far as the stereochemistry at the C–2 position was concerned, the H–2 proton was found to have a *cis* relationship with the H–1 proton. This stereochemical outcome was determined by the NOE difference experiment (Figure I–2).

Irradiation of the doublet at δ 3.61 (H–2) resulted in a 6.0% enhancement of the signal at δ 2.54 (ddd, H–1). This stereochemical result could be explained by the fact that the hydride attacks the carbonyl group only from the sterically less hindered side (*i.e.* from the convex side of the *cis* fused bicyclic system) to yield the hydroxy ester **146** as the only isolated diastereoisomer.

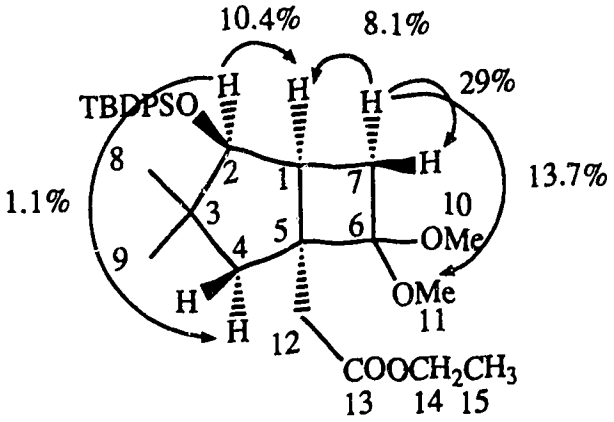
At this stage, it was set for the protection of the hydroxy group. Unfortunately, all attempts to protect the hydroxy group as its acetyl ester, benzyl ether or silyl ether by conventional methods failed. In all cases, only unreacted starting alcohol **146** was recovered quantitatively. Eventually, the alcohol **146** was protected as its *t*–butyldiphenylsilyl ether **147** in 89% yield by treatment with *n*–BuLi in THF–HMPA followed by silylation with *t*–$BuPh_2SiCl$[51] at 0°C.



147

The disappearance of the hydroxy group in the molecule was evident from the absence of its absorption in IR spectrum. The infrared absorption of **147** at 1731 cm^{-1} was attributed to the ester carbonyl group. The formation of the *tert*–butyldiphenylsiloxyl group was revealed by both the ^1H and ^{13}C NMR spectral data (Table I–14). In the ^1H NMR spectrum, ten aromatic protons were observed at δ 7.60–7.70 (4 H) and 7.30–7.40 (6 H). In the ^{13}C NMR spectrum, the aromatic carbons were observed at δ 136.11 (d), 136.01 (d),

134.68 (s), 134.37 (s), 129.57 (d), 127.46 (d) and 127.42 (d). For the *tert*–butyl group, the 3° carbon resonated at δ 19.59 as a singlet, whereas the other three methyl carbons were observed at δ 27.22 as a quartet. The C–2 carbon resonated at δ 81.86 as a doublet. The assignment of ^{1}H NMR spectral data was supported by the spin decoupling experiment (Table I–15) and NOE difference spectra (Figure I–3). Several important assignments should be pointed out. The assignment for the H–7α and H–7β protons was made on the basis of the NOE experiment. The coupling constants for H–1 and H–7α (J = 10 Hz), H–1 and H–7β (J = 7 Hz) also supported this assignment. The signal of the H–1 proton was deduced from the NOE difference spectrum. This proton appeared at δ 2.15 as a doublet of doublets of doublets which was eclipsed with the H–4β proton (d, J = 15 Hz). In the high resolution mass spectrum, the molecular ion peak was not observed, nor did the high resolution FAB and CI display the molecular ion peak. The elemental analysis supported the chemical composition of $C_{31}H_{44}O_5Si$.



147

Figure I–3. NOE Data for Compound **147**

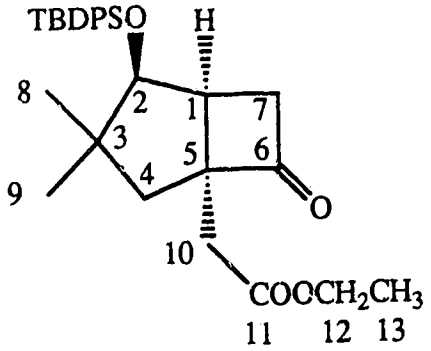
Table I–14. Partial ^{13}C and ^{1}H NMR Spectral Data for **147**

Carbon	δ (Multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–13	172.65 (s)	H–2	4.06	d (7)
C–6	101.38 (s)	H–14	3.91	m
C–2	81.86 (d)	H–10	3.11	s
C–14	59.93 (t)	H–11	3.10	s
C–5	52.99 (s)	H–12a	2.59	d (15)
C–10	49.28 (q)	H–12b	2.34	d (15)
C–11	48.61 (q)	H–7β	2.30	dd (13, 7)
C–12	44.91 (t)	H–1	2.15	ddd (10, 7, 7)
C–7	44.43 (t)	H–4β	2.14	d (15)
C–1	42.09 (d)	H–7α	1.89	dd (13, 10)
C–3	40.05 (s)	H–4α	1.50	d (15)
C–8	31.65 (q)	H–8	1.18	s
C–4	28.93 (t)	H–15	1.09	t (7)
$C(CH_3)_3$	27.22 (q)	$C(CH_3)_3$	1.08	s
C–9	25.20 (q)	H–9	0.82	s
$C(CH_3)_3$	19.59 (s)			
C–15	14.25 (q)			

Table I-15. Spin Decoupling Data for Compound **147**

Signal Irradiated (δ)	Signal Changed (*J* in Hz)
4.06, H–2 (d)	2.15, H–1 (ddd → dd, 10, 7)
2.59, H–12a (d)	2.34, H–12b (d → s)
2.15, H–1 (ddd)	4.06, H–1 (d → s); 2.30, H–7β (dd → d, 13); 1.89, H–7α (dd → d, 13)
1.89, H–7α (dd)	2.30, H–7β (dd → d, 7); 2.15, H–1 (ddd → dd, 7, 6); 1.50, H–4α (br d → s)
1.50, H–4α (br d)	2.14, H–4β (d → s)

Upon exposure to acetic acid, tetrahydrofuran and water (3:1:1) at 40°C, the dimethyl ketal **147** was readily converted into the required key intermediate **148** in nearly quantitative yield. The absence of the dimethyl ketal group was evident from both the ^{1}H and ^{13}C NMR spectra which exhibited no methoxy signals. The IR spectrum of the ketone **148** showed an absorption at 1780 cm^{-1}, indicating the presence of the four–membered ring ketone in the molecule. The existence of the ketone unit in the molecule was also confirmed by the ^{13}C NMR spectrum. A singlet at δ 214.74 was assigned to the ketone carbonyl carbon, while the other singlet at δ 170.62 was attributed to the ester carbonyl carbon. The high resolution mass spectrum of **148** showed the molecular ion peak at m/e 478.2539, consistent with the molecular formula $C_{29}H_{38}O_4Si$. The chemical composition of this formula was further supported by the elemental analysis.



148

The partial spectral data of the ^{13}C and ^{1}H NMR for the ketone **148** are tabulated in Table I–16. These assignments were also proven by the NOE difference spectra (Figure I–4). Several important assignments for the ^{1}H NMR spectrum should be pointed out. The assignments for H–7α and H–7β were made on the basis of the coupling constants of H–1 and H–7α (J = 10 Hz), H–1 and H–7β (J = 4.2 Hz) as well as the NOE difference spectra. Irradiation of the H–7α proton at δ 2.90 produced a 14.4% enhancement of H–1 proton signal at δ 2.46. Assignments for H–4α and H–4β were also established by the NOE difference spectra. Upon irradiation of the signal for the H–2 proton (δ 4.12), the signal at δ 1.30 (the H–4α proton) was enhanced by a 6.14 %. In addition, upon irradiation of the signal at δ 2.30 (H–10a), the signal at δ 1.30 was also increased by a 4.5%. These results indicated that the signal at δ 1.30 was at the α position. Accordingly, this doublet signal (δ 1.30) was attributed to the H–4α proton. The H–2 proton appeared at δ 4.12 as a doublet coupled with H–1 ($J_{1,2}$ = 8 Hz) which, in turn, resonated at δ 2.46 (ddd, J = 10, 8, 4.2 Hz). The methylene protons adjacent to the ester unit resonated at δ 2.60 and 2.30 as a pair of AB doublets (J = 17 Hz).

Table I–16. Partial ^{13}C NMR and ^{1}H NMR Spectral Data for Ketone **148**

Carbon	δ (Multiplicity)	Proton	δ	Multiplicity (*J* in Hz)
C–6	214.74 (s)	H–2	4.12	d (8)
C–11	170.62 (s)	H–12	4.01	m
C–2	81.34 (d)	H–7β	3.30	dd (18.5, 4.2)
C–12	66.94 (t)	H–7α	2.90	dd (18.5, 10)
C–5	60.61 (s)	H–10a	2.60	d (17)
C–7	47.02 (t)	H–1	2.46	ddd (10, 8, 4.2)
C–10	46.34 (t)	H–10b	2.30	d (17)
C–3	43.15 (s)	H–4β	1.92	d (14)
C–1	40.13 (d)	H–4α	1.30	d (14)
C–4	38.73 (t)	H–13	1.15	t (7)
C–8	30.13 (q)	$C(CH_3)_3$	1.10	s
$C(CH_3)_3$	27.20 (q)	H–8	1.06	s
C–9	23.61 (q)	H–9	0.88	s
$C(CH_3)_3$	19.55 (s)			

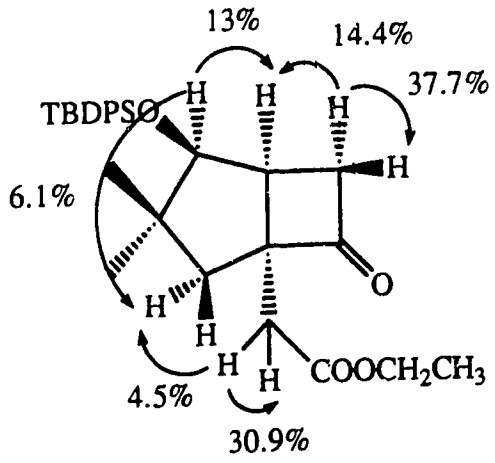
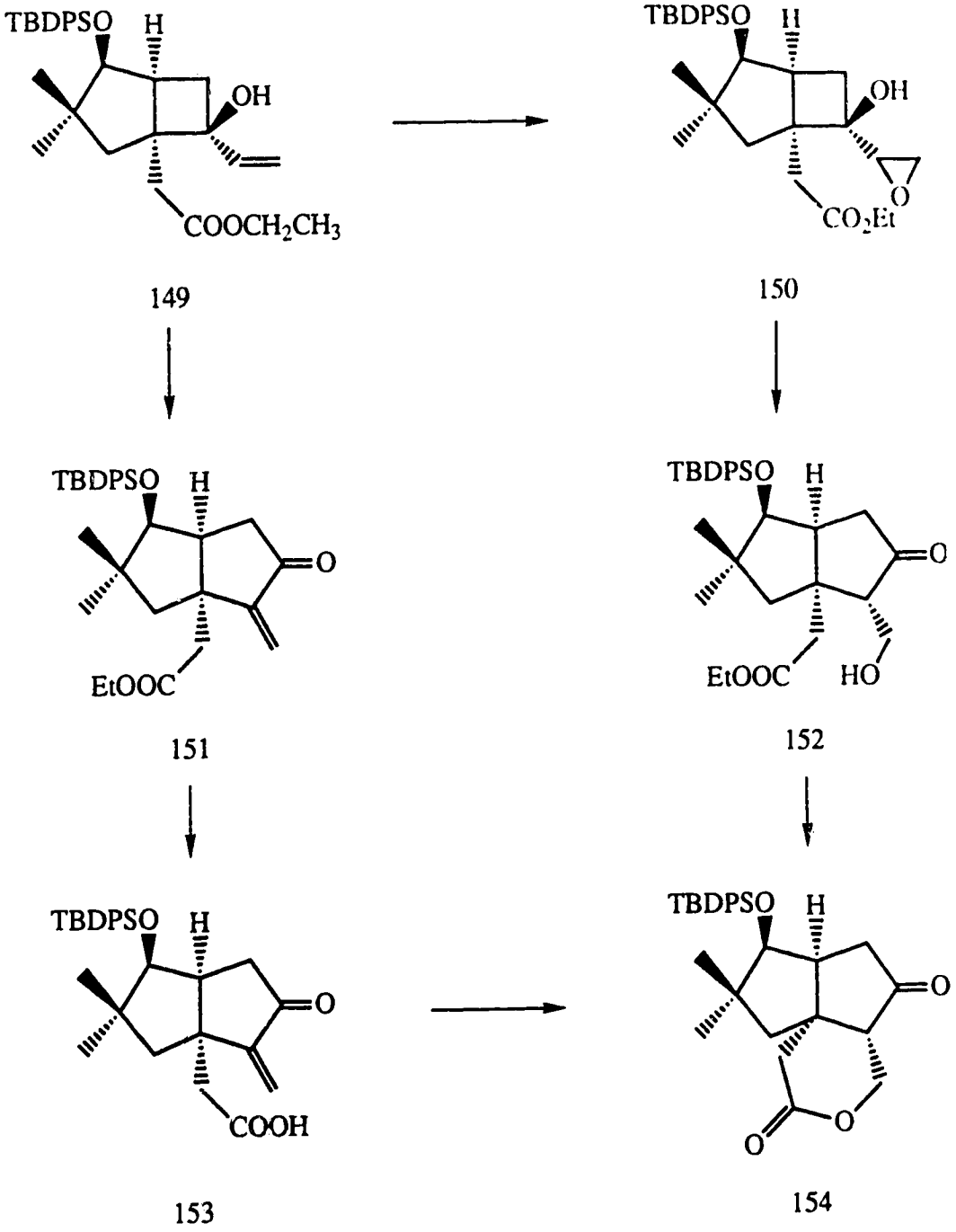
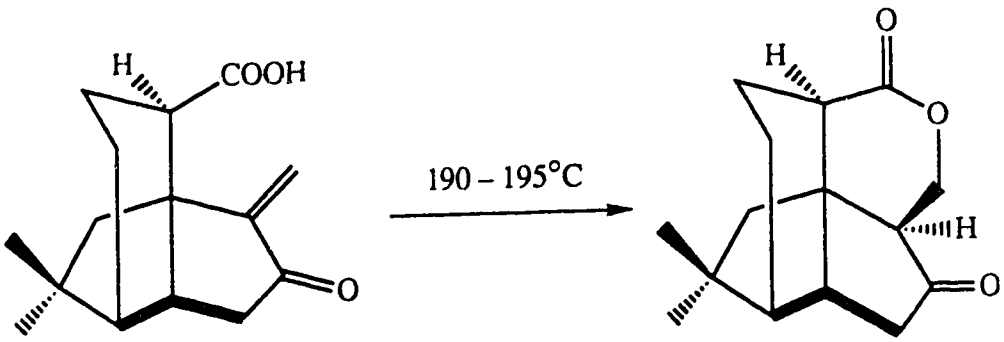


Figure I–4. NOE Data for Compound **148**

From the retrosynthetic analysis, the remaining key operation in this synthetic study is to regioselectively expand the four–membered ring ketone **148** to the functionalized ketones **151** or **152** through the intermediates **149** or **150**, both of which could be prepared by addition of a vinyl nucleophile to the four–membered ketone. Epoxidation of the allylic alcohol **149** with *m*–CPBA or *via* the Sharpless[52] method should give rise to the epoxide **150**. The examination of the ring expansion is progressing favorably. We expect that intramolecular lactonization of hydroxy ester **152** to tricyclic δ–lactone **154** should proceed without any difficulties. On the other hand, lactonization of enone **151** would require that the ester **151** be transformed to the acid **153**. Upon heating the compound **153**, the intramolecular lactonization should take place and result in the formation of δ–lactone **154** (Scheme I–21). In the total synthesis of quadrone **156**,[53] a similar lactonization reaction of acid **155** was utilized as one of the key steps.

Scheme I-21


TBDPSO
H
OH
COOCH2CH3
149
TBDPSO
H
OH
O
CO2Et
150
TBDPSO
H
O
EtOOC
151
TBDPSO
H
O
EtOOC
HO
152
TBDPSO
H
O
COOH
153
TBDPSO
H
O
O
O
154



155 156

If the preparation of the key intermediate δ–lactone **154** could be achieved, total synthesis for pentalenolactones E, F, G, and H and pentalenolactone itself could be accomplished by following the similar procedures. For example, in the case of pentalenolactones E and F, it would be necessary to remove the siloxyl group by deoxygenation reaction. With respect to the synthesis of pentalenolactones G and H, conversion of the siloxyl group to the ketone unit would be required.

EXPERIMENTAL

General

All melting points were determined on a Köfler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared spectra (IR) were recorded on a Perkin–Elmer model 457 or Nicolet 7–119 FT–IR spectrophotometer and were normally obtained in chloroform cast unless otherwise stated. High resolution mass spectra (HRMS) were obtained using Kratos AEI MS–50 high resolution mass spectrometer. Chemical ionization mass spectra (CIMS) were obtained using an AEI MS–12 mass spectrometer, using ammonia as the reagent gas. Data were reported as m/e values. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker WH–300 (300 MHz) and WH–400 (400 MHz) spectrometers and were obtained from solutions in deuteriochloroform using tetramethylsilane as an internal reference. Chemical shift measurements were reported in ppm downfield from TMS in delta (δ) units. The coupling constants (*J* in Hz) were reported to within ±0.5 Hz. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Carbon–13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker WH–300 (75 MHz). Carbon–13 multiplicities were derived from off–resonance or Carr–Purcel–Meiboom–Gill spin echo J–modulated experiments (APT or Attached Proton Test).[54] Methyl and methine groups are shown as signals possessing an antiphase (doublet, quartet) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbon atoms and carbonyl groups appear in phase (singlet, triplet)

with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer–subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements were defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with helium gas for 5 minutes prior to use.

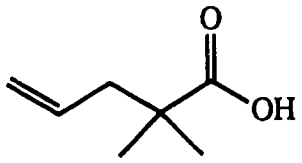
All reactions were carried out under a positive pressure of argon gas. Argon was passed through a column of 4A molecular sieves and self indicating silica gel. Reactions requiring anhydrous conditions were performed in oven–dried glassware which was then assembled and allowed to cool while being purged with an inert gas. All reactions were monitored by analytical thin–layer chromatography (TLC). Analytical TLC was carried out on aluminium sheets precoated (0.20 mm layer thickness) with Merck Kiesel silica gel 60F–254 containing a fluorescent indicator. For TLC, the visualization of the chromatograms was completed either by iodine or by dipping in an ethanol solution of vanillin (5%, w/v) in sulfuric acid (50%, v/v) followed by hot plate charring. Alternatively, an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%, w/v) in sulfuric acid (3%, v/v) was used, followed by careful charring on a hot plate. Ultraviolet active materials were detected by visualization under a UV lamp (254 or 350 nm). All evaporations were carried out under reduced pressure on a rotary evaporator. Flash column chromatography developed by Still[55] was used routinely for purification and separation of product mixtures using silica gel of 230–400 mesh. The concentrations of the solvent systems used in column chromatography were given by volumes, *e.g.*, 20% ethyl acetate in hexane means 20 parts ethyl acetate

by volume to 80 parts hexane by volume. Almost all isolated products were determined to be pure by the elemental analysis. The purity of all other isolated products was judged to be at least >95% by the ^{1}H NMR spectroscopy.

Materials

The anhydrous solvents used for reactions were purified by distillation under an argon atmosphere. Tetrahydrofuran (THF), diethyl ether and 1,2-dimethoxyethane (DME) were freshly distilled from a blue solution of sodium benzophenone ketyl. Methanol and ethanol were distilled from magnesium turnings. Diisopropylamine, benzene and toluene were obtained by distillation from sodium. Hexamethylphosphoramide (HMPA) was also distilled from sodium under reduced pressure. Dimethyl sulfoxide (DMSO), pyridine, dichloromethane, acetonitrile, triethylamine and chlorotrimethylsilane were distilled from calcium hydride. Hexane and ethyl acetate were purified by simple distillation for use in chromatographic purifications.

2,2-Dimethyl-4-pentenoic acid (106).



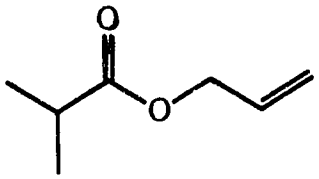
(a) From isobutyric acid

To a stirred solution of diisopropylamine (15 mL, 10.83 g, 107 mmol) in tetrahydrofuran (50 mL) was added *n*–butyllithium (130 mL, 0.9 M in hexane, 117 mmol) at 0°C and the resulting solution was allowed to stir for 15 min at the same temperature. To this solution of lithium diisopropylamide, was added a solution of isobutyric acid (4.50 g, 50.80 mmol) in tetrahydrofuran (20 mL) dropwise. The resulting solution was stirred at 0°C for 30 min, then warmed up to 25°C and further stirred for 1 h to ensure the complete formation of the enolate. Allyl bromide (9.10 g, 75.40 mmol) in tetrahydrofuran (15 mL) was added at 0°C over 10 min. After the mixture was stirred for 5 h at 0°C and 5 h at 25°C, it was acidified with 1N HCl (150 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water, brine and dried over $MgSO_4$. The solvents were then removed by distillation through a vigreux column, leaving a colorless oil. Fractional distillation *via* a 25 cm vigreux column gave 2,2–dimethyl–4–pentenoic acid (**106**)[34] (4.10 g, 63%) as a colorless liquid: bp 60°C (0.5 mmHg); ^1H NMR (300 MHz, $CDCl_3$) δ 11.8 (br s, 1 H, COOH), 5.78 (m, 1 H, C**H**=CH_2), 5.11 (m, 1 H, CH**H**=), 5.06 (m, 1 H, CH**H**=), 2.30 (dt, J = 7, 1 Hz, 2 H, CH_2CH=), 1.20 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.53 (s, C=O), 133.94 (d, CH=), 118.25 (t, CH_2=), 44.46 (s, CC=O), 42.21 (t, CH_2C=), 24.60 (q, 2 × CH_3); FT–IR ($CHCl_3$) 3200 (COOH), 1702 (C=O) cm^{-1}; HRMS M^+ 128.0840 (calcd for $C_7H_{12}O_2$ 128.0837); Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.46; H, 9.53.

(b) From allyl isobutyrate

A mixture of sodium hydride (22.50 g, 0.75 mol, 80% dispersion in mineral oil) and dry toluene (100 mL) was heated to 110°C, and then allyl isobutyrate (**107**) (96 g, 0.75 mol) was added dropwise over a 2 h period. Heating was continued for 1 h at 110°C. The reaction mixture became quite thick and difficult to stir as the reaction proceeded. The mixture was then cooled and methanol (110 mL) was added slowly to decompose any unused sodium hydride. The reaction mixture was acidified with 1N HCl (30 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water and saturated sodium chloride and dried over $MgSO_4$. Fractional distillation *via* a 30 cm vigreux column afforded 2,2–dimethyl–4–pentenoic acid (**106**)[35] (65 g, 68%): bp 104–106°C (20 mmHg); Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.46; H, 9.53.

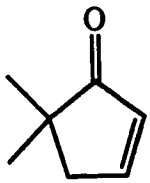
Allyl isobutyrate (107).



A solution of isobutyric acid (17.10 g, 0.19 mol) and thionyl chloride (21 mL, 34.40 g, 0.29 mol) was refluxed at 100°C for 2 h and then the excess thionyl chloride was distilled off through a vigreux column. To this acid chloride solution in dichloromethane (10 mL), was added a solution of allylic alcohol (20 mL, 17.08 g, 0.29 mol) and pyridine (16 mL, 15.65 g, 0.20 mol) at 0°C

dropwise. The resulting mixture was stirred for 12 h at 25°C and then quenched with water (10 mL) and extracted with dichloromethane (3 × 20 mL). The organic extracts were washed with water, brine and dried over $MgSO_4$. Fractional distillation of the oil residue *via* a 25 cm vigreux column gave allyl isobutyrate (**107**) (23.00 g, 95%) as a colorless liquid: bp 80–82°C (50 mmHg); ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddt, J = 17, 10, 5.5 Hz, 1 H, $CH{=}CH_2$), 5.32 (ddt, J = 17, 1.5, 1.5 Hz, 1 H, *trans* CHH=CH), 5.22 (ddt, J = 10, 1.5, 1.5 Hz, 1 H, *cis* CHH=CH), 4.58 (dt, J = 5.5, 1.5 Hz, 2 H, OCH_2), 2.59 (septet, J = 7 Hz, 1 H, Me_2CH), 1.20 (d, J = 7 Hz, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.75 (s, C=O), 132.45 (d, CH=), 117.82 (t, CH_2=), 64.87 (t, OCH_2), 34.00 (d, $CHMe_2$), 18.98 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1738 (C=O) cm^{-1}; HRMS M^+ 128.0836 (calcd for $C_7H_{12}O_2$ 128.0837); Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.41; H, 9.39.

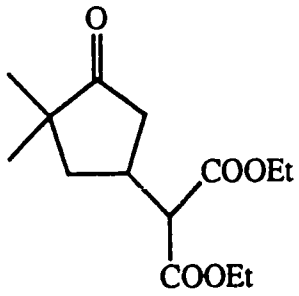
5,5–Dimethyl–2–cyclopentenone (105).



A mixture of 2,2–dimethyl–4–pentenoic acid (**106**) (2.00 g, 15.60 mmol) and thionyl chloride (3 mL, 3.70 g, 31 mmol) was heated at 100°C for 1 h and then excess thionyl chloride was removed *in vacuo*. The crude acyl chloride in 10 mL of CS_2 was added dropwise to 2.2 g of $AlCl_3$ in 10 mL of CS_2. The reaction mixture was stirred at reflux for 2.5 h, then carefully poured onto ice

and extracted with ether. The organic extracts were washed with saturated $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvents were distilled off under normal pressure through a 20 cm vigreux column. Fractional distillation (90–92°C, 60 mmHg) of the residue *via* a 20 cm vigreux column gave 5,5–dimethyl–2–cyclopentenone (**105**)[33] (1.00 g, 59%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (dt, J = 5.8, 2.5 Hz, 1 H, CH=), 6.14 (dt, J = 5.8, 2 Hz, 1 H, CH=), 2.58 (t, J = 2.5 Hz, 2 H, CH_2), 1.12 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.79 (s, C=O), 161.76 (d, CH=), 131.85 (d, CH=), 45.59 (s, CC=O), 42.63 (t, CH_2), 24.87 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1708 (C=O), 1589 cm^{-1}; HRMS M^+ 110.0731 (calcd for $C_7H_{10}O$ 110.0731).

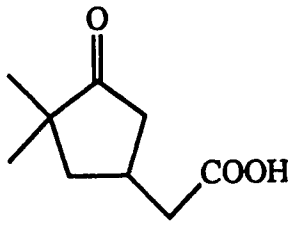
Diethyl (3,3–dimethyl–4–oxocyclopentyl)malonate (104).



To a solution of of sodium ethoxide (2.70 mmol, prepared from 62 mg of sodium in 10 mL of ethanol) and diethyl malonate (440 mg, 2.75 mmol) in 10 mL of ethanol, was added a solution of enone **105** (266 mg, 2.41 mmol) in 2 mL of ethanol. The resulting mixture was stirred for 2.5 h at room temperature and after this time TLC indicated that no more starting material was present in the mixture. The reaction mixture was then cooled to 0°C,

quenched with 5 mL of 1N HCl and extracted with ether (3 × 20 mL). The organic extracts were washed with water and brine and dried over $MgSO_4$. The solvent and low boiling materials were removed *in vacuo*. Bulb–to–bulb distillation (80°C, 0.2 mmHg) afforded keto ester **104** (520 mg, 82%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (m, 4 H, 2 × CH_2O), 3.27 (d, J = 9.5 Hz, 1 H, $CH(CO_2Et)_2$), 2.88 (m, 1 H, $CHCH_2$), 2.64 (ddd, J = 18.5, 7.5, 2 Hz, 1 H, O=CCHH), 2.06 (dd, J = 18.5, 11 Hz, 1 H, O=CCHH), 2.05 (ddd, J = 12.5, 6.5, 2 Hz, 1 H, CHHCH), 1.54 (dd, J = 12.5, 12 Hz, 1 H, CHHCH), 1.29 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.10 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.72 (s, C=O, ketone), 168.13 (s, C=O, ester), 61.62 (t, OCH_2), 57.05 (d, $CH(CO_2Et)_2$), 46.02 (t, CH_2), 42.99 (s), 41.95 (t, CH_2), 32.41 (d, $CHCH_2$), 24.13 (q, CH_3), 23.99 (q, CH_3), 14.12 (q, 2 × OCH_2CH_3); FT–IR ($CHCl_3$) 1734 (C=O) cm^{-1}; HRMS M^+ 270.1469 (calcd for $C_{14}H_{22}O_5$ 270.1468); Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15. Found: C, 62.30; H, 8.23.

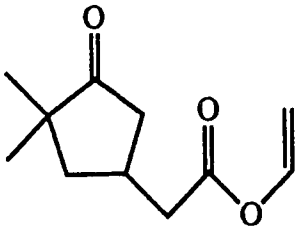
4–Carboxymethyl–2,2–dimethylcyclopentanone (103).



A solution of keto ester **104** (270 mg, 1.00 mmol) in 5 mL of 3N HCl and 5 mL of ethanol was refluxed for 20 h to ensure that the ester hydrolysis and decarboxylation reactions were complete. The reaction mixture was then

cooled to room temperature and extracted with chloroform. The organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a colorless oil which was subjected to bulb–to–bulb distillation (85°C, 0.2 mmHg) to give keto acid **103** (160 mg, 94%) as a white solid: mp 62–64°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (m, 2 H, O=CC**H**HC**H**), 2.52 (m, 2 H, CH_2CO_2H), 2.10 (ddd, J = 12.5, 6.5, 2.5 Hz, 1 H, C**H**HCH), 1.96 (dd, J = 20, 13 Hz, 1 H, O=CCH**H**), 1.46 (dd, J = 12.5, 11 Hz, 1 H, CH**H**CH), 1.10 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.70 (s, C=O, ketone), 177.98 (s, C=O, ester), 46.31 (s, C–2), 44.91 (t, C–5), 43.59 (t, CH_2COOH), 39.86 (t, C–3), 29.14 (d, CH), 24.19 (q, 2 × CH_3); FT–IR ($CHCl_3$) 3202 (OH), 1740 and 1709 (C=O) cm^{-1}; HRMS M^+ 170.0944 (calcd for $C_9H_{14}O_3$ 170.0943); Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.51; H, 8.34.

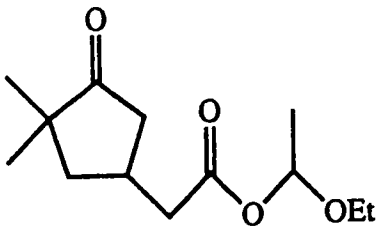
Vinyl (3,3–dimethyl–4–oxocyclopentyl)acetate (102).



Keto acid **103** (1.01g, 6.0 mmol) was dissolved in vinyl acetate (3.4 mL, 3.17g, 37 mmol). Mercuric acetate (20 mg, 0.063 mmol) was added to the solution and the mixture was stirred for 20 min at room temperature. Sulfuric acid (20 μL, 5 mg) was added and the reaction mixture was stirred for 60 h at room temperature. After this period of stirring, the TLC indicated the absence of the

keto acid. The reaction mixture was then quenched with 5 mL of saturated $NaHCO_3$ and extracted with dichloromethane (3 × 20 mL). The organic extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and then the residue was chromatographed by flash column (silica gel, 10% ethyl acetate in hexane) to provide vinyl ester **102** (1.10 g, 94%) as a colorless oil: ^1H NMR (300 MHz, $CHCl_3$) δ 7.28 (dd, J = 14, 6 Hz, 1 H, OCH=), 4.91 (dd, J = 14, 1.5 Hz, 1 H, *trans* CHH=), 4.59 (dd, J = 6, 1.5 Hz, 1 H, *cis* CHH=), 2.64 (m, 2 H, O=CCHHCH), 2.53 (m, 2 H, CH_2CO_2), 2.10 (ddd, J = 13, 6, 2.5 Hz, 1 H, CHCHH), 1.98 (dd, J = 20, 12 Hz, 1 H, O=CCHH), 1.44 (dd, J = 12.5, 11 Hz, 1 H, CHCHH), 1.18 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.36 (s, C=O, ketone), 169.25 (s, C=O, ester), 141.01 (d, OCH=), 98.07 (t, CH_2=), 46.29 (t, CH_2), 44.94 (t, CH_2), 43.57 (s), 39.80 (t, CH_2), 29.17 (d, CH), 24.18 (q, CH_3), 18.17 (d, CH_3); IR ($CHCl_3$) 1742 (C=O), 1616 (C=C) cm^{-1}; HRMS M^+ 196.1103 (calcd for $C_{11}H_{16}O_3$ 196.1099); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.24; H, 8.17.

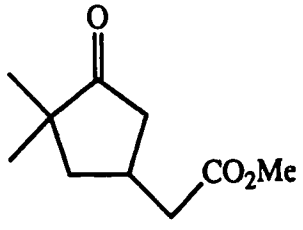
1-Ethoxyethyl (3,3-dimethyl-4-oxocyclopentyl)acetate (110).



To a stirred solution of keto acid **103** (79.8 mg, 0.47 mmol) in diethyl ether (5 mL), was added ethyl vinyl ether (0.2 mL, 0.15 g, 2.09 mmol; distilled from

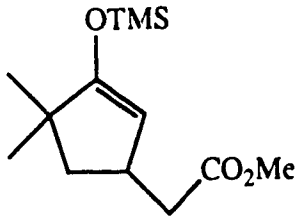
K_2CO_3) and *p*–toluenesulfonic acid (0.1 mg) at 0°C. The resulting solution was stirred at 0°C for 2 h under an atmosphere of argon, then quenched with saturated aqueous sodium hydrogen carbonate and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with water and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by bulb–to–bulb distillation (85°C, 0.1 mmHg) to furnish keto ester **110** (89 mg, 100%) as an oil and as a mixture of two diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 and 5.95 (each q, *J* = 5 Hz, *J* = 5 Hz, 1 H, O=COCH), 3.71 and 3.70 (each dq, *J* = 9 and 7 Hz, *J* = 9 and 7 Hz, 1 H, OCHHCH$_3$), 3.55 and 3.54 (each dq, *J* = 9 and 7 Hz, *J* = 9 and 7 Hz, 1 H, OCHHCH$_3$), 2.62 and 2.61(each m, 2 H), 2.46 and 2.45 (each m, 2 H), 2.08 (ddd, *J* = 12.5, 5.5 and 2.5 Hz, 1 H), 1.94 and 1.93 (each dd, *J* = 20 and 12 Hz, *J* = 20 and 12 Hz, 1 H), 1.46 (dd, *J* = 12.5 and 12 Hz, 1 H), 1.41 (d, *J* = 5 Hz, 3 H), 1.21 (t, *J* = 7 Hz, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.64 (s, C=O, ketone), 171.91 (s, C=O, ester), 96.47 and 96.42 (each d, OCHO), 64.75 (t, OCH_2), 46.27 (t), 44.99 (t), 43.58 (t), 40.47 (t), 39.61 (s), 29.33 and 29.16 (each d, CH), 24.20 and 24.16 (each q, OCHCH$_3$), 20.90 (q, CH_3), 15.04 (q, CH_2CH_3); FT–IR ($CDCl_3$) 1739 (C=O) cm^{-1}; HRMS M$^+$ 242.1519 (calcd for $C_{13}H_{22}O_4$ 242.1515); Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 64.28; H, 9.24.

Methyl (3,3–dimethyl–4–oxocyclopentyl)acetate (101).



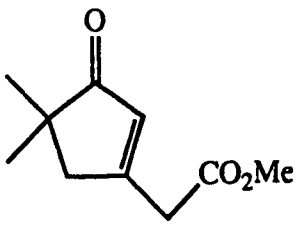
A solution of keto acid **103** (2.26 g, 13.3 mmol) and concentrated sulfuric acid (5 drops) in methanol (20 mL) was heated at reflux under an atmosphere of argon for 2 h. The reaction mixture was then cooled to room temperature and the excess methanol was evaporated by means of a water aspirator. The residue was taken up in dichloromethane (20 mL), more water (10 mL) was added and the organic phase was separated. The aqueous phase was then extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate and water and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was subjected to bulb–to–bulb distillation (50°C, 0.5 mmHg) to afford keto ester **101** (2.40 g, 100%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3 H, OCH_3), 2.62 (m, 2 H, O=CC**H**HC**H**), 2.44 (dd, *J* = 15, 6 Hz, 1 H, C**H**HCO_2Me), 2.43 (dd, *J* = 15, 7 Hz, 1 H, CH**H**CO_2Me), 2.08 (ddd, *J* = 12, 6, 2 Hz, 1 H, CH**H**CH), 1.89 (dd, *J* = 18, 12 Hz, 1 H, O=CC**H**H), 1.42 (dd, *J* = 12, 11 Hz, 1 H, C**H**HCH), 1.08 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.66 (s, C=O, ketone), 172.59 (s, C=O, ester), 51.61 (q, OCH_3), 46.23 (s, C–2), 44.95 (t, O=CCH_2), 43.62 (t, CH_2), 39.91 (t, CH_2), 29.34 (d, CH), 24.17 (q, CH_3), 24.13 (q, CH_3); FT–IR ($CHCl_3$) 1739 (C=O) cm^{-1}; HRMS M^+ 184.1098 (calcd for $C_{10}H_{16}O_3$ 184.1100); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.60; H, 8.68.

Methyl (4,4–dimethyl–3–trimethylsiloxy–2–cyclopentenyl)acetate (113).



To a magnetically stirred solution of diisopropylamine (0.51 mL, 367 mg, 3.63 mmol) in tetrahydrofuran (5 mL), was added *n*–butyllithium (1.5 mL, 2.5 M in hexane, 3.64 mmol) dropwise. The resulting solution was stirred for 30 min at -78°C. A solution of keto ester **101** (556 mg, 3.02 mmol) in tetrahydrofuran (5 mL) was added dropwise at -78°C and the resulting mixture was stirred at -78°C for 40 min under an atmosphere of argon. Trimethylsilyl chloride (0.46 mL, 397 mg, 3.65 mmol; freshly distilled from calcium hydride) was added in one portion at -78°C and the mixture was stirred for 2 h at -78°C, then gradually warmed to 0°C and stirred for 1 h at 0°C. The solution was poured into ice–cold 10% aqueous sodium hydrogen carbonate solution and the resulting mixture was extracted with diethyl ether (3 × 15 mL). The organic extracts were washed with water, dried over magnesium sulfate and filtered. The solvents were removed *in vacuo* to afford crude silyl enol ether **113** as a colorless oil which was used without purification in the subsequent oxidation step.

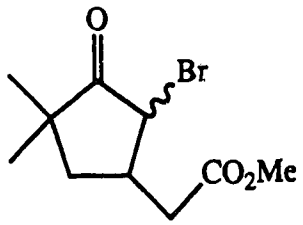
3–Carbomethoxymethyl–5,5–dimethyl–2–cyclopenten–1–one (95).



To a solution of palladium acetate (250 mg, 1.10 mmol) and *p*–benzoquinone (119 mg, 1.10 mmol) in acetonitrile (20 mL), was added the crude silyl enol ether solution in acetonitrile (10 mL) at room temperature under argon. The resulting mixture was stirred at 25°C for 40 h. The mixture was diluted with ether (20 mL), filtered and concentrated. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexane as eluant) to give keto ester **101** (300 mg, 1.63 mmol) as a colorless oil.

Further elution with 20% ethyl acetate in hexane yielded enone ester **95** (51 mg, 9.2%) as a light brown liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (quintet, J = 1.5 Hz, 1 H, CH=), 3.74 (s, 3 H, OCH_3), 3.44 (d, J = 1 Hz, 2 H, CH_2CO_2), 2.56 (dt, J = 1.5, 1 Hz, 2 H, CH_2), 1.12 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.67 (s, C=O, ketone), 169.29 (s, C=O, ester), 169.07 (s, C=), 129.92 (d, CH=), 52.30 (q, OCH_3), 48.12 (t, CH_2CO_2), 44.55 (s, Me_2C), 38.51 (t, CH_2), 24.96 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1743 (C=O, ester), 1707 (C=O, enone) and 1622 (C=C) cm^{-1}; HRMS M^+ 182.0944 (calcd for $C_{10}H_{14}O_3$ 182.0944); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.98; H, 7.46.

Methyl (2–bromo–4,4–dimethyl–3–oxocyclopentyl)acetate (114).

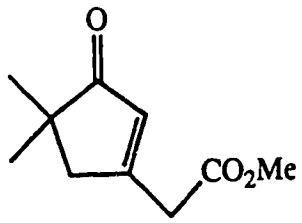


To a magnetically stirred solution of diisopropylamine (0.9 mL, 649.6 mg, 6.42 mmol) in tetrahydrofuran (20 mL), was added *n*–butyllithium (2.60 mL, 2.5 M in hexane, 6.42 mmol) dropwise at -40°C under an atmosphere of argon. The resulting solution was stirred for 30 min at -40°C. A solution of keto ester **101** (875 mg, 4.76 mmol) in tetrahydrofuran (10 mL) was added dropwise at -78°C and the resulting mixture was stirred at this temperature for 40 min. A solution of trimethylsilyl chloride of the supernatant centrifugate from a 3:1 mixture of chlorotrimethylsilane (1.20 mL, 1.03 g, 9.50 mmol; freshly distilled from calcium hydride) and triethylamine (0.4 mL, 304 mg, 3.0 mmol) in THF (10 mL) was added rapidly at -78°C and the reaction mixture was stirred for 2 h at -78°C and 1 h at 0°C. The solvent was removed under reduced pressure and the residue was taken up in petroleum ether. The petroleum ether solution was filtered through a short column of Florisil. After removal of the solvent *in vacuo*, the crude silyl enol ether **113** (1.33 g) was obtained as a colorless oil which was used directly for bromination without purification.

A solution of bromine (20 μL, 62 mg, 0.39 mmol) in carbon tetrachloride (5 mL) was added slowly to the silyl enol ether **113** solution (100 mg, 0.39 mmol) in carbon tetrachloride (5 mL) at -20°C over 20 min. The rate of addition was maintained such that the solution was always colorless to pale orange. The resulting colorless solution was warmed to room temperature and the solvent was removed *in vacuo* to produce the crude α–bromo ketone. This material was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to afford the α–bromo ketones **114** (64 mg, 64%) as a mixture of two diastereisomers in a ratio of 1:1 as determined by high resolution ^{1}H NMR integration of characteristic peaks at δ 4.50 and 4.16: ^{1}H NMR (300 MHz,

$CDCl_3$) δ 4.50 (dd, J = 4.5, 1.5 Hz, 1 H, CHBr), 4.16 (d, J = 11 Hz, 1 H, CHBr), 3.73 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 2.84 (dd, J = 15.5, 4 Hz, 1 H, C**H**HCO$_2$), 2.50–2.70 (m, 4 H), 2.42 (dd, J = 16, 8.5 Hz, 1 H, CH**H**CO$_2$), 2.23 (dd, J = 13, 6 Hz, 1 H, C**H**HCH), 1.91 (ddd, J = 13, 6, 1 Hz, 1 H, CH**H**CH), 1.81 (dd, J = 12, 12.5 Hz, 1 H, C**H**HCH), 1.55 (dd, J = 12.5, 12 Hz, 1 H, CH**H**CH), 1.30 (s, 3 H, CH_3), 1.16 (br s, 6 H, 2 × CH_3), 1.10 (s, 3 H, CH_3); FT–IR ($CHCl_3$) 1738 (C=O) cm^{-1}; HRMS M^+ 264.0178 and 262.0177 (calcd for $C_{10}H_{15}O_3Br$ 264.0184 and 262.0205).

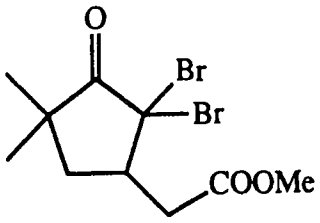
3–Carbomethoxymethyl–5,5–dimethyl–2–cyclopenten–1–one (95) from α–bromo ketones 114.



A solution of crude α–bromo ketones **114** (100 mg) in pyridine (5 mL) was heated at reflux for 20 min. TLC showed that no more starting material was present after this period. Pyridine was removed under reduced pressure and the residue was taken up in dichloromethane (10 mL) and water (10 mL). The organic phase was separated and the remaining aqueous phase was extracted with CH_2Cl_2. The extracts were washed with 1N hydrochloric acid (5 mL), water and brine. After the organic solution was dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to afford the enone

ester **95** (20 mg, 30%) as a light yellow oil: Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 66.07; H, 7.60.

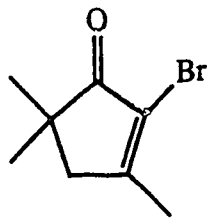
Methyl (2,2-dibromo-4,4-dimethyl-3-oxocyclopentyl)acetate (116).



A mixture of keto ester **101** (450 mg, 2.45 mmol), pyridinium bromide perbromide (2.24 g, 80%, 5.60 mmol) in dichloromethane (20 mL) and acetic acid (5 mL) was stirred at 0°C for 3 h and at 25°C for 4 h. Water (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (20% ethyl acetate in hexane as eluant) to give the dibromo ketone **116** (783 mg, 94%) as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3 H, OCH_3), 3.05 (dd, J = 16, 3 Hz, 1 H, $CHHCO_2$), 2.82 (dddd, J = 12, 9.6, 6, 3 Hz, 1 H, CH), 2.55 (dd, J = 16, 9.6 Hz, 1 H, $CHHCO_2$), 2.10 (dd, J = 12.5, 6 Hz, 1 H, **CH**H), 1.70 (dd, J = 12.5, 12 Hz, 1 H, CH**H**), 1.38 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.40 (s, C=O, ketone), 171.56 (s, C=O, ester), 69.54 (s, CBr_2), 52.01 (q, OCH_3), 47.25 (d, CH), 42.99 (t, CH_2CO_2), 41.12 (s, CMe_2), 36.04 (t, CH_2), 27.62 (q, CH_3), 26.08 (q, CH_3); FT-IR ($CHCl_3$) 1761 (C=O, ketone) and 1740 (C=O, ester) cm^{-1}; HRMS M^+ 343.9281, 341.9304 and 339.9321 (calcd for

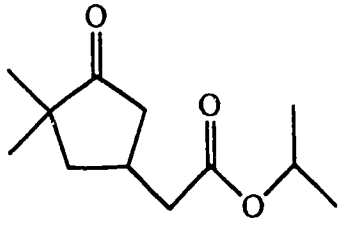
$C_{10}H_{14}O_3Br_2$ 343.9269, 341.9289 and 339.9309); Anal. Calcd for $C_{10}H_{14}O_3Br_2$: C, 35.12; H, 4.13. Found: C, 35.42; H, 4.12.

2-Bromo-3,5,5-trimethyl-2-cyclopentenone (117).



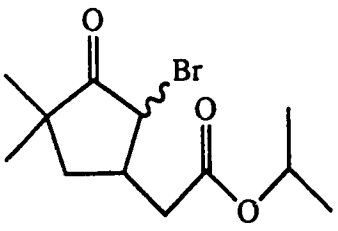
A solution of dibromo ketone **116** (120 mg, 0.35 mmol) in pyridine (10 mL) was refluxed for 2 h. Pyridine was then removed under reduced pressure. Water (5 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The extracts were washed subsequently with aqueous saturated sodium hydrogen carbonate (10 mL) and water (10 mL) and dried over magnesium sulfate. Flash column chromatography of the residue on silica gel (20% ethyl acetate in hexane) gave bromo enone **117** (67 mg, 94%) as a colorless solid whose melting point was 25–30°C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (q, J = 1 Hz, 2 H, CH_2), 2.16 (t, J = 1 Hz, 3 H, $=CCH_3$), 1.16 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.09 (s, C=O), 170.28 (s, $=CCH_3$), 120.78 (s, =CBr), 48.98 (s, CMe_2), 43.10 (t, CH_2), 25.28 (q, 2 × CH_3), 18.85 (q, CH_3); FT-IR ($CHCl_3$) 1722 (C=O) and 1624 (C=C) cm^{-1}; HRMS M^+ 203.9927 and 201.9950 (calcd for $C_8H_{11}OBr$ 203.9973 and 201.9993); Anal. Calcd for $C_8H_{11}OBr$: C, 47.33; H, 5.46. Found: C, 47.24; H, 5.50.

Isopropyl (3,3-dimethyl-4-oxocyclopentyl)acetate (118).



A mixture of keto acid **103** (2.0 g, 11.76 mmol), isopropyl alcohol (15 mL) and concentrated sulfuric acid (4 drops) was heated at reflux overnight. The resulting solution was then cooled to room temperature and the excess alcohol was removed *in vacuo*. The colorless oil residue was then taken up in water (15 mL) and extracted with dichloromethane (3 × 20 mL). The organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a clear oil which was then subjected to bulb–to–bulb distillation. The keto ester **118** (2.50 g, 100%) was isolated as a clear, colorless oil: bp 50°C (0.3 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (septet, J = 6 Hz, 1 H, C**H**Me$_2$), 2.60 (m, 2 H, O=CC**H**HC**H**), 2.42 (dd, J = 15, 6 Hz, 1 H, C**H**HCO$_2$), 2.36 (dd, J = 15, 7.5 Hz, 1 H, CH**H**CO$_2$), 2.06 (ddd, J = 12, 6, 2 Hz, 1 H, C**H**HCH), 1.92 (dd, J = 20, 13 Hz, 1 H, O=CCH**H**), 1.45 (dd, J = 12.5, 11 Hz, 1 H, CH**H**CH), 1.24 (d, J = 6 Hz, 6 H, CH(C**H**$_3$)$_2$), 1.09 (s, 3 H, CH$_3$), 1.04 (s, 3 H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.85 (s, C=O, ketone), 171.71 (s, C=O, ester), 67.91 (d, OCH), 46.25 (s, CMe$_2$), 45.02 (t, CH$_2$), 43.66 (t, CH$_2$), 40.65 (t, CH$_2$), 29.53 (d, CH), 24.24 (q, CH$_3$), 24.21 (q, CH$_3$), 21.88 (q, 2 × CH$_3$); IR ($CHCl_3$) 1740 (C=O) cm^{-1}; HRMS M$^+$ 212.1411 (calcd for $C_{12}H_{20}O_3$ 212.1412); Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 6.43. Found: C, 67.79; H, 6.27.

Isopropyl (2–bromo–4,4–dimethyl–3–oxocyclopentyl)acetate (119).

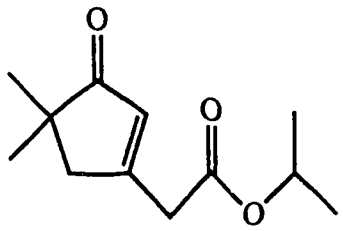


To a magnetically stirred solution of diisopropylamine (0.9 mL, 649.6 mg, 6.42 mmol) in tetrahydrofuran (20 mL), was added *n*–butyllithium (2.60 mL, 2.5 M in hexane, 6.42 mmol) dropwise at -40°C and the resulting solution was stirred for 30 min at -40°C. A solution of keto ester **118** (1.00 g, 4.76 mmol) in tetrahydrofuran (20 mL) was added dropwise to the LDA solution precooled to -78°C and the resulting mixture was stirred at -78°C for 40 min under an atmosphere of argon. A solution of trimethylsilyl chloride of the supernatant centrifugate from a 3:1 mixture of chlorotrimethylsilane (1.20 mL, 1.03 g, 9.50 mmol; freshly distilled from calcium hydride) and triethylamine (0.4 mL, 304 mg, 3.0 mmol) in THF (10 mL) was rapidly added to the above enolate solution at -78°C. The reaction mixture was stirred for 2 h at -78°C, warmed up to 0°C and further stirred for 1 h at this temperature. The solvent was removed under reduced pressure and the residue was taken up in petroleum ether. The petroleum ether solution was filtered through a short column of Florisil. After removal of the solvent *in vacuo*, the crude silyl enol ether (1.45 g) was obtained as a colorless oil which was used directly for bromination without purification.

A solution of bromine (20 µL, 62 mg, 0.39 mmol) in carbon tetrachloride (5 mL) was added slowly to the silyl enol ether solution (111 mg, 0.39 mmol) in carbon tetrachloride (5 mL) at -20°C over 20 min. The rate of addition was

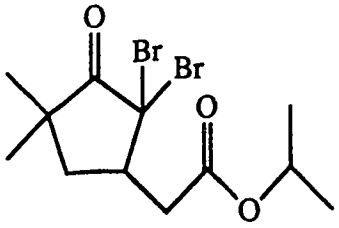
maintained such that the solution was always colorless to pale orange. The resulting colorless solution was warmed to room temperature and the solvent was removed *in vacuo* to produce the crude α–bromo ketone (115 mg) which was used to carry out the dehydrobromination without further purification.

3–Carboisopropoxymethyl–5,5–dimethyl–2–cyclopenten–1–one (120).



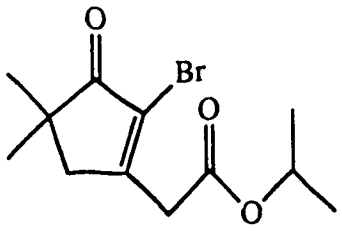
A solution of crude α–bromo ketone **119** (111 mg, *ca.* 0.38 mmol) in pyridine (5 mL) was heated at reflux until no starting material was present by TLC inspection (about 30 min). Pyridine was removed under reduced pressure, the residue was taken up in dichloromethane (10 mL) and the organic phase was separated. The aqueous phase was then extracted with CH_2Cl_2. The organic extracts were washed with hydrochloric acid (1N, 5 mL), water and brine. After the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to afford enone ester **120** (16 mg, 20%) as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (quintet, J = 1.5 Hz, 1 H, CH=), 5.06 (septet, J = 6 Hz, 1 H, OCH), 3.40 (q, J = 1 Hz, 2 H, CH_2CO_2), 2.56 (m, 2 H, CH_2), 1.28 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 1.12 (s, 6 H, 2 × CH_3).

Isopropyl (2,2-dibromo-4,4-dimethyl-3-oxocyclopentyl)acetate (121).



A mixture of keto ester **118** (300 mg, 1.41 mmol), pyridinium bromide perbromide (1.24 g, 80%, 3.10 mmol) in dichloromethane (20 mL) and acetic acid (5 mL) was stirred at 0°C for 3 h. The temperature was raised to 25°C and the reaction mixture was further stirred for 4 h. Water (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The extracts were washed with water and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to afford dibromo ketone **121** (524 mg) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (septet, J = 5.5 Hz, 1 H, OCH), 3.05 (dd, J = 16, 3 Hz, 1 H, **CH**HCO$_2$), 2.82 (dddd, J = 12, 9.6, 6, 3 Hz, 1 H, CH), 2.55 (dd, J = 16, 9 Hz, 1 H, CH**H**CO$_2$), 2.10 (dd, J = 12, 6 Hz, 1 H, **CH**HCH), 1.70 (dd, J = 12.5, 12 Hz, 1 H, CH**H**CH), 1.38 (s, 3 H, CH_3), 1.30 (d, J = 6 Hz, 6 H, CH(**CH**$_3$)$_2$), 1.20 (s, 3 H, CH_3).

2-Bromo-3-carboisopropoxymethyl-5,5-dimethyl-2-cyclopenten-1-one (122).

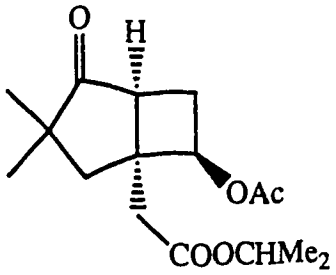


A mixture of dibromo ketone **121** (524 mg, 1.41 mmol) in pyridine (20 mL) was refluxed for 30 min. Pyridine was then removed under reduced pressure. Water (5 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The extracts were subsequently washed with aqueous saturated sodium hydrogen carbonate (10 mL) and water (10 mL) and dried over magnesium sulfate. Flash column chromatography on silica gel (20% ethyl acetate in hexane) gave bromo enone **117** (157 mg, 56%) as a colorless solid whose melting point was 25–30°C: Anal. Calcd for $C_8H_{11}OBr$: C, 47.33; H, 5.46. Found: C, 47.20; H, 5.52.

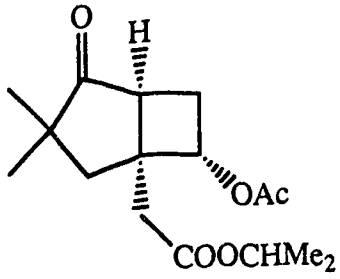
Further elution with 20% ethyl acetate in hexane provided enone ester **122** (128 mg, 32%) as a light brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (septet, J = 6 Hz, 1 H, OCH), 3.56 (br t, J = 1 Hz, 2 H, CH_2CO_2), 2.62 (br t, J = 1 Hz, 2 H, CH_2), 1.26 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 1.19 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.84 (s, C=O, ketone), 167.28 (s, C=O, ester), 165.04 (s, C=), 123.24 (s, =CBr), 69.30 (d, OCH), 47.35 (t, CH_2CO_2), 43.29 (s, CMe_2), 38.42 (t, CH_2), 25.19 (q, 2 × CH_3), 21.76 (q,2 × CH_3); IR ($CHCl_3$) 1729 (C=O), 1620 (C=C) cm^{-1}; HRMS M^+ 290.0335 and 288.0355 (calcd for $C_{12}H_{17}O_3Br$ 290.0306 and 288.0361).

(1*S, 5*S**, 6*R**)-(123) and (1*S**, 5*S**, 6*S**)-(124)-6-Acetoxy-5-carboisopropoxymethyl-3,3-dimethylbicyclo[3.2.0]heptan-2-one.**

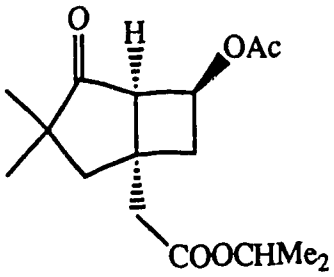
(1*S, 5*S**, 6*S**)-(125) and (1*S**, 5*S**, 6*R**)-(126)-7-Acetoxy-5-carboisopropoxymethyl-3,3-dimethylbicyclo[3.2.0]heptan-2-one.**



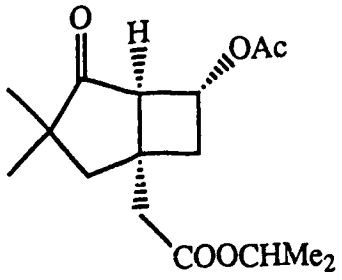
123



124



125

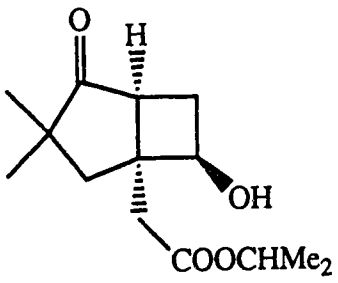


126

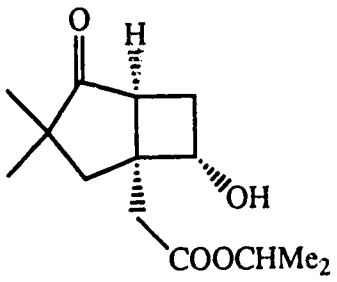
A degassed benzene (300 mL) solution of enone ester **120** (830 mg, 3.95 mmol) and vinyl acetate (5.5 mL, 5.1 g, 59 mmol) was placed in a photochemical apparatus which was suspended in a large Dewar flask. An ice–water slush mixture was added to the Dewar flask, and the mixture was allowed to cool to 0°C. The solution was irradiated using a 450–W Hanovia high pressure mercury lamp, through a Pyrex filter for 2.5 h. At the end of this time TLC indicated that no more starting enone was present. The solvent and excess vinyl acetate were removed *in vacuo*, and the residue was subjected to

flash chromatography on silica gel. Elution with 20% ethyl acetate in hexane gave an inseparable mixture of at least four isomers **123–126** (1.16 g, 99%) as a colorless oil: IR ($CHCl_3$) 1732 cm^{-1}; HRMS M^+ 296.1620 (calcd for $C_{16}H_{24}O_5$ 296.1624).

(1*S, 5*S**, 6*R**)-(127) and (1*S**, 5*S**, 6*S**)-(128)-5-Carboisopropoxymethyl-6-hydroxy-3,3-dimethylbicyclo[3.2.0] heptan-2-one.**



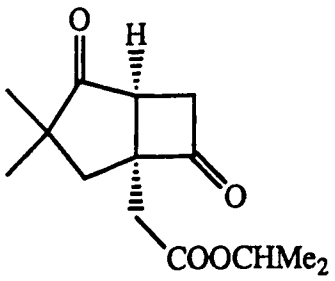
127



128

Sodium hydride (11 mg, 80%, 0.38 mmol) was dissolved in isopropyl alcohol (2 mL) at 25°C to form sodium isopropoxide. A mixture of keto esters of **123**, **124**, **125** and **126** (80 mg, 0.27 mmol) in isopropyl alcohol (1 mL) was added dropwise at 25°C. After stirring for 20 min, acetic acid (2 mL) was added to the mixture to neutralize any excess base. The resulting mixture was extracted with chloroform. The extracts were washed with water and saturated sodium chloride and dried over magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane) to afford the hydroxy esters **127** and **128** (37 mg) as a colorless oil which showed quite a complex ^1H NMR spectrum: IR ($CHCl_3$) 3500 (OH), 1731 (C=O) cm^{-1}.

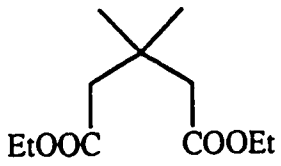
(1*S, 5*S**)-5-Carboisopropoxymethyl-3,3-dimethylbicyclo[3.2.0] heptan-2,6-dione (131).**



To a solution of oxalyl chloride (60 μL, 87 mg, 0.69 mmol) in dichloromethane (10 mL), was added DMSO (94 μL, 103 mg, 1.32 mmol) dropwise over 5 min at -60°C. After stirring at -60°C for 15 min, a solution of hydroxy esters **127** and **128** (140 mg, 0.55 mmol) in dichloromethane (10 mL) was added dropwise and the resultant mixture was stirred for 20 min. at -60°C. Triethylamine (0.38 mL, 278 mg, 2.75 mmol) was added dropwise to the reaction mixture over 5 min. After stirring for 5 min, the mixture was slowly warmed to room temperature and stirred for 20 min. The reaction mixture was then poured into a saturated sodium chloride solution and extracted with chloroform. The organic extracts were washed with water and brine and dried over magnesium sulfate. After the solvent was removed *in vacuo*, the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to give the diketo isopropyl ester **131** (85 mg, 62%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (septet, J = 6 Hz, 1 H, OC**H**Me_2), 3.74 (dd, J = 18, 11 Hz, 1 H, H–7α), 3.20 (dd, J = 11, 5 Hz, 1 H, H–1), 3.04 (ddd, J = 18, 5, 1 Hz, 1 H, H–7β), 2.94 (d, J = 17 Hz, 1 H, C**H**HCO_2), 2.63 (d, J = 17 Hz, 1 H, CH**H**CO_2), 2.22 (d, J = 14 Hz, 1 H, H–4α), 1.81 (d, J = 14 Hz, 1 H, H–4β), 1.24 (d, J = 6.5 Hz, 3 H, MeCHC**H**$_3$), 1.23 (d, J = 6.5 Hz, 3

H, CH_3CHMe), 1.16 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CHCl_3$) δ 221.00 (s, C=O, five–membered ring ketone), 208.90 (s, C=O, four–membered ring ketone), 169.86 (s, C=O, ester), 68.89 (d, $OCHMe_2$), 64.72 (s, C–5), 50.71 (t, C–7), 47.13 (s, C–3), 44.11 (t, CH_2CO_2), 42.32 (d, O=CCH), 39.20 (t, C–4), 26.20 (q, CH_3), 26.07 (q, CH_3), 21.80 (q, $2 \times CH_3$); FT–IR ($CHCl_3$) 1786 (C=O, four–membered ring ketone) and 1730 (C=O, five–membered ring ketone) cm^{-1}; HRMS M^+ 252.1362 (calcd for $C_{14}H_{20}O_4$ 252.1362); Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.67; H, 7.94. Found: C, 66.50; H, 8.03.

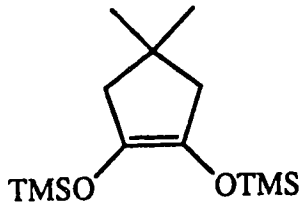
Diethyl 3,3–dimethylglutarate (139).



In a 250 mL, round–bottomed flask were combined 3,3–dimethylglutaric acid (10 g, 62.4 mmol), dry ethanol (100 mL), dry toluene (25 mL) and concentrated sulfuric acid (4 mL). A soxhlet apparatus containing a thimble of anhydrous potassium carbonate (30 g) was attached and the solution was brought to reflux. After 40 h, the solution was concentrated by rotatory evaporator to a slurry which was taken up in chloroform (100 mL), washed with water and saturated sodium hydrogen carbonate, and dried over magnesium sulfate. The solution was filtered and concentrated by rotatory evaporator to afford a yellow oil which was distilled under vacuum (50°C, 0.3 mmHg, lit.[49] 128–131°C, 20 mmHg) to give diester **139** (13.5 g, 100%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7 Hz, 4 H,

2 × OCH_2), 2.40 (s, 4 H, 2 × CH_2), 1.26 (t, J = 7 Hz, 6 H, 2 × CH_3), 1.11 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.53 (s, 2 × C=O), 59.69 (t, 2 × OCH_2), 45.11 (t, 2 × CH_2), 32.36 (s, CMe_2), 27.39 (q, 2 × CH_3), 14.02 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1734 (C=O) cm^{-1}; HRMS M^+ 216.1359 (calcd for $C_{11}H_{20}O_4$ 216.1361).

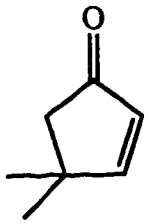
1,2–Bis(trimethylsiloxy)–4,4–dimethyl–1–cyclopentene (140).



A three–necked, 300 mL, round–bottomed flask was fitted with a dropping funnel, a condenser and a high–speed mechanical stirrer. All subsequent operations were carried out under an argon atmosphere. A mixture of sodium (3.4 g, 0.148 mmol) and dry toluene (150 mL) was brought to reflux by means of a heating mantle. When the sodium melted, it was dispersed into a fine sand by high–speed stirring for about 2–5 min. The stirrer speed was reduced. While the solvent was still refluxing, a solution of diester **139** (8.0 g, 37 mmol) and chlorotrimethylsilane (19 mL, 16 g, 0.148 mol) in dry toluene (50 mL) was added dropwise over a 1.5 h period. The reaction was exothermic and a dark purple precipitate appeared within a few minutes (the color changed from light tan to dark purple during the addition). The reaction mixture was maintained at reflux during and after the addition. At the end of the addition, a further portion of toluene (25 mL) was added in order to rinse the dropping funnel.

Stirring and heating were continued for 24 h and additional chlorotrimethylsilane (10 mL, each) was added at the end of 4 h and 20 h to replace any losses (total chlorotrimethylsilane added was 32 g, 0.296 mol). At the end of this period, TLC indicated that no starting diester was present and the mixture was allowed to cool to room temperature. The solids were removed by suction filtration and washed with dry ether. The filtrate was concentrated by rotatory evaporation to give a colorless oil which was distilled *in vacuo* (60°C, 3 mmHg) to afford bis(trimethylsiloxy)–cyclopentene **140**[49] (10.1 g, 100%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 4 H, 2 × CH_2), 0.9 (s, 6 H, 2 × CH_3), 0.00 (s, 18 H, 2 × $OSiMe_3$); FT–IR ($CHCl_3$) 2930, 1252 cm^{-1}; HRMS M^+ was not observed in the high resolution mass spectrum.

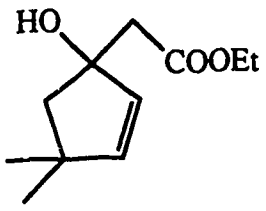
4,4–Dimethyl–2–cyclopenten–1–one (134).



To a 50–mL round–bottomed flask containing bis(trimethylsiloxy)cyclopentene **140** (10 g, 37 mmol) was added with stirring phosphoric acid (8.5 mL, 85%). After the contents were mixed, the flask was fitted with a short–path condenser and a dry ice–cooled receiving flask. The reaction flask was immersed into an oil bath preheated to 95~100°C and the pressure was reduced using an aspirator to 40 mmHg over a 10 min period. The initially vigorous distillation became

slower after *ca.* 15 min and the bath temperature was raised to 150°C. After 30 min, when distillation again slowed down, the pressure was further reduced to 30 mmHg. After a 20 min period of slow distillation, the reaction was terminated. The two phase distillate was taken up in diethyl ether (20 mL) and separated. The aqueous portion was extracted with two portions of ether (2 × 30 mL). The combined ether extracts were dried over magnesium sulfate. After filtration, ether was removed by distillation under normal pressure to leave a pale–yellow oil, which was distilled *in vacuo* (65–68°C, 35 mmHg) to afford 4,4–dimethylcyclopentenone **134**[49] (3.8 g, 93%) as a clear, colorless, sharp–smelling mobile liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 5.5 Hz, 1 H, =CH), 6.0 (d, J = 5.5 Hz, 1 H, =CH), 2.25 (s, 2 H, CH_2), 1.24 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.07 (s, C=O), 173.91 (d, =CH), 131.11 (d, =CH), 49.89 (t, CH_2), 41.52 (s, CMe_2), 28.00 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1730 and 1710 (C=O) cm^{-1}; HRMS M$^+$ 110.0733 (calcd for $C_7H_{10}O$ 110.0731).

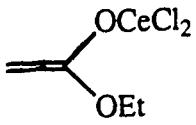
1–Carboethoxymethyl–4,4–dimethyl–2–cyclopenten–1–ol (133) using the lithium enolate of ethyl acetate.



To a stirred solution of diisopropylamine (0.36 mL, 263 mg, 2.6 mmol) in dry tetrahydrofuran (10 mL), was added *n*–butyllithium (1.04 mL, 2.5 M in

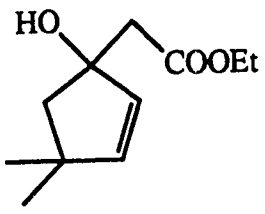
hexane, 2.60 mmol) dropwise at -78°C. The resulting solution was stirred for 20 min at this temperature. Ethyl acetate (0.21 mL, 192 mg, 2.18 mmol) in dry tetrahydrofuran (2 mL) was added to the LDA solution at -78°C dropwise and the resulting solution stirred for 30 min. Then a solution of 4,4-dimethylcyclopentenone **134** (200 mg, 1.82 mmol) in dry tetrahydrofuran (3 mL) was introduced. After stirring for 2 h, saturated ammonium chloride (5 mL) was poured into the reaction mixture and the resulting mixture was extracted with ether (3 × 20 mL). The organic extracts were washed with water and brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane as eluant) to afford the β-hydroxy ester **133** (175 mg, 50%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 5.5 Hz, 1 H, CH=), 5.60 (d, J = 5.5 Hz, 1 H, CH=), 4.19 (q, J = 7 Hz, 2 H, OCH_2), 3.63 (s, 1 H, OH), 2.68 (d, J = 16 Hz, 1 H, C**H**HCO_2), 2.64 (d, J = 16 Hz, 1 H, CH**H**CO_2), 1.92 (d, J = 14 Hz, 1 H, C**H**H), 1.81 (d, J = 14 Hz, 1 H, CH**H**), 1.29 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.19 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.81 (s, C=O), 144.97 (d, =CH), 131.70 (d, =CH), 83.35 (s, COH), 60.75 (t, OCH_2), 52.98 (t, CH_2), 45.89 (s, CMe_2), 44.78 (t, CH_2), 30.05 (q, CH_3), 29.19 (q, CH_3), 14.25 (q, CH_3); FTIR ($CDCl_3$) 3500 (OH), 1733 (C=O), 1718 (C=O) cm^{-1}; HRMS M^+ 198.1249 (calcd for $C_{11}H_{18}O_3$ 198.1256); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.60; H, 9.02.

Cerium enolate of ethyl acetate (142).



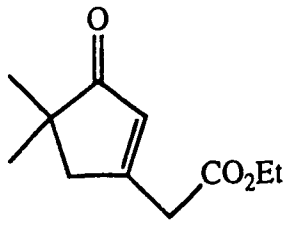
Powdered cerium trichloride heptahydrate (1.35 g, 3.64 mmol) was dried at 100°C (0.1 mmHg) for 10 h, then at 150°C (0.1 mmHg) for 2 h. The dried cerium chloride was cooled to room temperature under vacuum and vented to an argon atmosphere. Dry tetrahydrofuran (7 mL, *ca.* 2 mL for 1 mmol of $CeCl_3$) was added and the resulting suspension was stirred vigorously for 2 h under argon to get a fine suspension of cerium chloride in THF. To a stirred solution of diisopropylamine (0.53 mL, 385 mg, 3.8 mmol) in dry tetrahydrofuran (10 mL) was added *n*–BuLi (1.6 mL, 2.5 M in hexane, 4.0 mmol) dropwise at -78°C and the resulting solution was stirred for 20 min. Ethyl acetate (0.36 mL, 326 mg, 3.70 mmol) in dry tetrahydrofuran (2 mL) was added to the LDA solution at -78°C dropwise and stirred for 30 min. This solution of lithium ester enolate in dry tetrahydrofuran was transferred to the cerium chloride suspension in tetrahydrofuran, precooled to -78°C, *via* a cannula. The resulting mixture was stirred for 2 h at -78°C to generate cerium enolate **142.**

1–Carboethoxymethyl–4,4–dimethyl–2–cyclopenten–1–ol (133) using cerium ester enolate 142.



A solution of 4,4–dimethylcyclopentenone **134** (170 mg, 1.55 mmol) in dry tetrahydrofuran (3 mL) was added to the cerium enolate solution **142** at -78°C and the resulting mixture was stirred at -78°C for 2 h. Saturated ammonium chloride (10 mL) was added and the resulting mixture was extracted with ether (3 × 20 mL). The organic extracts were washed with water and brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane as eluant) to afford β–hydroxy ester **133** (300 mg, 98%) as a colorless oil.

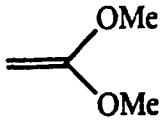
3–Carboethoxymethyl–5,5–dimethyl–2–cyclopenten–1–one (132).



To a stirred solution of allylic alcohol **133** (210 mg, 1.06 mmol) in dichloromethane (5 mL), was added pyridinium chlorochromate (457 mg, 2.12 mmol) in small portions. The resulting dark red–black mixture was stirred at room temperature for 12 h under an atmosphere of argon. TLC indicated that the starting material was no longer present after this period of time. The reaction mixture was concentrated *in vacuo* and the residue was taken up in diethyl ether (10 mL). The ethereal solution was passed through a short–path Florisil column and the column was eluted with diethyl ether. The combined ethereal solutions were concentrated *in vacuo* and the residue was

chromatographed on silica gel (20% ethyl acetate in hexane) to give the enone ester **132** (125 mg, 60%) as a light yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (m, 1 H, CH=), 4.20 (q, *J* = 7 Hz, 2 H, OCH_2), 3.42 (br d, *J* = 1 Hz, 2 H, CH_2C=O), 2.56 (m, 2 H, CH_2), 1.29 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.12 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.75 (s, C=O, enone), 169.35 (s, C=O, ester), 168.82 (s, C=), 129.82 (d, CH=), 61.35 (t, OCH_2), 48.17 (t, CH_2COO), 44.54 (s, O=CC), 38.85 (t, CH_2), 24.97 (q, CH_3), 24.77 (q, CH_3), 14.16 (q, CH_2CH_3); FT–IR ($CHCl_3$) 1739 (C=O, ester), 1708 (C=O, ketone), 1622 (C=C) cm^{-1}; HRMS M^+ 196.1099 (calcd for $C_{11}H_{16}O_3$ 196.1099); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.30; H, 8.04.

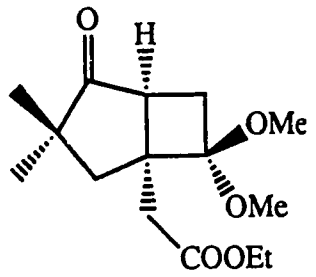
1,1–Dimethoxyethylene (143).



In a 2–L round–bottomed flask were placed α–terpineol (1.01 L, 943 g), which had been previously dried over calcium hydride, and potassium (39.1 g, 1 gram–atom). A condenser was attached to the flask and the mixture was warmed up to 80°C to dissolve all the potassium (*ca.* 4 h). The solution was allowed to cool slightly and 2–chloro–1,1–dimethoxyethane (125 g, 1.0 mol) was added dropwise while the temperature was maintained at about 70°C. A brown precipitate appeared immediately. The reaction mixture was allowed to reflux under argon for 2 h at 120–200°C and was then distilled. The fraction (60.7 g, bp 85–95°C) was redistilled with a vigreux column (88–91°C) to obtain 1,1–dimethoxyethylene (**143**)[28] (50 g, 57%) as a colorless liquid which had to

be used immediately to avoid polymerization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 6 H), 3.08 (s, 2 H).

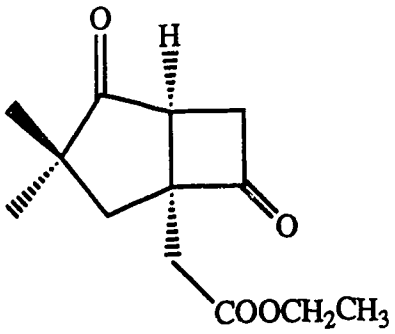
(1*S, 5*S**)-5-Carboethoxymethyl-6,6-dimethoxy-3,3-dimethyl bicyclo[3.2.0]heptan-2-one (144).**



A solution of enone **132** (2.0 g, 10.2 mmol) and 1,1-dimethoxyethylene (9.0 g, 102 mmol) in pentane (300 mL) was irradiated using a 450 W high pressure mercury lamp through a Pyrex filter at 0°C for 3 h (the reaction was monitored by TLC) under an atmosphere of argon. The solvent and excess 1,1-dimethoxyethylene were then removed under reduced pressure and the resulting residue was separated by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to provide the desired bicyclic ketal **144** (2.32 g, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (m, 2 H, OCH_2), 3.18 (s, 3 H, OCH_3), 3.14 (s, 3 H, OCH_3), 2.84 (d, J = 16 Hz, 1 H, CHHCOO), 2.82 (dd, J = 11, 5 Hz, 1 H, O=CCH), 2.60 (d, J = 16 Hz, 1 H, CHHCOO), 2.50 (dd, J = 13, 11 Hz, 1 H, H-7α), 2.40 (d, J = 14 Hz, 1 H, CHH), 2.10 (dd, J = 13, 5 Hz, 1 H, H-7β), 1.84 (d, J = 14 Hz, 1 H, CHH), 1.26 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.20 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.06 (s, C=O, ketone), 172.00 (s, C=O, ester), 102.00 (s, $C(OMe)_2$), 60.39 (t, OCH_2), 50.79 (s), 49.60 (q, OCH_3), 49.50 (q, OCH_3), 47.39 (s, C-3), 42.33

(d, O=CCH), 41.01 (t, CH_2), 38.37 (t, CH_2), 32.83 (t, CH_2), 27.62 (q, CH_3), 25.89 (q, CH_3), 14.27 (q, CH_3); FT–IR ($CHCl_3$) 1733 (C=O) cm^{-1}; HRMS M^+ 284.1622 (calcd for $C_{15}H_{24}O_5$ 284.1623); Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.38; H, 8.45. Found: C, 63.29; H, 8.37.

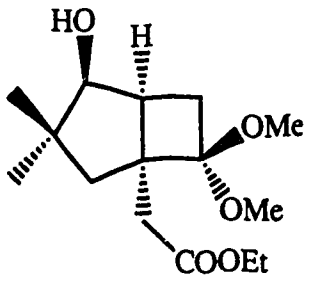
(1*S, 5*S**)–5–Carboethoxymethyl–3,3–dimethylbicyclo[3.2.0] heptane–2,6–dione (145).**



A solution of ketal **144** (100 mg, 0.35 mmol) in HCl (1N, 4 mL) and tetrahydrofuran (10 mL) was stirred at room temperature under an argon atmosphere until no starting material was present (about 1 week). The progress of the reaction was monitored by TLC analysis. Water (5 mL) was added to the reaction mixture and the resulting solution was extracted with chloroform (3 × 10 mL). The organic extracts were washed with saturated sodium hydrogen carbonate and water and dried over magnesium sulfate. Concentration followed by flash chromatography (silica gel, 30% ethyl acetate in hexane as eluant) afforded the diketone **145** (72 mg, 86%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, J = 7 Hz, 2 H, OCH_2), 3.74 (dd, J = 18, 11 Hz, 1 H, H–7α), 3.21 (dd, J = 11, 4.8 Hz, 1 H, O=CCH), 3.04 (ddd, J = 18,

4.8, 1 Hz, 1 H, H–7β), 2.97 (d, J = 17.6 Hz, 1H, CHHCOO), 2.67 (d, J = 17.6 Hz, 1 H, CHHCOO), 2.22 (d, J = 14 Hz, 1 H, CHH), 1.82 (d, J = 14 Hz, 1 H, CHH), 1.26 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.16 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.91 (s, C=O, five–membered ring ketone), 208.86 (s, C=O, four–membered ring ketone), 170.38 (s, C=O, ester), 64.62 (t, OCH_2CH_3), 61.12 (t, C–5), 50.69 (t, C–7), 47.11 (s, C–3), 44.05 (t, CH_2COO), 42.29 (d, C–1), 38.85 (t, C–4), 26.18 (q, CH_3), 26.04 (q, CH_3), 14.13 (q, CH_3); FT–IR ($CHCl_3$) 1785 (C=O, cyclobutanone) and 1733 (C=O, five–membered ring ketone and ester) cm^{-1}; HRMS M^+ 238.1203 (calcd for $C_{13}H_{18}O_4$ 238.1205); Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65.16; H, 7.85.

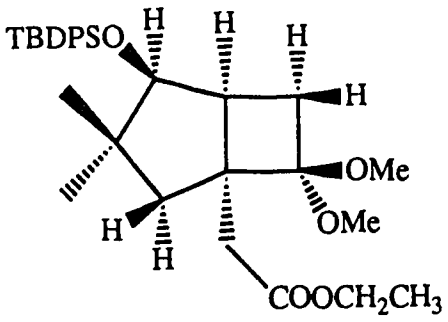
(1*S, 2*S**, 5*S**)–5–Carboethoxymethyl–6,6–dimethoxy–3,3–dimethyl bicyclo[3.2.0]heptan–2–ol (146).**



To a solution of ketone **144** (208 mg, 1.1 mmol) in absolute ethanol (10 mL), was added sodium borohydride (84 mg, 2.20 mmol) in small portions at 0°C. The reaction mixture was stirred for 3 h at 0°C under an atmosphere of argon. TLC indicated that there was no starting ketone left in the solution after this period of time. The reaction mixture was then cooled to -30°C and water (10

mL) was added to destroy excess sodium borohydride. The resulting solution was then extracted with chloroform (3 × 20 mL) and the organic extracts were washed with water and brine and dried over magnesium sulfate. Concentration followed by column chromatography of the residue on silica gel (20% ethyl acetate in hexane) gave alcohol **146** (308 mg, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 2 H, OCH_2), 3.61 (br d, 1 H, *J* = 6 Hz, HOCH), 3.22 (s, 3 H, OCH_3), 3.14 (s, 3 H, OCH_3), 2.64 (d, *J* = 16 Hz, 1 H, CHHCOO), 2.55 (d, *J* = 16 Hz, 1 H, CHHCOO), 2.54 (s, 1 H, OH), 2.54 (ddd, *J* = 9.5, 6.5, 4.5 Hz, 1 H, H–1), 2.23 (dd, *J* = 13.5, 9.5 Hz, 1 H, H–7α), 2.16 (dd, *J* = 13.5, 4.5 Hz, 1 H, H–7β), 2.05 (d, *J* = 14 Hz, 1 H, CHH), 1.57 (dd, 1 H, *J* = 14, 1 Hz, CHH), 1.25 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 1.10 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.73 (s, C=O), 103.69 (s, $C(OMe)_2$), 81.20 (d, C–2), 60.12 (t, OCH_2), 56.16 (t, CH_2COO), 50.54 (q, OCH_3), 49.74 (q, OCH_3), 46.83 (s, C–5), 41.24 (s, C–3), 41.23 (d, C–1), 41.00 (t, C–4), 28.51 (q, CH_3), 27.85 (t, CH_2), 23.90 (q, CH_3), 14.41 (q, CH_3); FT–IR ($CHCl_3$) 3490 (OH), 3483 (OH), 1734 (C=O), 1466 cm^{-1}; HRMS M^+ 286.1781 (calcd for $C_{15}H_{26}O_5$ 286.1780); Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.90; H, 9.09. Found: C, 63.12; H, 9.21.

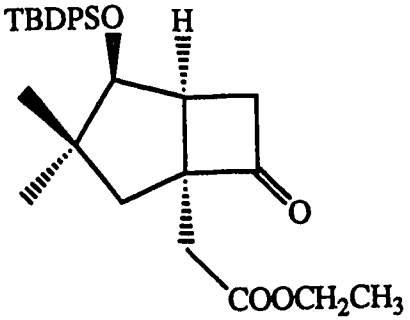
(1*S, 2*S**, 5*S**)–2–(*t*–Butyldiphenylsiloxy)–5–carboethoxymethyl–6,6–dimethoxy–3,3–dimethylbicyclo[3.2.0]heptane (147).**



To a stirred solution of alcohol **146** (105 mg, 0.37 mmol) in dry tetrahydrofuran (5 mL), was added *n*–BuLi (0.16 mL, 2.5 M in hexane, 0.40 mmol) at -78°C. The resulting mixture was stirred at the same temperature for 20 min under an atmosphere of argon. A solution of HMPA (3 mL) and THF (2 mL) was introduced and the resulting solution was stirred for 20 min at 0°C. *t*–Butyldiphenylchlorosilane (203 mg, 0.74 mmol) in THF (3 mL) was added to the reaction mixture at 0°C. After the mixture was stirred for 4 h at 0°C, TLC indicated that there was no more alcohol left in the reaction mixture. Saturated ammonium chloride (10 mL) was added and the mixture extracted with hexane–ether (1:1, 3 × 20 mL). The organic extracts were washed with water and saturated lithium chloride to remove HMPA and then dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (5% ethyl acetate in hexane as eluant) to afford the silyl ether **147** (165 mg, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, ArH), 7.40 (m, 6 H, ArH), 4.06 (d, J = 7 Hz, 1 H, CHOSi), 3.91 (m, 2 H, OCH_2), 3.11 (s, 3 H, OCH_3), 3.10 (s, 3 H, OCH_3), 2.59 (d, J = 15 Hz, 1 H, C**H**HCOO), 2.34 (d, J = 15 Hz, 1 H, CH**H**COO), 2.30 (dd, J = 13, 7 Hz, 1 H, H–7β), 2.15 (ddd, J = 10, 7, 7 Hz, 1 H, SiOC**H**CH), 2.14 (d, J = 15 Hz, 1 H, C**H**H), 1.89 (dd, J = 13, 10 Hz, 1 H, H–7α), 1.50 (d, J = 15 Hz, 1 H, CH**H**), 1.18 (s, 3 H, CH_3). 1.09 (t, J = 7 Hz, 3 H,

OCH_2CH_3), 1.08 (s, 9 H, 3 × CH_3), 0.82 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.65 (s, C=O), 136.11 (d, Ph), 136.01 (d, Ph), 134.68 (s, Ph), 134.37 (s, Ph), 129.57 (d, Ph), 127.46 (d, Ph), 127.42 (d, Ph), 101.38 (s, $C(OMe)_2$), 81.86 (d, CHOSi), 59.93 (t, OCH_2), 52.99 (s, C–5), 49.28 (q, OCH_3), 48.61 (q, OCH_3), 44.91 (s, C–3), 44.43 (t, CH_2COO), 42.09 (d, CH), 40.05 (t, C–7), 31.65 (q, CH_3), 28.93 (t, CH_2, C–4), 27.22 (q, $C(CH_3)_3$), 25.20 (q, CH_3), 19.59 (s, CMe_3), 14.25 (q, CH_3); FT–IR ($CHCl_3$) 1731 (C=O) and 1427 cm^{-1}; HRMS M^+ was not observed. Found for $(M–OMe)^+$ 493.2745 [calcd for ($C_{31}H_{44}O_5Si$–OMe) 493.2743]; FABMS M^+ 524.38 (calcd for $C_{31}H_{44}O_5Si$ 524.30); Anal. Calcd for $C_{31}H_{44}O_5Si$: C, 70.99; H, 8.40. Found: C, 70.83; H, 8.70.

(1*S, 2*S**, 5*S**)–2–(*t*–Butyldiphenylsiloxy)–5–carboethoxymethyl–3,3–dimethylbicyclo[3.2.0]heptan–6–one (148).**



A solution of ketal **147** (80 mg, 0.15 mmol) in acetic acid (3 mL), tetrahydrofuran (1 mL) and water (1 mL) was stirred at 40°C under an atmosphere of argon. After 7 h, TLC showed that the starting ketal was completely consumed. Water (5 mL) was added and the mixture extracted with chloroform (3 × 10 mL). The organic extracts were washed with water and

brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to afford ketone **148** (70 mg, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, ArH), 7.40 (m, 6 H, ArH), 4.12 (d, J = 8 Hz, 1 H, CHOSi), 4.01 (m, 2 H, OCH_2), 3.30 (dd, J = 18.5, 4.2 Hz, 1 H, H–7β), 2.90 (dd, J = 18.5, 10 Hz, 1 H, H–7α), 2.61 (d, J = 17 Hz, 1 H, C**H**HCOO), 2.46 (ddd, J = 10, 7.5, 4.2 Hz, 1 H, SiOCHC**H**), 2.30 (d, J = 17 Hz, 1 H, CH**H**COO), 1.92 (d, J = 14 Hz, 1 H, C**H**H), 1.30 (d, J = 14 Hz, 1 H, CH**H**), 1.15 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.10 (s, 9 H, 3 × CH_3), 1.06 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.74 (s, C=O, ketone), 170.62 (s, C=O, ester), 136.12 (d, Ph), 136.01 (d, Ph), 134.85 (d, Ph), 134.21 (s, Ph), 133.74 (s, Ph), 129.85 (d, Ph), 127.77 (d, Ph), 127.62 (d, Ph), 127.62 (d, Ph), 81.34 (d, CHOSi), 66.94 (t, O=CCH_2), 60.61 (t, OCH_2), 47.02 (t, CH_2COO), 46.34 (s, C-5), 43.15 (s, C–3), 40.13 (d, SiOCHCH), 38.73 (t, CH_2), 30.13 (q, CH_3), 27.20 (q, C(CH_3)$_3$), 23.61 (q, CH_3), 19.55 (s, CMe_3), 14.17 (q, CH_3); FT–IR ($CHCl_3$) 1780 (C=O, ketone), 1735 (C=O, ester) cm^{-1}; HRMS M^+ 478.2539 (calcd for $C_{29}H_{38}O_4Si$ 478.2540); Anal. Calcd for $C_{29}H_{38}O_4Si$: C, 72.80; H, 7.95. Found: C, 72.56; H, 7.86.

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CHAPTER II

CERIUM ESTER ENOLATES IN ORGANIC SYNTHESIS: ADDITION TO CARBONYL COMPOUNDS

INTRODUCTION

I. Historical Development and Preparation of Organocerium Reagents

The nucleophilic addition of the Grignard or organolithium reagents to carbonyl compounds is undoubtedly one of the most fundamental and versatile reactions in synthetic organic chemistry and has wide synthetic applications.[1] However, it is also well recognized that the addition of the Grignard or organolithium reagents to carbonyl compounds is often accompanied by so–called abnormal reactions such as enolization, conjugate addition, reduction and condensation. In some cases, such abnormal reactions prevail over normal addition, resulting in very poor yields of the desired products.

It is synthetically important to enhance the yields of normal addition products and eliminate any abnormal reactions. For several years, Imamoto and his collaborators have been interested in this important synthetic problem and have deveioped a new method which is highly effective in circumventing the abnormal reactions and also has broad synthetic applicability. They discovered that organocerium(III) reagents could be prepared by transmetallation reaction of the corresponding organolithium or the Grignard reagents with anhydrous cerium(III) chloride. The derived organocerium(III) reagents showed strong reactivities towards carbonyl compounds by coordinating to the carbonyl oxygen more strongly than lithium or other elements. Organocerium reagents could add efficiently to various carbonyl compounds including highly enolizable and sterically hindered ketones to which the corresponding organolithium or Grignard reagents fail to add. In addition, unlike normal organolithium or

Grignard reagents, organocerium reagents add to α,β–unsaturated carbonyl compounds preferentially in 1,2–addition fashion.

(1) Organocerium(III) Reagents Derived from Organolithium Reagents

(a) Addition to Saturated Carbonyl Compounds

In 1982, Imamoto *et al.*[2] reported, for the first time, the generation and reactivities of organocerium(III) reagents. Initial generation of organocerium reagents occurred *via* transmetallation of *n*–butyllithium (or RLi) with cerium(III) iodide, prepared *in situ* by the reaction of cerium metal with iodine in THF from 0°C to 25°C. In a typical procedure, *n*–butyllithium (or RLi) was added at -65°C to a slurry of cerium(III) iodide in THF under an argon atmosphere and the resulting suspension was vigorously stirred at -65°C for 30 min (Eq. 1).

$$RLi + CeI_3 \xrightarrow[-65°C]{THF} RCeI_2 + LiI \qquad [1]$$

Reaction of ketones with the derived organocerium reagents proceeded very readily at -65°C and the desired alcohols were obtained in excellent yields (Table II–1) even though the substrates were readily subjected to enolization or possessed halogen atoms in vinylic positions. These results were in sharp contrast to those obtained by the use of organolithium reagents, in that the yields of products were remarkably lowered due to competitive enolization or metal–exchange. The most striking example was the addition of *n*–butylcerium dichloride to *p*–iodoacetophenone in which a quantitative yield of the alcohol

was isolated. However, use of *n*–butyllithium did not give rise to any desired product, nor was the starting material recovered, probably due to metal halogen exchange. In the case of 1,3–diphenyl–2–propanone, *n*-butylcerium added to the ketone to give the desired alcohol in excellent yield, whereas *n*–butyllithium furnished the alcohol only in 33% yield along with a 61% recovery of the starting material, probably owing to competitive enolization. Obviously, the organocerium reagents exhibited higher reactivities towards ketones than the corresponding organolithium reagents.

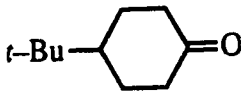
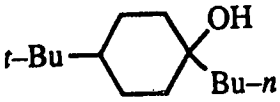
Table II–1. The Reaction of CeI_3–RLi or RLi Reagents with Ketones

Reagent	Ketone	Product	Yield (%)
n–BuLi–CeI_3	Bn_2CO	$Bn_2C(OH)Bu$–*n*	98
n–BuLi	Bn_2CO	$Bn_2C(OH)Bu$–*n*	36
n–BuLi–CeI_3	*p*–IPhCOMe	*p*–IPhC(OH)MeBu–*n*	99
n–BuLi	*p*–IPhCOMe	*p*–IPhC(OH)MeBu–*n*	0
s–BuLi–CeI_3	PhCOMe	PhC(OH)MeBu–*s*	98
s–BuLi	PhCOMe	PhC(OH)MeBu–*s*	53

In 1984, Imamoto *et al.*[3] examined the use of commercially available lanthanoid chlorides ($CeCl_3 \cdot 7H_2O$, $LaCl_3 \cdot 7H_2O$, $NdCl_3 \cdot 6H_2O$, $PrCl_3 \cdot 7H_2O$, $SmCl_3 \cdot 6H_2O$, $YbCl_3 \cdot 6H_2O$). These hydrated salts were dried *in vacuo* at 140°C for 2 h and the dried $LnCl_3$ was vigorously stirred in THF at 25°C for 2 h, then treated with *n*–butyllithium (1.0 equiv.) at -78°C. And, the resulting

reagents were subjected to reaction with carbonyl compounds. As shown in Table II–2, excellent results were obtained for cerium chloride, lanthanum chloride, neodymium chloride and ytterbium chloride, while the use of praseodymium chloride and samarium chloride resulted in relatively low yields probably owing to insufficient dehydration of the salts. Screening of the lanthanoid salts suggests that cerium trichloride ($CeCl_3$) is the best for the reaction as it is readily available at a moderate price and its anhydrous salt can be easily obtained.

Table II–2. The Reaction of *n*–BuLi–$LnCl_3$ with Carbonyl Compounds

Reagent	Ketone	Product	Yield (%)
n–BuLi–$CeCl_3$	$(PhCH_2)_2CO$	$(PhCH_2)_2C(OH)Bu$–*n*	96
n–BuLi–$LaCl_3$	$(PhCH_2)_2CO$	$(PhCH_2)_2C(OH)Bu$–*n*	96
n–BuLi–$NdCl_3$	$(PhCH_2)_2CO$	$(PhCH_2)_2C(OH)Bu$–*n*	98
n–BuLi–$PrCl_3$	$(PhCH_2)_2CO$	$(PhCH_2)_2C(OH)Bu$–*n*	85
n–BuLi–$SmCl_3$	$(PhCH_2)_2CO$	$(PhCH_2)_2C(OH)Bu$–*n*	60
n–BuLi–$YbCl_3$			97

The facile addition of the *n*–BuLi–$CeCl_3$ reagent observed for other carbonyl compounds (Table II–3) also indicated the high reactivity of organocerium reagent towards carbon–oxygen double bond. These characteristic reactivities of organocerium reagents are mainly ascribed to low basicity of the reagents and a strong affinity of trivalent cerium for oxygen atom.

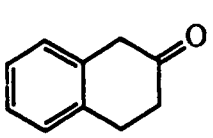
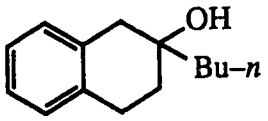
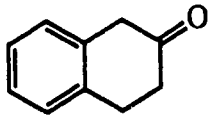
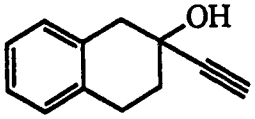
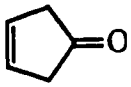
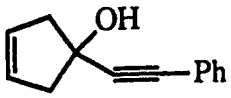
Table II–3. The Reaction of *n*–BuLi–$CeCl_3$ Reagent with Carbonyl Compounds

Ketone	Product	Yield (%)
o–MeOPhCHO	*o*–MeOPhCH(OH)Bu–*n*	97
hCOMe	PhC(OH)MeBu–*n*	98
p–BrPhCOMe	*p*–BrPhC(OH)MeBu–*n*	96
p–MeOPhCOMe	*p*–MeOPhC(OH)MeBu-*n*	99

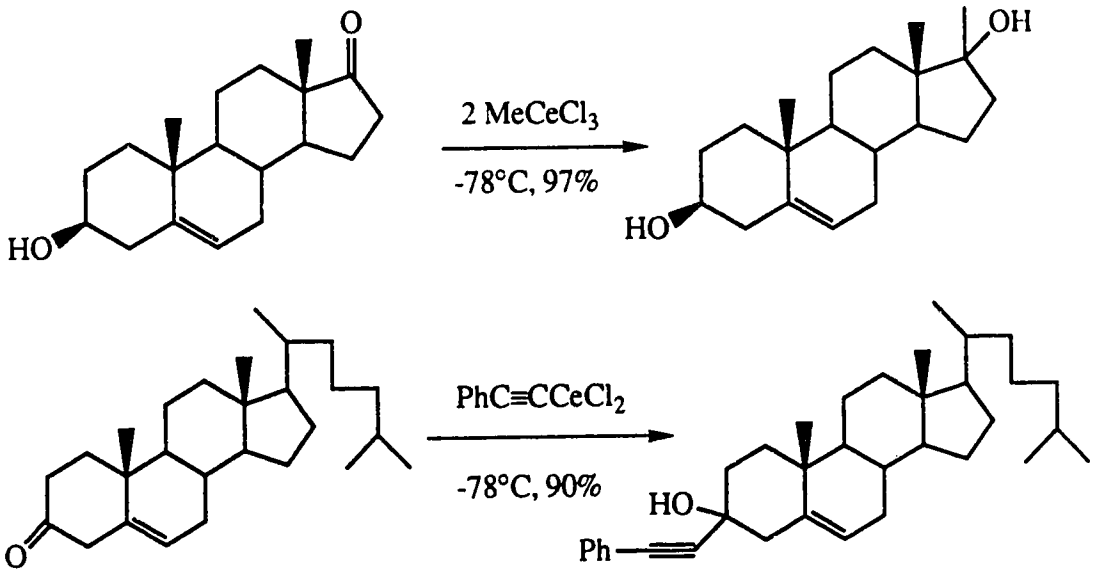
(b) Addition to Highly Enolizable Ketones

Imamoto and his collaborators[4] also discovered that organocerium reagents could react cleanly with easily enolizable ketones at -78°C, affording the addition products in good yields (Table II–4). On the other hand, use of the corresponding Grignard or organolithium reagents resulted mainly in the formation of enolates, owing to the strong basicity of these reagents. One of the most striking examples was shown in the reaction of *p*–$BrPhCOCH_2Br$ which is extremely enolizable. Treatment of this α–bromoketone with an alkynylcerium reagent gave the desired alcohol in 95% yield, while the corresponding organolithium reagent did not afford a trace amount of the addition product. It can be concluded that the cerium(III) reagents are distinctly less basic than the Grignard or lithium counterparts, and that they possess a pronounced affinity for the carbonyl group. Moreover, not only alkyl, but also alkenyl and alkynyl organocerium reagents could be prepared and their reactions with enolizable ketones also gave excellent yields of alcohols.

Table II–4. Comparison of the Reactivity of Organocerium, Grignard, and Organolithium Reagents with Readily Enolizable Ketones

Ketone	Reagent	Product	Yield (%)
$(PhCH_2)_2CO$	*n*–$BuCeCl_2$	$(PhCH_2)_2C(OH)Bu$–*n*	96
$(PhCH_2)_2CO$	*n*–BuMgBr	$(PhCH_2)_2C(OH)Bu$–*n*	10
$(PhCH_2)_2CO$	$HC{\equiv}CCeCl_2$	$(PhCH_2)_2C(OH)C{\equiv}CH$	95
$(PhCH_2)_2CO$	$HC{\equiv}CLi$	$(PhCH_2)_2C(OH)C{\equiv}CH$	60
	*n*–$BuCeCl_2$		88
	n–BuMgBr		6
	$HC{\equiv}CCeCl_2$		89
	$HC{\equiv}CLi$		10
	$PhC{\equiv}CCeCl_2$		89
	$PhC{\equiv}CLi$		30
p–$BrPhCOCH_2Br$	$PhC{\equiv}CCeCl_2$	*p*–$BrPhC(OH)(CH_2Br)C{\equiv}Ph$	95
p–$BrPhCOCH_2Br$	$PhC{\equiv}CLi$	*p*–$BrPhC(OH)(CH_2Br)C{\equiv}Ph$	0

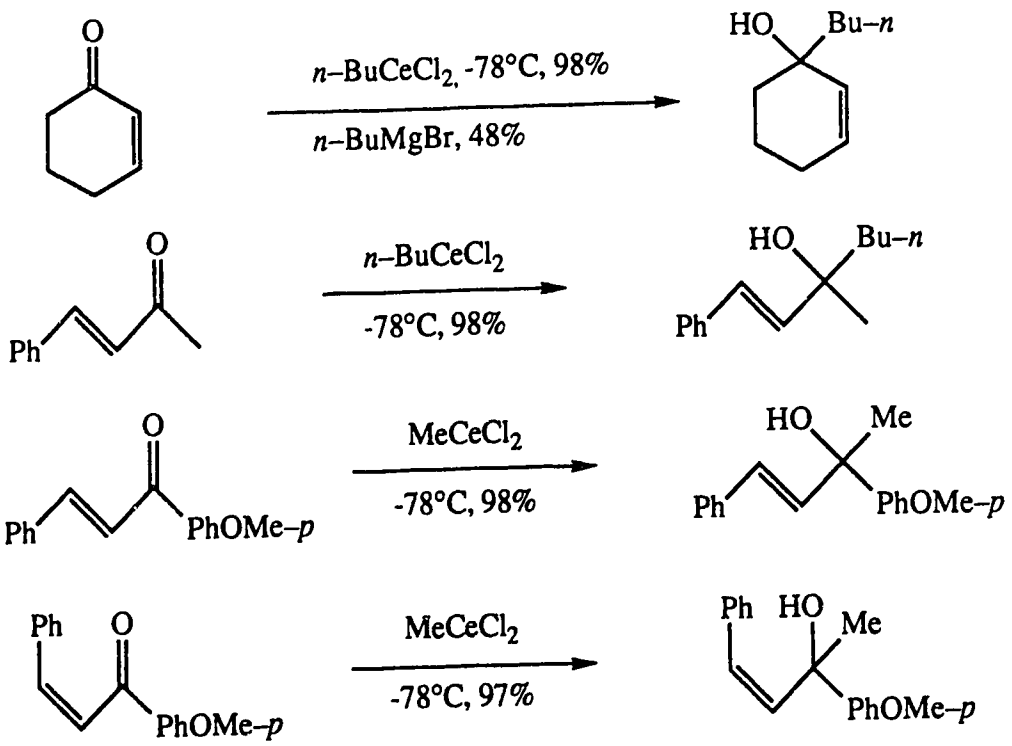
The additions of organocerium reagents to a few steroids possessing an enolizable functionality such as in cyclopentanone or β,γ–enone moiety were also examined (Eq. 2). For example, treatment of dehydroisoandrosterone with methylcerium reagent gave rise to 17–methyl–5–androstene–3,17–diol in almost quantitative yield. This result was superior to that obtained by the use of methylmagnesium iodide (65% yield).



[2]

(c) Addition to α,β–Unsaturated Carbonyl Compounds

It is well established that α,β–unsaturated ketones can be regioselectively reduced by $NaBH_4$ in the presence of $CeCl_3$ to give 1,2–reduction product and this methodology has been widely employed for the preparation of allylic alcohols.[5] This observation coupled with the low basicity and strong carbonylophilicity of organocerium(III) reagents prompted Imamoto *et al.*[6] to study the addition of organocerium reagents to α,β–enones. In 1985, they observed that organocerium(III) reagents reacted with α,β–unsaturated carbonyl compounds to afford 1,2–addition products with higher regioselectivity in comparison with the corresponding organolithium or Grignard reagents. In most cases, exclusive formation of the 1,2–addition product was observed (Eq. 3).



[3]

The *n*–butylcerium reagent reacted cleanly with α,β–enones, such as 2–cyclohexenone and 4–phenyl–3–buten–2-one, in THF at -78°C to afford the corresponding allylic alcohols in essentially quantitative yields. On the other hand, reaction of *n*–BuMgBr with 2–cyclohexenone produced 1,2– and 1,4–addition products in 48% and 21% yields, respectively. α,β–Enones conjugated with an aryl group are known to be readily susceptible to 1,4–addition with Grignard reagents. However, excellent 1,2–regioselectivities of organocerium reagents towards (*E*)– and (*Z*)–1–(*p*–methoxyphenyl)–3–phenyl–2–propen–1–one were also achieved. These results were in contrast to those obtained by means of the Grignard or organolithium reagents, in which considerable amounts of 1,4–addition products were produced.

(2) Organocerium Reagents Derived from the Grignard Reagents

(a) Additions to Saturated Ketones Including Enolizable Ketones

Similar to the organocerium reagents derived from RLi–$CeCl_3$ system, organocerium reagents prepared from the Grignard reagents and $CeCl_3$ also showed excellent nucleophilicity and reacted readily with ketones at 0°C to give the corresponding tertiary alcohols.

Imamoto *et al.*[7, 8] systematically studied the effects of solvents and molar ratios of cerium trichloride using 1,3–diphenyl–2–propanone as a substrate (Table II–5). Without the addition of cerium chloride, the product was formed in 18–36% yield and a large amount of ketone was recovered. This result was ascribed to the strong basicity of the Grignard reagent and the nature of the ketone, which was prone to enolization in the presence of base. The yield of the alcohol was significantly improved by the use of cerium chloride. The reagent (*n*–BuMgBr–$CeCl_3$) with a molar ratio of 1:1 afforded the addition product in almost quantitative yield. The use of less amounts of cerium chloride decreased the yield of the product; no catalytic activity of cerium chloride was observed. The choice of the solvent was also important. THF or a mixed solvent system of THF and diethyl ether provided higher yields, while the reaction in diethyl ether alone resulted in lower yields. The cerium chloride promoted Grignard addition can be carried out at 0°C. On the other hand, the addition of organocerium reagents, prepared from organolithium reagents, to ketones must be carried out at low temperature (-78°C).

Table II–5. Reactions of 1,3–Diphenyl–2–propanone with *n*–BuMgBr–$CeCl_3$ Reagent System

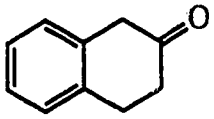
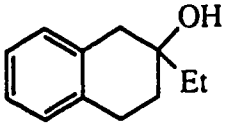
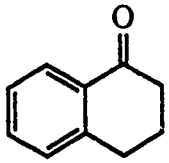
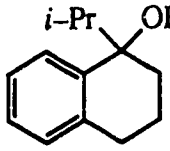
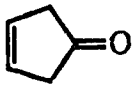
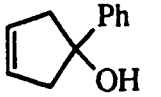
$$(PhCH_2)_2CO \xrightarrow{n\text{–BuMgBr / } CeCl_3} (PhCH_2)_2C(OH)Bu\text{–}n$$

Reagent	Conditions	Yield (%)
n–BuMgBr	THF, 0°C	18–36
n–BuMgBr/$CeCl_3$ (1:1)	THF, 0°C	98
n–BuMgBr/$CeCl_3$ (1:0.5)	THF, 0°C	84
n–BuMgBr/$CeCl_3$ (1:0.1)	THF, 0°C	21
n–BuMgBr/$CeCl_3$ (1:1)	THF/Et_2O (4:1), 0°C	91
n–BuMgBr/$CeCl_3$ (1:1)	Et_2O, 0°C	45
n–BuLi/$CeCl_3$ (1:1)	THF, -78°C	96
n–BuLi/$CeCl_3$ (1:1)	THF, 0°C	28

The reactions of various ketones with RMgBr–$CeCl_3$ reagents were also examined. As shown in Table II–6, the addition of Grignard reagent to ketone is significantly enhanced by $CeCl_3$. The reaction of 3,3–diethyl–2–pentanone with MeMgBr is a typical example. The reaction without $CeCl_3$ afforded not even a trace of the addition product; deprotonation occurred almost exclusively. In sharp contrast, the reaction in the presence of $CeCl_3$ provided the adduct in 95% yield. Even easily enolizable ketones were found to undergo facile nucleophilic addition with RMgX–$CeCl_3$ reagents. For example, 1,3–diphenyl–2–propanone and α–tetralone reacted with various Grignard reagents in the presence of $CeCl_3$ to give the corresponding alcohols in satisfactory yields.

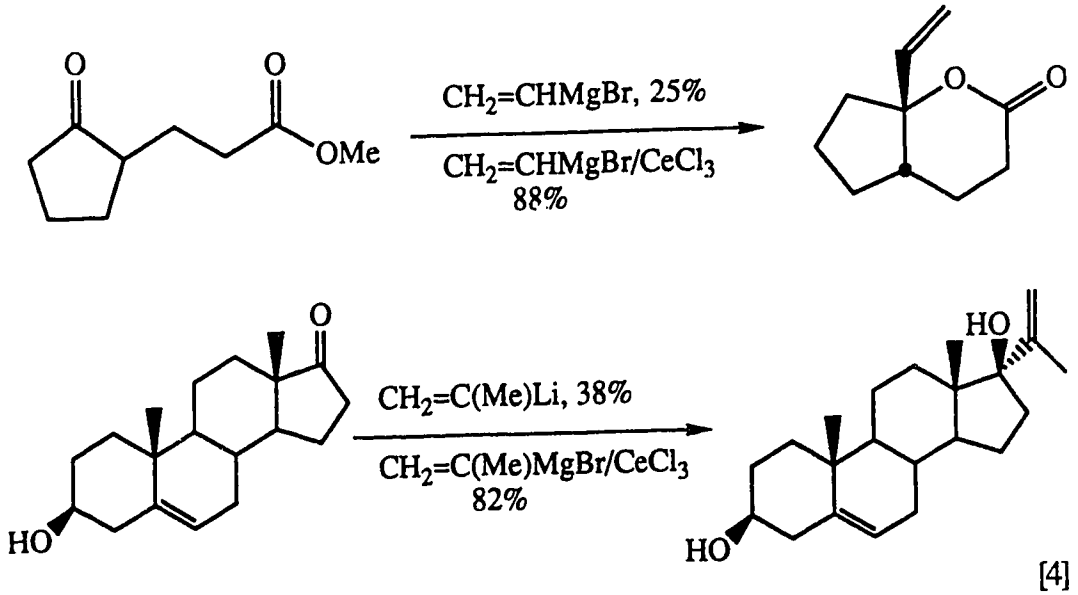
Furthermore, contrary to the general recognition that the *t*–butyl Grignard reagent acts as a good reducing agent rather than a nucleophile, the corresponding cerium reagent (*t*–BuMgCl–$CeCl_3$) was shown to undergo addition reaction with 1,3–diphenyl–2–propanone to provide a satisfactory yield of the adduct.

Table II–6. Reactions of Carbonyl Compounds with Grignard Reagents With or Without $CeCl_3$

Ketone	[illegible]	Product	Yield (%)
Et_3CCOMe	[illegible]	$Et_3CC(OH)Me_2$	0
Et_3CCOMe	$MeMgBr–CeCl_3$	$Et_3CC(OH)Me_2$	95
	EtMgCl		8
	$EtMgCl–CeCl_3$		76
	*i*–PrMgCl		15
	i–$PrMgCl–CeCl_3$		73
	PhMgBr		47
	$PhMgBr–CeCl_3$		93
Bn_2CO	*t*–BuMgCl	$Bn_2C(OH)Bu–t$	0
Bn_2CO	*t*–$BuMgCl–CeCl_3$	$Bn_2C(OH)Bu–t$	67

Imamoto *et al.* used $RMgX–CeCl_3$ reagents to effect the preparation of several key synthetic precursors of natural products. The $RMX–CeCl_3$ reagents were

shown to be much more effective than the corresponding Grignard or organolithium reagents (Eq. 4).



[4]

(b) Additions to α,β–Unsaturated Ketones

The addition of RMgX–$CeCl_3$ reagent system to enones also exhibited high regioselectivity to afford 1,2–addition products,[7, 8] while the Grignard reagents always afforded a mixtures of 1,2– and 1,4–addition products. As shown in Table II–7, most of the reactions in the presence of cerium chloride gave rise to 1,2–adducts in higher yields than those of the Grignard reagents alone. In some cases, the reaction of Grignard reagent with ketone afforded 1,4–addition product predominantly.

Table II-7. Reactions of α, β–Enones with RMgX–$CeCl_3$ Reagents and Grignard Reagents

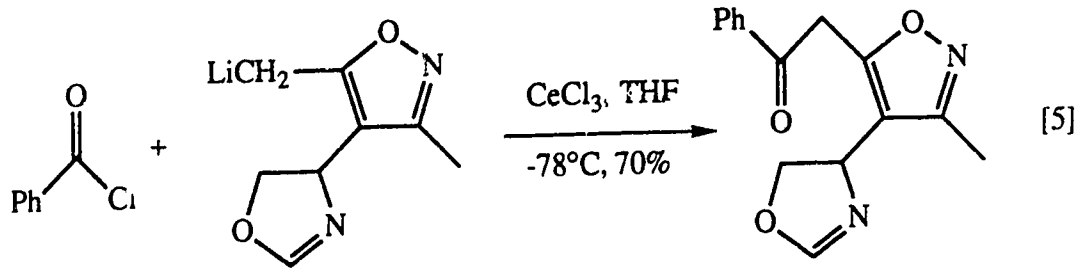
α,β–Enone	Reagent	Yield (%) 1,2–adduct	Yield (%) 1,4–adduct
PhCH=CHCOPh	PhMgBr	5	81
PhCH=CHCOPh	PhMgBr–$CeCl_3$	89	11
PhCH=CHCOMe	*i*–PrMgCl	12	53
PhCH=CHCOMe	*i*–PrMgCl–$CeCl_3$	91	5
(Z)–PhCH=CHCOPh	PhMgBr	15	83
(Z)–PhCH=CHCOPh	PhMgBr–$CeCl_3$	90	10

In summary, anhydrous cerium chloride ($CeCl_3$) significantly promotes additions of the organolithium or Grignard reagents to carbonyl compounds with a remarkable suppression of abnormal reactions. Organocerium reagents are of low basicity and show strong carbonylophilicity. Moreover, the additions of organocerium reagents to enone system always exhibited excellent 1,2–regioselectivity, whereas organolithium or Grignard reagents showed relatively low selectivity. All these characteristics make the organocerium reagents very useful in organic synthesis. Within several years, cerium(III) mediated reagents have been extensively applied in synthetic organic chemistry and a great number of key intermediates to biologically active natural products have been prepared by the use of organocerium reagents.

(II) Synthetic Applications of Organocerium Reagents

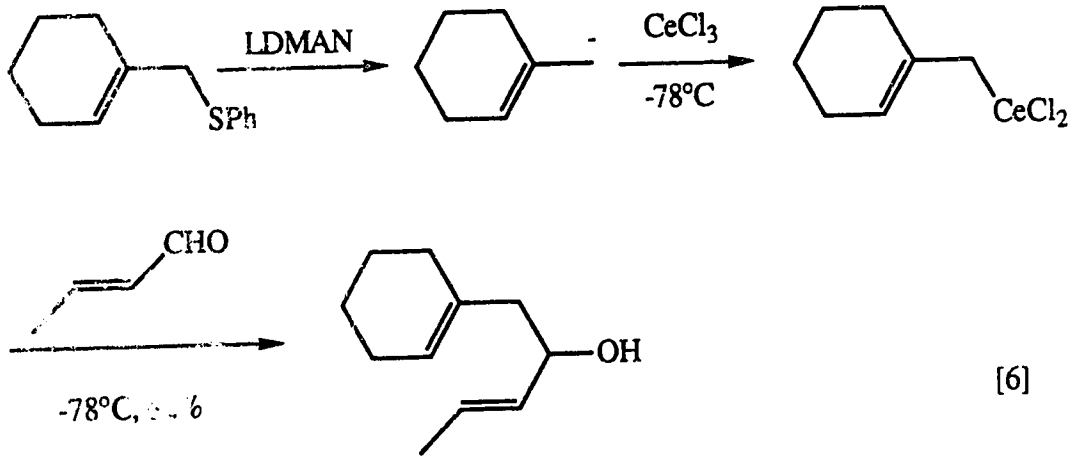
(1) Alkyl Organocerium Reagents

In 1986, Natale *et al.*[9] prepared various β–keto isoxazoles by the reaction of lithio alkylisoxazoles with an acid chloride in the presence of cerium trichloride (Eq. 5).



[5]

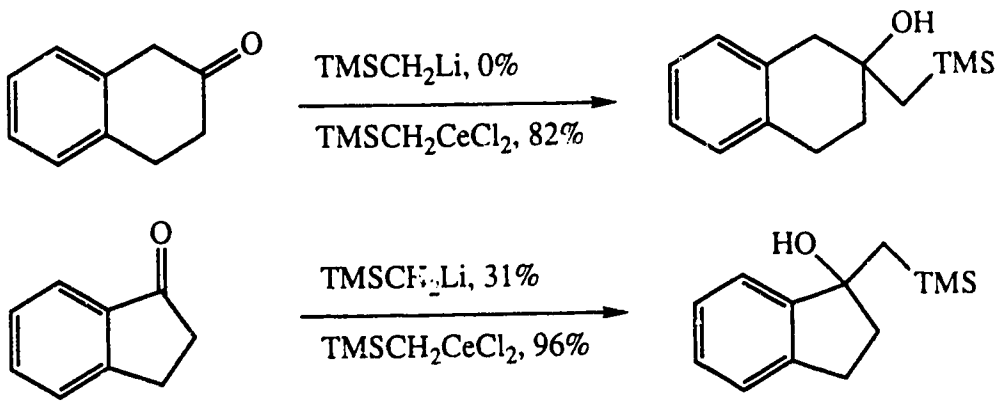
In 1987, Cohen *et al.*[10] described a simple procedure for the generation of allylcerium(III) reagent, which reacted with aldehydes predominantly at the least sterically hindered terminus to produce homoallylic alcohols with high regiochemical control (Eq. 6).



[6]

The Peterson methylenation procedure has many redeeming points, yet its utility in synthesis is often limited by high basicity and lack of chemoselectivity

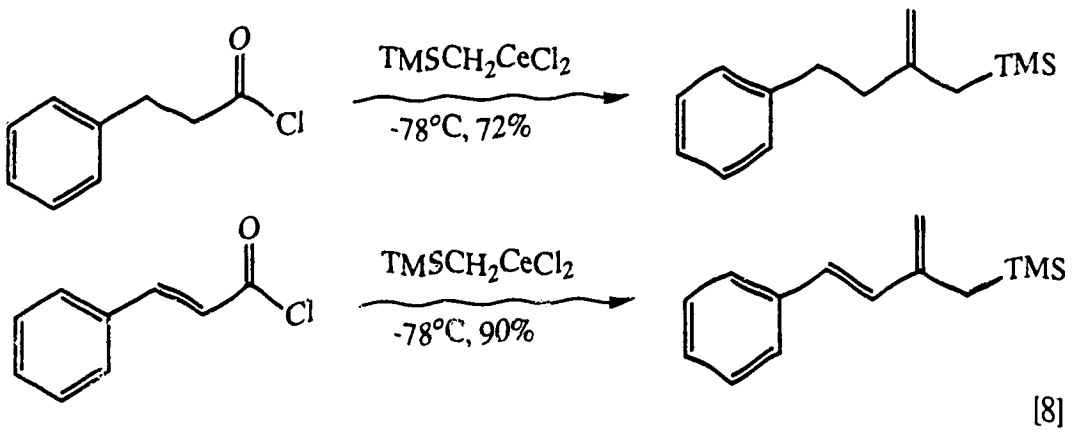
of the lithium reagent. Johnson *et al.*[11] has modified the Peterson reaction by means of organocerium reagents (Eq. 7).



[7]

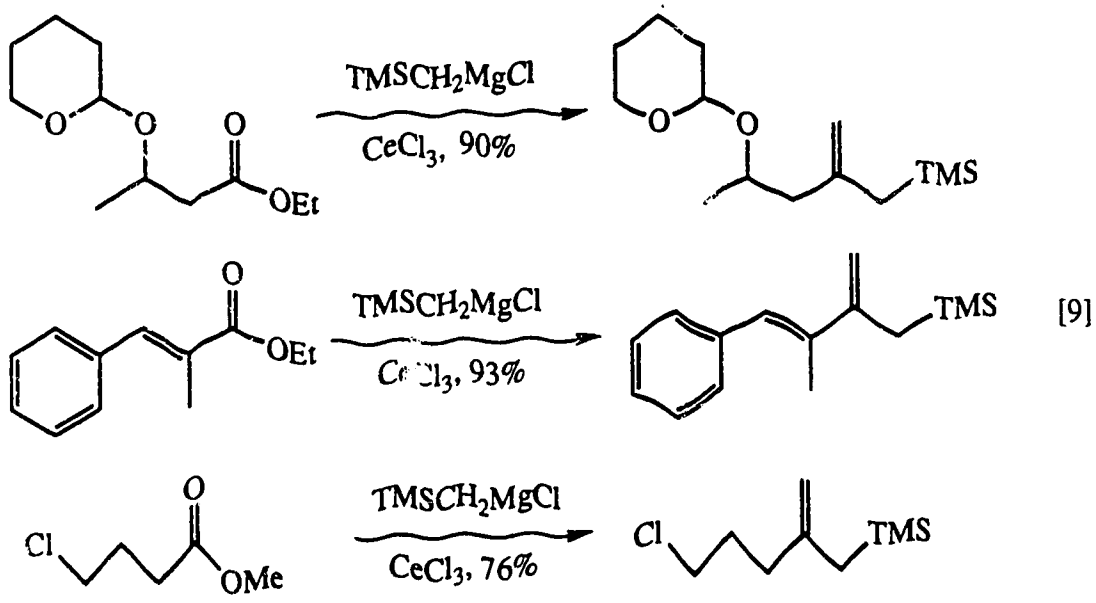
Allylsilanes are exceptionally versatile compounds with well established utility in organic synthesis. The addition of two equivalents of α–trimethylsilylmethyl metal reagent to a carboxylic acid derivative followed by Peterson olefination to prepare an allylsilane is a known process. Unfortunately, this method is highly substrate dependent; more sterically congested esters failed to undergo the second addition due to preferential enolization of the α–silyl ketone intermediate to yield the α–silyl enolate.

The nucleophilic organocerium reagents having the properties of high oxophilicity and reduced basicity offered the possibility of an expedient solution to the enolization problem. In 1987, Fuchs *et al.*[12] reported a new approach to allylsilanes based on addition of the organocerium reagent ($TMSCH_2Li$–$CeCl_3$) to acyl chlorides (Eq. 8). In all cases examined, organocerium reagents provided allylsilanes in good yields. However, use of the organolithium or Grignard reagents only afforded low yields of allylsilanes.



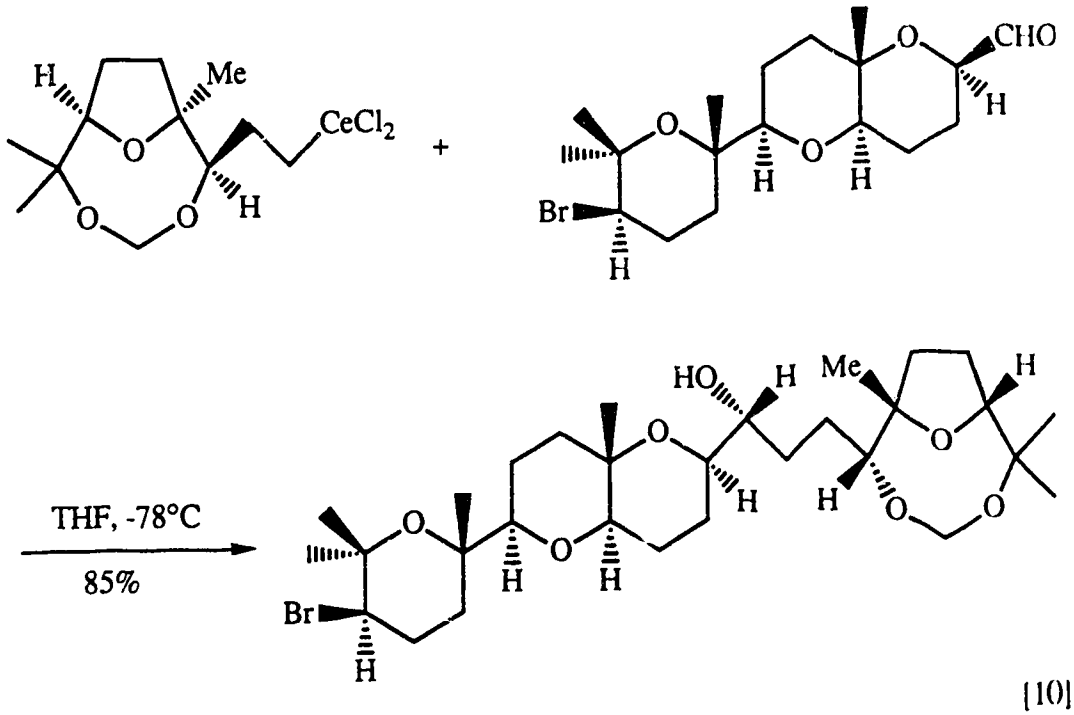
[8]

In the same year, Bunnelle *et al.*[13] also observed that reaction of esters with $TMSCH_2MgCl$–$CeCl_3$ reagent system in THF resulted in efficient formation of allylsilanes (Eq. 9). It should be pointed out that the organocerium reagent derived from $TMSCH_2Li$–$CeCl_3$ was effective towards acyl chloride, whereas the organocerium reagent from the $TMSCH_2MgCl$–$CeCl_3$ system was effective towards esters. Lee *et al.*[14, 15] found that $TMSCH_2MgCl$–$CeCl_3$ chemoselectively added to ester groups in the presence of other functionalities (Eq. 9).



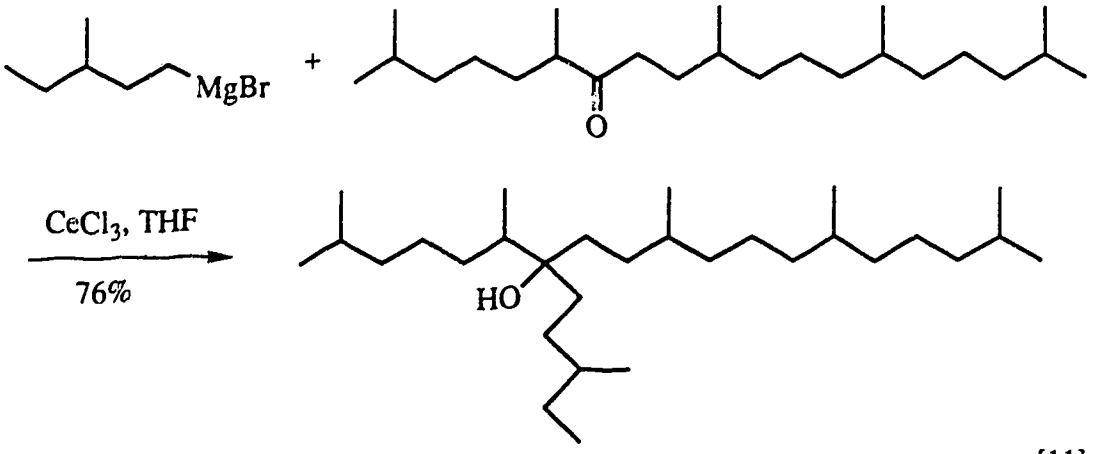
[9]

Corey and Ha[16] utilized a cerium mediated nucleophilic addition to a chiral aldehyde successfully without epimerizing the adjacent chiral center to assemble the skeleton of venustatriol (Eq. 10). The alcohol was isolated in satisfactory yield and with high stereoselectivity.



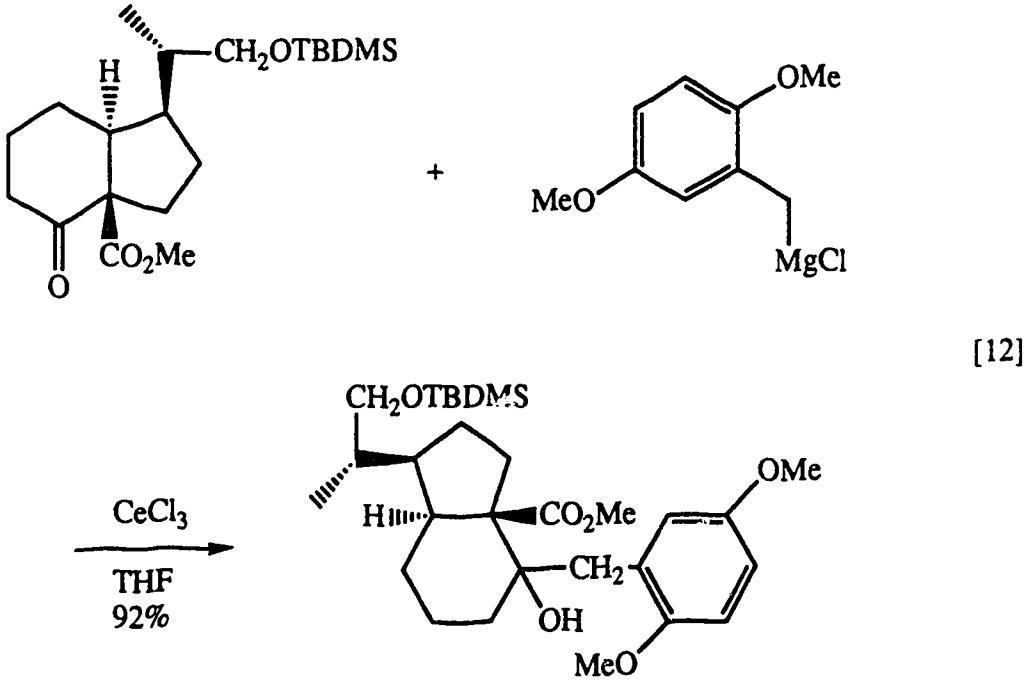
[10]

Organocerium reagents have also been used by Rowland *et al.*[17] in 1988 in the synthesis of a highly branched C_{30} sedimentary hydrocarbon. Coupling of the ketone with a Grignard reagent in the presence of cerium chloride produced the alcohol in 76% yield compared to 2% yield without $CeCl_3$ (Eq. 11).



[11]

The following cerium(III) mediated Grignard addition to a sterically hindered ketone was applied by Hart *et al.*[18] in the synthesis of (±)–pleurotin and (±)–dihydropleurotin acid (Eq. 12).

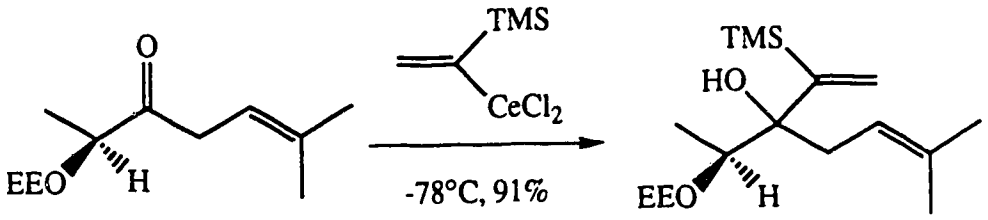


[12]

(2) Alkenyl Organocerium Reagent

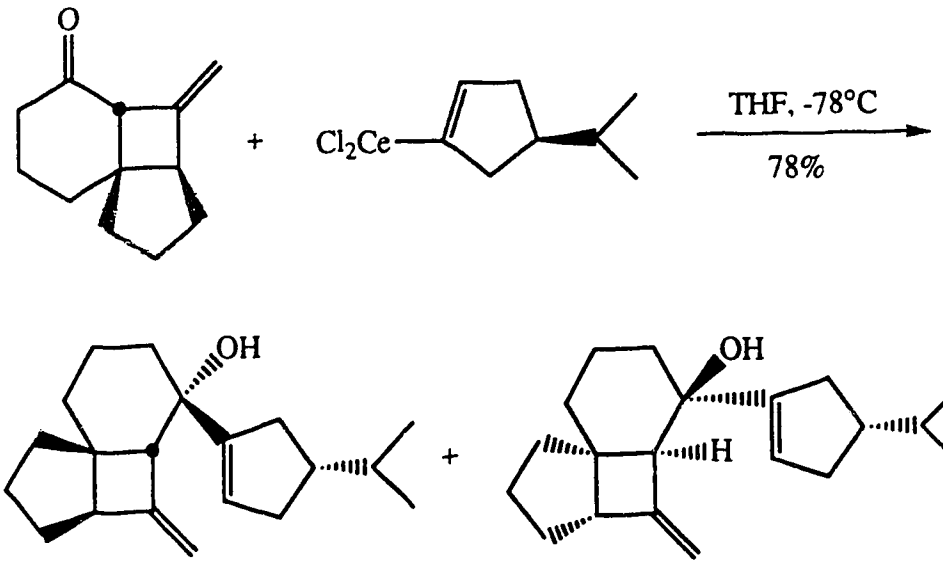
Alkenyl organocerium reagents also exhibit high reactivity towards carbonyl compounds. Their wide synthetic applications are evidenced by the preparation of key intermediates for many natural products.

In the enantio– and diastereo–controlled synthesis of a chiral pheromone, alkenylcerium(III) reagent was applied in 1985 by Tsuchiashi *et al.*[19] to introduce the vinylsilane moiety. The same transformation using the corresponding organolithium or Grignard reagents was unsatisfactory due to the highly enolizable nature of the ketone (β,γ–enone) (Eq. 13).



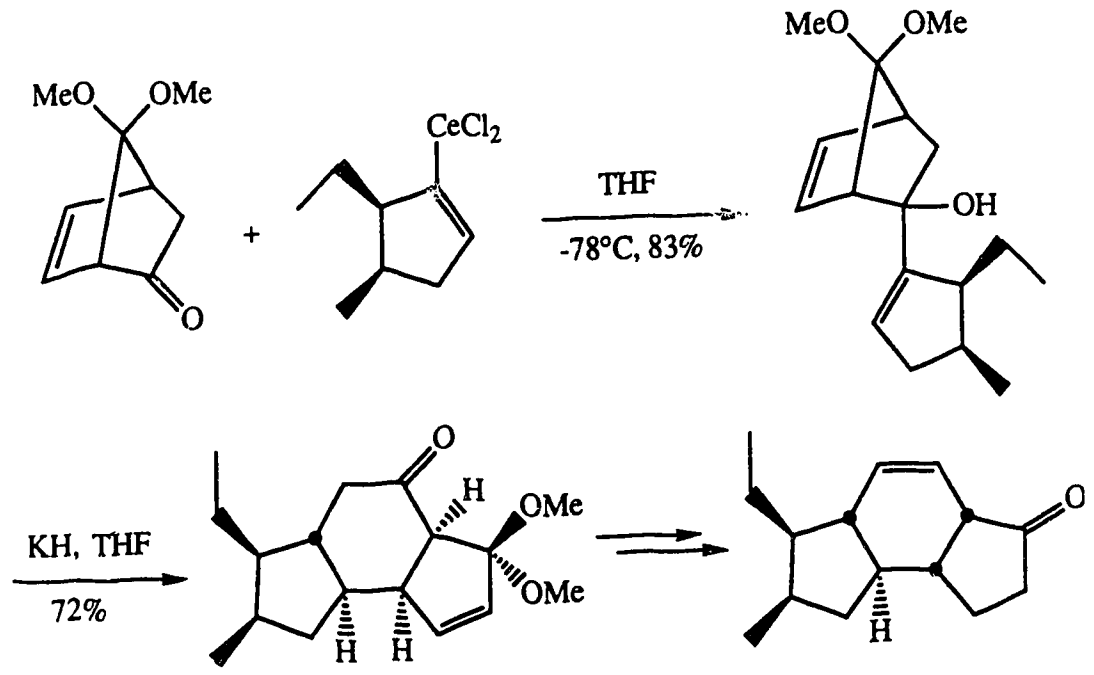
[13]

Paquette and his coworkers[20–29] have extensively investigated the anionic oxy–Cope rearrangement for the asymmetric induction of C–C bonds. The requisite intermediates were normally produced by the efficient nucleophilic addition of alkenylcerium reagents to β,γ–unsaturated ketones. Paquette *et al.* also noticed that the π–facially controlled nucleophilic additions of chiral alkenyl organocerium to chiral β,γ–unsaturated ketones proceeded in an excellent double diastereoselective manner (Eq. 14). However, use of the corresponding organolithium or Grignard reagents afforded only low yields of the alcohols.



[14]

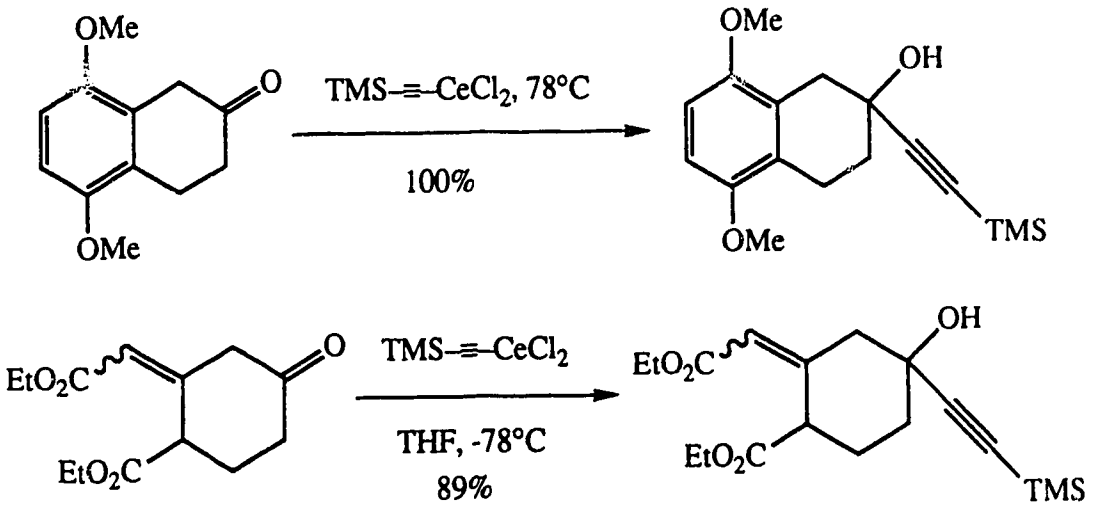
Paquette *et al.*[30] applied this asymmetric synthesis methodology to the preparation of a principal subunit of the ikarugamycin structure (Eq. 15).



[15]

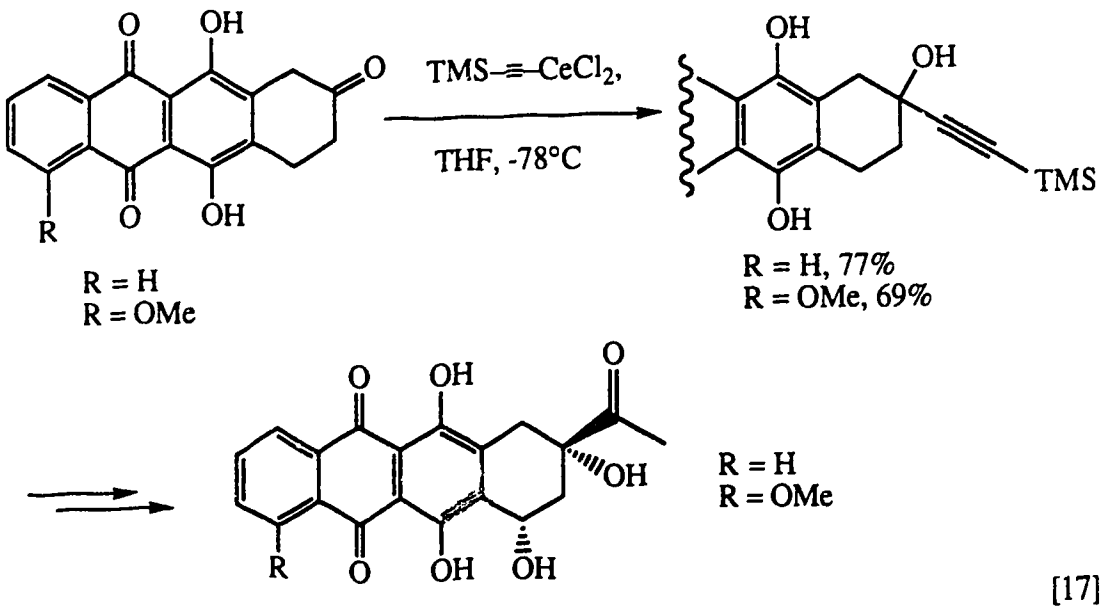
(3) Alkynyl Organocerium Reagent

Both Terashima[19, 31] and Tamura[32–36] developed novel ethynylcerium reagents as efficient tools for constructing the α–hydroxy methyl ketone unit of several key synthetic intermediates of natural and unnatural anthracyclinones with anticancer activity. They found that 2–trimethylsilylethynylcerium(III) dichloride could react with highly enolizable ketones such as β–tetralone very efficiently, providing addition products in excellent yields (Eq. 16). However, use of the corresponding organolithium, Grignard reagents led to unsatisfactory yields due to inefficient nucleophilicity of the reagents and the nature of the ketones (enolization).



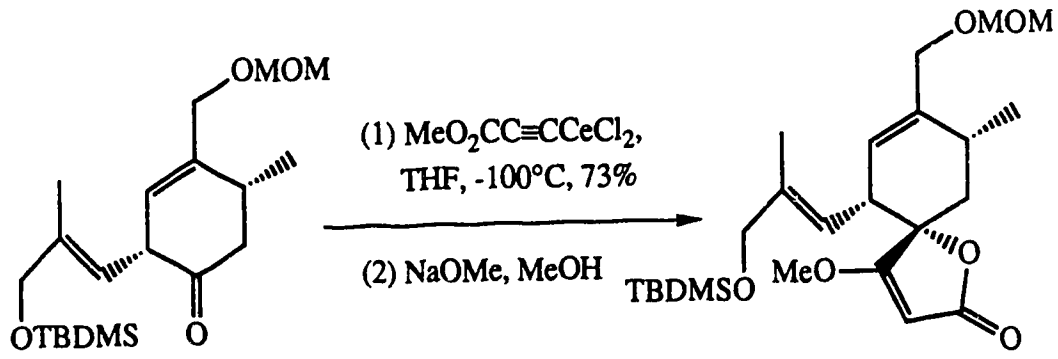
[16]

Tamura *et al.* extensively applied this alkynylcerium reagent in the syntheses of antitumor agents such as 4–demethoxy–11–deoxy–daunomycin, 11–deoxydaunomycin, daunomycinone and their analogues (Eq. 17).



[17]

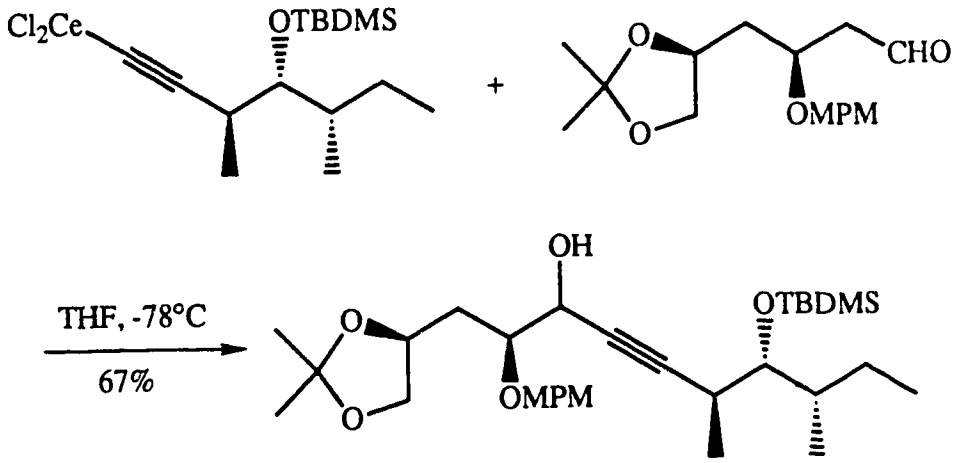
In the synthesis of (±)–28,29–bisnorkijanolide, Yoshii[37] in 1988 employed the acetylenic organocerium reagent, dichlorocerium methoxycarbonylacetylide, which added to a highly epimerizable β,γ–unsaturated ketone in good yield for the construction of the key intermediate spirotetronate (Eq. 18).



[18]

In the course of the enantioselective synthesis of avermectin, White *et al.*[38] applied the alkynylcerium reagent whose addition to aldehyde was used as one of the key transformations (Eq. 19). However, the corresponding lithium

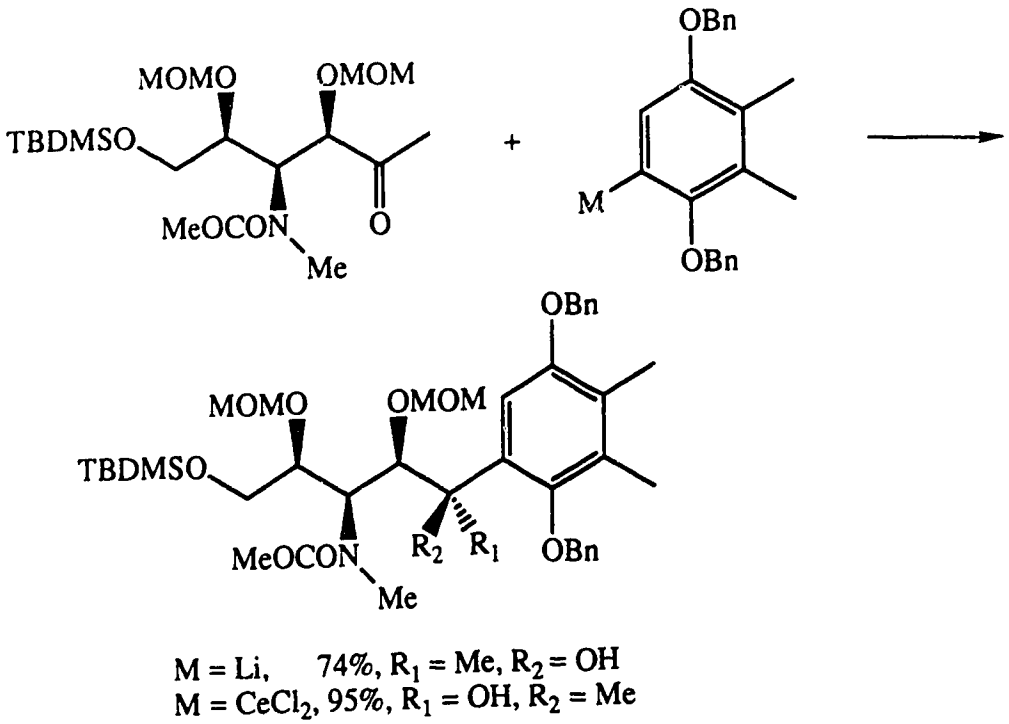
acetylide only gave a poor yield of the alcohol probably due to the elimination of the OMPM group which is β to aldehyde.



[19]

(4) Aryl Organocerium Reagent

It is interesting to note that organocerium and organolithium reagents do not necessarily give the same stereochemistry upon addition to a carbonyl group which is part of a chiral molecule. Terashima *et al.*[39] noticed that nucleophilic addition of related aryllithium and arylcerium compounds to a chiral open-chain ketone occurred in the opposite manner (Eq. 20). This addition constituted a key step to diastereoselectively construct the desired chiral center in the total synthesis of the DEF-ring system of nogalamycin, an antitumor antibiotic of the anthracycline family. These results were rationalized by assuming a strong intramolecular coordination between cerium and the adjacent benzyl ether, whereas lithium prefers to coordinate to a THF molecule. Accordingly, the addition with arylcerium seems to proceed through the transition state corresponding to the Felkin-Anh model.[40, 41]

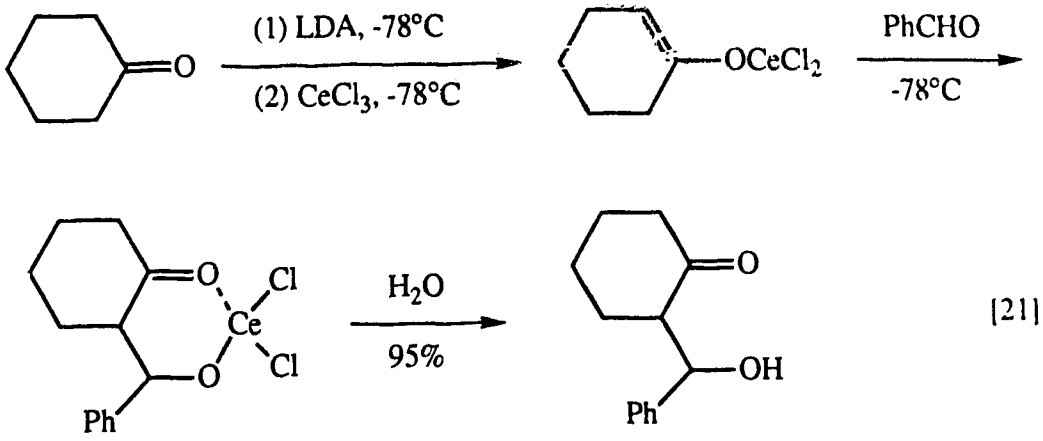


[20]

M = Li, 74%, R_1 = Me, R_2 = OH
M = $CeCl_2$, 95%, R_1 = OH, R_2 = Me

(5) Cerium Mediated Aldol Reactions

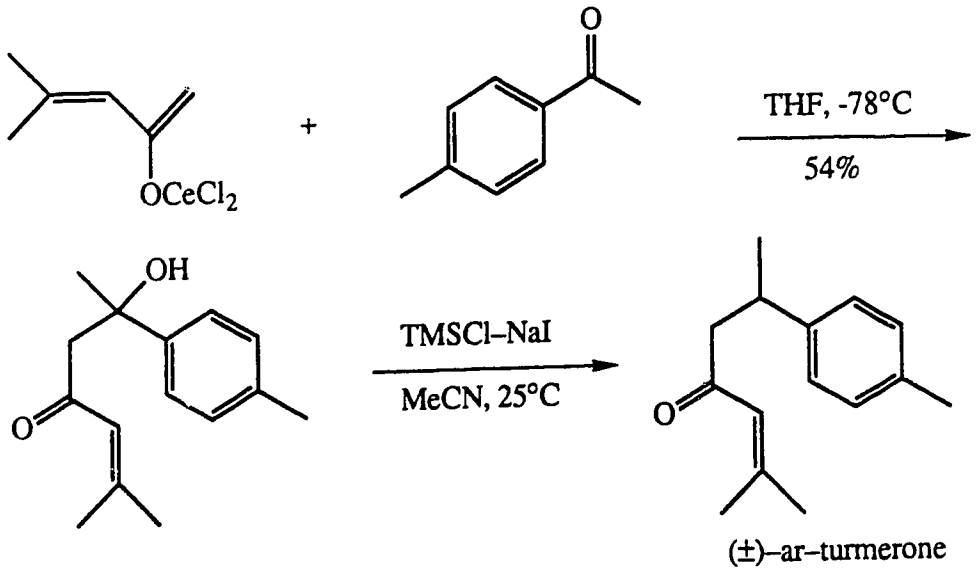
Aldol reactions are useful transformations which have been performed in various ways. Nevertheless, several side reactions always accompany the normal aldol addition such as enolization and cross–aldol reaction. An additional method *via* cerium enolates was described in 1983 by Imamoto *et al.*[42] The cerium enolate was prepared by transmetallation of the corresponding lithium enolate with $CeCl_3$ in THF at -78°C. This new aldol process suppressed retro–aldol and/or cross–enolization and gave higher yields than the reaction with the corresponding lithium enolates. However, no differences in stereoselectivities were observed between the two enolate systems.



[21]

These results can be reasonably interpreted by assuming that the transmetallation of lithium enolates with cerium chloride proceeded without change of the geometry of the enolates, and that the generated cerium enolates reacted with carbonyl compounds *via* well recognized six-membered ring transition state. The stereochemistry of the products, therefore, originated from the geometry of the initially formed lithium enolates. Cerium(III) ion played a role for the effective interception of intermediate aldol adduct by forming a chelate more tightly than the lithium ion, suppressing retro-aldol and/or cross enolization, and hence the aldols were produced in high yields.

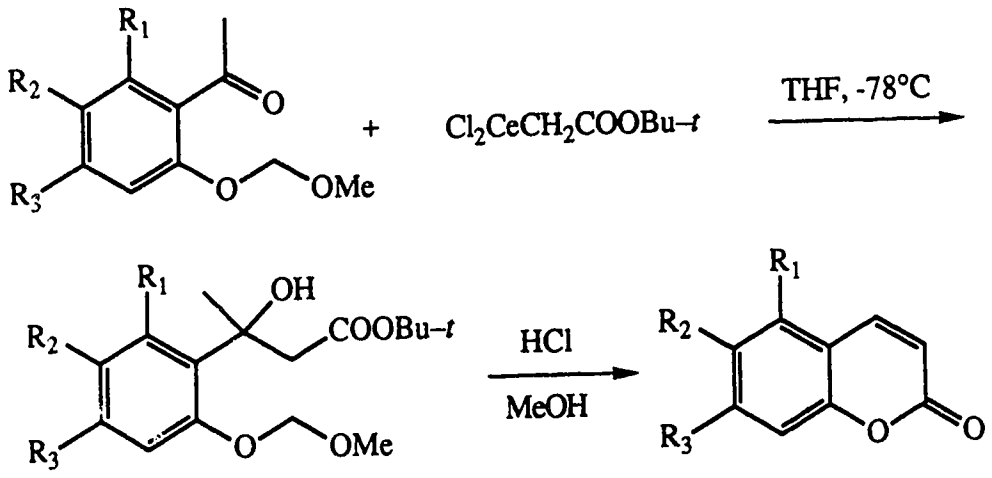
In 1987, Sakai *et al.*[43] synthesized (±)-ar-turmerone by use of a cerium mediated aldol reaction as the key step (Eq. 22), whereas without $CeCl_3$, very low yield of the aldol product was obtained.



[22]

(±)–ar–turmerone

In 1985, Nagasawa *et al.*[44], for the first time, exploited the cerium ester enolate, Cl_2CeCH_2COOBu–*t*, which was prepared from $CeCl_3$ and $LiCH_2COOBu$–*t* in THF at -78°C. The organocerium(III) enolate reacted with acetophenone derivatives to afford β–hydroxy esters virtually in quantitative yields (Eq. 23). Side reactions, such as enolization and self-condensation, were not observed. However, $LiCH_2COOBu$–*t* did not add at all; only the starting materials were recovered owing to enolization.



[23]

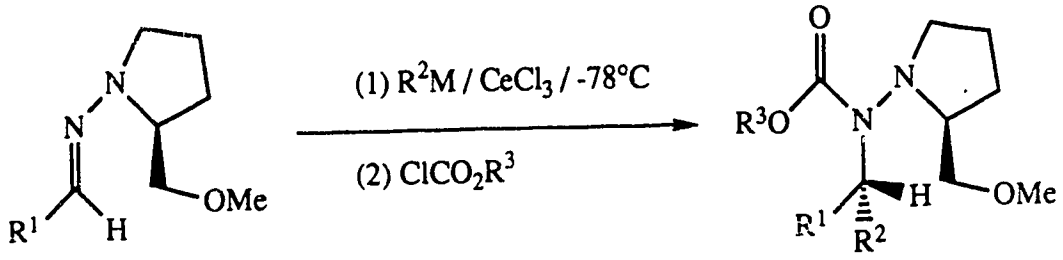
(7) Additions of Organocerium Reagents to Imine Related Compounds

Chiral amine moieties are found in many natural products and methods for constructing them in a stereoselective manner are highly desirable. One of the most direct methods for synthesizing chiral amines is the diastereoselective nucleophilic addition of organometallic reagents to chiral imines and derivatives (oximes, hydrazones *etc.*). However, due to the poor electrophilicity of C=N double bond compared with C=O double bond, organolithium, Grignard and other organometallic reagents failed to add to C=N double bond and its synthetic applications were greatly limited. The characteristics of organocerium reagents, possessing high reactivity towards carbonyl group and low basicity, promised an alternative to this very important problem in organic chemistry.

In 1987, Denmark *et al.*[45] reported a new method for the asymmetric synthesis of chiral amines by use of organocerium reagents to induce addition with SAMP–hydrazone type compounds since organolithium reagents, Grignard reagents and other nucleophiles in conjunction with additives ($BF_3 \cdot OEt_2$, TMEDA) could not add to C=N double bond due to the poor electrophilicity of C=N and easy enolization of hydrazones with α–hydrogens. They found that organocerium(III) reagents could add to SAMP–hydrazones in good yields with high diastereoselectivitiy. The optimal conditions were using THF as solvent and a 2:2:1 ratio of RLi, $CeCl_3$ and hydrazone. Using less $CeCl_3$ led to lower selectivity. Experimental results also suggested that organocerium reagents were involved since precomplexation of hydrazone with $CeCl_3$ followed by addition of RLi gave poor results.

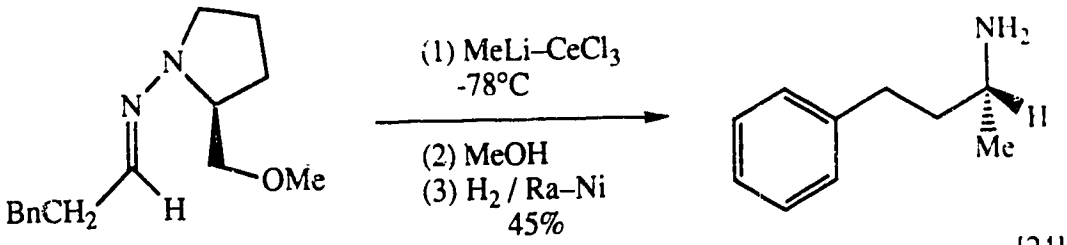
Various organocerium reagents and SAMP–hydrazones were examined (Table II–8) and nearly all types of simple organocerium reagents could be employed. Organocerium(III) reagents could react even with highly enolizable, aromatic and α,β–unsaturated hydrazones with high efficiency and excellent diastereoselectivity. Of particular note was the selective 1,2–addition of organocerium reagents to α,β–unsaturated hydrazone compounds. This was in keeping with the behavior of organocerium reagents with α,β–unsaturated carbonyl compounds.

Table II–8. RM/$CeCl_3$ Addition to SAMP–Hydrazones



Hydrazone (R^1)	R^2M/$CeCl_3$	R^3	Yield (%)	de	Confign
$PhCH_2CH_2$	MeLi/$CeCl_3$	Me	81	98:2	*R*
$PhCH_2CH_2$	*i*–PrMgBr/$CeCl_3$	Me	67	99:1	*R*
$PhCH_2CH_2$	*t*–BuLi/$CeCl_3$	Me	72	96:4	*R*
$PhCH_2CH_2$	PhLi/$CeCl_3$	Me	72	96:4	*R*
$PhCH_2CH_2$	*i*–$Pr_3SiCH{\equiv}CCeCl_2$	Me	74	97:3	*R*
$PhCH_2$	MeLi/$CeCl_3$	Bn	83	96:4	*R*
(*E*)–MeCH=CH	MeLi/$CeCl_3$	Me	82	96:4	*R*

The optically active amines were prepared by cleaving the N–N bond by hydrogenolysis as shown in Eq. 24.

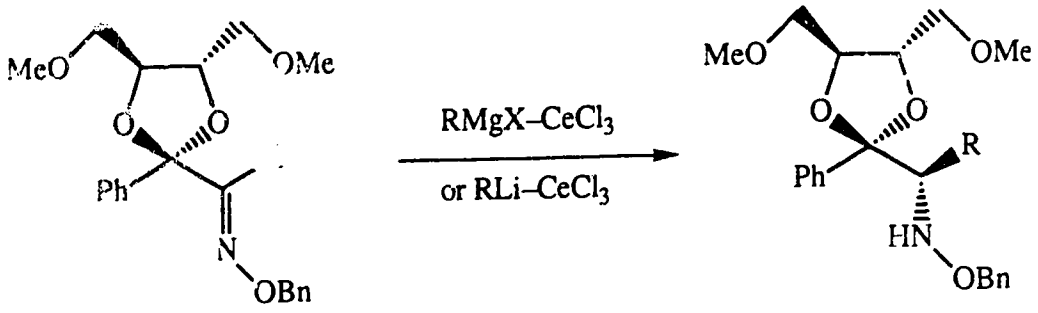


[24]

In 1989, Fujioka *et al.*[46] also described a new asymmetric synthesis of chiral amines by addition of organocerium(III) reagents to chiral α–aldoxime–ether acetals. They discovered that organocerium reagents (RMgBr–$CeCl_3$, RLi–$CeCl_3$) were superior to other organometallic reagents both in reactivity and stereoselectivity towards the chiral oxime acetals. The *N*–oxygenated chiral amine derivatives were obtained in a highly diastereoselective manner by use of organocerium reagents, whereas Grignard and organolithium reagents afforded no product. Some of the results are illustrated in Table II–9.

It is interesting to note that extremely high diastereoselectivity was realized in the reactions of the organocerium reagent prepared from RMgX–$CeCl_3$, while the organocerium reagent from RLi–$CeCl_3$ showed somewhat lower selectivity.

Table II–9. Additions of Organocerium Reagents to Chiral Oxime Derivative



RM	T (°C)	Yield (%)	de
$MeMgBr/CeCl_3$	0	84	>99 : <1
$MeLi/CeCl_3$	-78	70	90 : 10
n–$BuMgCl/CeCl_3$	0	81	97 : 3
n–$BuLi/CeCl_3$	-78	75	75 : 25
$CH_2{=}CHCH_2CH_2MgCl/CeCl_3$	-23	67	95 : 5

The *si*–face selectivity in the reaction of organocerium reagents with the chiral α–aldoxime–ether acetal was rationalized by assuming a chelation model. Namely, cerium metal is fixed by chelation between the nitrogen atom, the methoxy oxygen atom, and one of the acetal oxygen atoms leading to a rigid structure (Figure II–1) in the transition state of the reaction. Thus, the alkyl groups of the reagents attack the *si*–face of the C=N double bond.

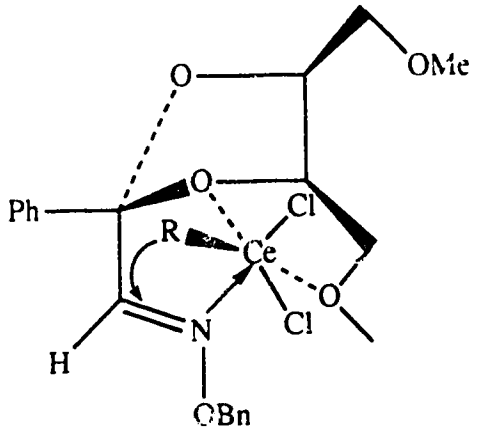
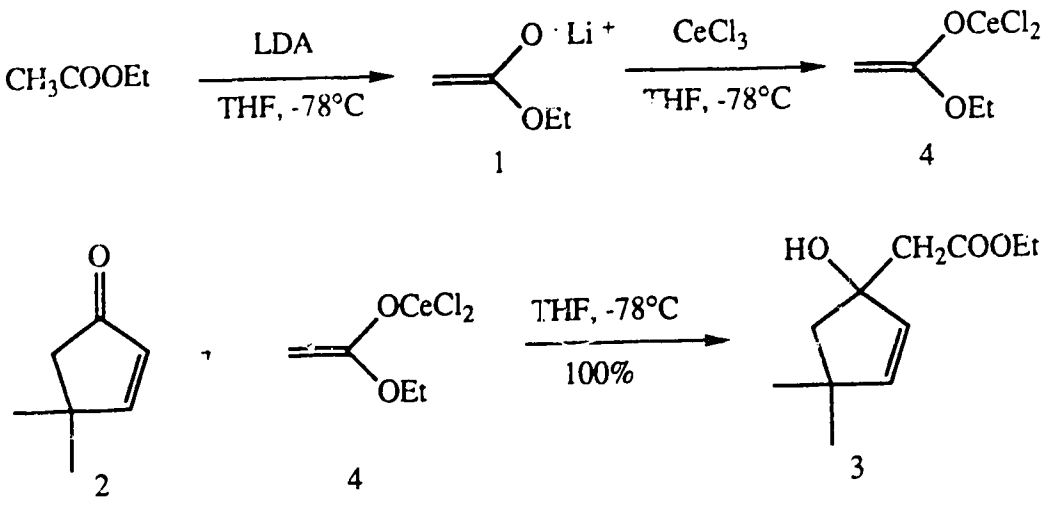


Figure II–1. Transition State for the Addition of Cerium Reagent to Imine

As discussed in Chapter I, during the course of the synthetic studies on pentalenolactone, we needed to prepare β–hydroxy ester **3** by the aldol reaction of lithium enolate **1** with 4,4–dimethyl–2–cyclopenten–1–one (**2**). Disappointingly, only a low yield of the desired product **3** was obtained. All attempts to improve the yield of **3** by increasing the amount of **1** failed. Even excess of lithio ethyl acetate (**1**) only afforded about 50% of the desired product with about 50% of starting enone **2** recovered, probably due to enolization in the addition process.

In view of the lower basicity and stronger nucleophilicity of organocerium reagents than the corresponding organolithium reagents, the use of cerium enolate **4** was explored. It was observed that the addition of cerium ester enolate **4** to enone **2** in THF at -78°C proceeded readily to afford the desired alcohol **3** in quantitative yield and with complete 1,2–regioselectivity.



Based on this finding, we suspected that cerium ester enolates could be highly useful in synthetic organic chemistry and decided to carry out a more detailed investigation, especially on the aldol type reaction, since few studies have been done concerning the chemistry of cerium ester enolates.

The addition of lithium ester enolates to carbonyl compounds constitutes an important process for the formation of carbon–carbon bonds. However, the addition is often complicated by reversibility, enolization and conjugate addition.[47] As a result, the desired addition products were frequently obtained in low yields and in some cases, exclusive 1,4–addition products were isolated.[48] The undesirable side reactions considerably limit the synthetic application of lithium ester enolates.

The results of our investigation will be presented in two parts. Chapter II will discuss the additions of cerium ester enolates to carbonyl compounds and Chapter III will involve the additions of cerium ester enolates to imines and related compounds.

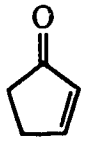
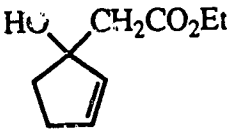
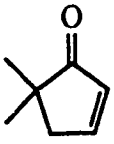
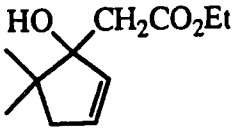
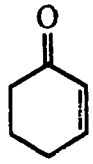
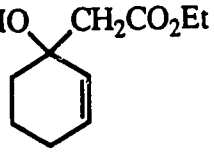
RESULTS and DISCUSSION

The additions of cerium ester enolate **4** to several enones were investigated first. For the purpose of comparing the reactivity and regioselectivity of cerium enolate with lithium enolate, the reactions of lithio ethyl acetate (**1**) with these enones were also carried out under the same conditions. The results are summarized in Table II–10. As shown in Table II–10, in every case, the cerium ester enolate **4** dramatically enhanced the efficiency of addition to the carbonyl group and the reaction proceeded readily at -78°C within a few hours, giving a much higher yield of the desired β–hydroxy ester than with a lithio ethyl acetate (**1**). As well, cerium enolate **4** always added to enones in a 1,2–addition fashion, providing the corresponding allylic alcohols in excellent yields. On the other hand, the addition of lithium enolate often gave a mixture of 1,2– and 1,4–adducts. For examples, in the case of enones **5** and **9**, the additions of lithio ethyl acetate (**1**) were always accompanied by a significant amount of 1,4–addition products (about 25%).

The carbonyl group in enone **7** is sterically hindered by the geminal dimethyl group, inhibiting the ester enolate addition. Surprisingly, the addition of cerium enolate **4** to enone **7** took place very easily at -78°C to afford β–hydroxy ester **8** in 97% yield. The high resolution mass spectrum of compound **8** displayed the molecular ion peak at m/e 198.1257, corresponding to the molecular formula $C_{11}H_{18}O_3$. This chemical composition was also confirmed by the elemental analysis. In the IR spectrum, both the hydroxy and ester groups showed strong infrared absorptions at 3500 (OH) and 1716 (C=O) cm^{-1} respectively. The vinylic protons resonated at δ 5.88 and 5.79, each as a

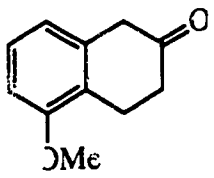
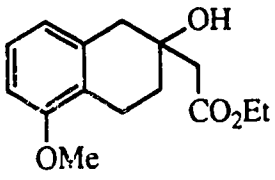
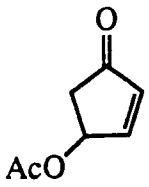
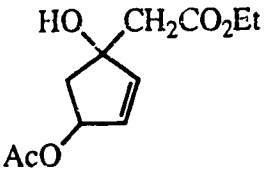
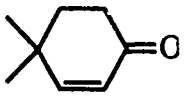
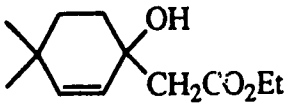
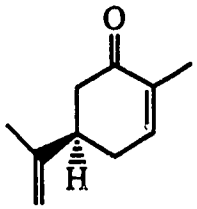
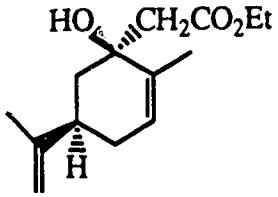
doublet of triplets, in the ^1H NMR spectrum. The methylene protons adjacent to the ester unit resonated as a set of AB doublets at δ 2.58 and 2.48 with geminal coupling constant of 15.6 Hz. The methylene protons in the five-membered ring also showed a large geminal coupling constant of 16 Hz. Their resonance signals were observed at δ 2.34 and 2.09, each as a doublet of doublets of doublets (J = 16, 2, 2 Hz). The carbonyl carbon resonated at δ 173.52 as a singlet in its ^{13}C NMR spectrum. The double bond carbons appeared at δ 135.40 and 132.77, each as a doublet. The carbon bearing the hydroxy group appeared at δ 84.08 as a singlet.

Table II-10. The Comparison of Cerium Ester Enolate 4 with Lithio Ethyl Acetate (1) Towards Enones

Enone	Ester Enolate	Product	Yield (%)
	$Cl_2CeCH_2CO_2Et$		96
	$LiCH_2CO_2Et$		76
5		6	
	$Cl_2CeCH_2CO_2Et$		97
	$LiCH_2CO_2Et$		60
7		8	
	$Cl_2CeCH_2CO_2Et$		100
	$LiCH_2CO_2Et$		30
9		10	

Having established that the cerium enolate **4** was a better nucleophile than the lithium enolate towards enones, we carried out more reactions in order to examine the generality and basicity of cerium enolate **4**. Various ketones and enones, especially highly enolizable ones, were selected to react with cerium enolate **4**. The results are summarized in Table II–11.

Table II–11. The Addition of Cerium Enolate **4** to Carbonyl Compounds

Enone or Ketone	Product	Time (h)	Yield (%)
		15	92
11	12		
		6	98
13	14a, 14b		
		4	96
15	16		
		6	100
17	18		

As shown in Table II–11, cerium ester enolate **4** is a nucleophile of low basicity which could add to highly enolizable ketones readily, giving alcohols in excellent yields. For example, cerium ester enolate **4** efficiently added to the highly enolizable ketone **11** to afford the β–hydroxy ester **12** in 92% yield as a white solid. Its high resolution mass spectrum indicated the molecular ion peak at m/e 264.1366, corresponding to the molecular formula $C_{15}H_{20}O_4$. This molecular formula was also in agreement with the elemental analysis. Compound **12** showed strong infrared absorptions at 3500, 1728 and 1715 cm^{-1} in the IR spectrum. The band at 3500 cm^{-1} was due to the hydroxy group. The absorptions at 1728 and 1715 cm^{-1} were due to the ester carbonyl group which may also exist in a hydrogen–bonding form. The hydroxy proton appeared in the ^1H NMR spectrum at δ 3.74 as a singlet. The methylene protons adjacent to the carbonyl unit resonated at δ 2.58 and 2.54 as a pair of doublets (J_{gem} = 16 Hz). In the ^{13}C NMR APT spectrum, two singlets at δ 172.90 and 69.21 were assigned to the ester carbonyl carbon and the carbon bearing the hydroxy group respectively. The methoxy carbon appeared at δ 55.24 as a quartet.

We also selected the enone **13** to study the basicity of cerium ester enolate **4**. Enone **13** is quite sensitive to basic reagents since an acetoxy group, which is quite a good leaving group, is β to the ketone unit. Treatment of enone **13** with cerium ester enolate **4** in THF at -78°C for 6 h provided a mixture of diastereoisomers **14a** and **14b** in 98% yield with a ratio of 9:1 as determined by the high resolution ^1H NMR spectrum. From this finding, it can be concluded that cerium ester enolate **4** is of low basicity.

The major product was determined by NOE measurement to be β–hydroxy ester **14a**. Upon irradiation of the signal at δ 5.55 for the methine proton, the doublet at δ 2.59 (corresponding to one of the methylene protons next to the ester unit) was enhanced by 5% (Figure II–2). Other NOE results are also shown in Figure II–2.

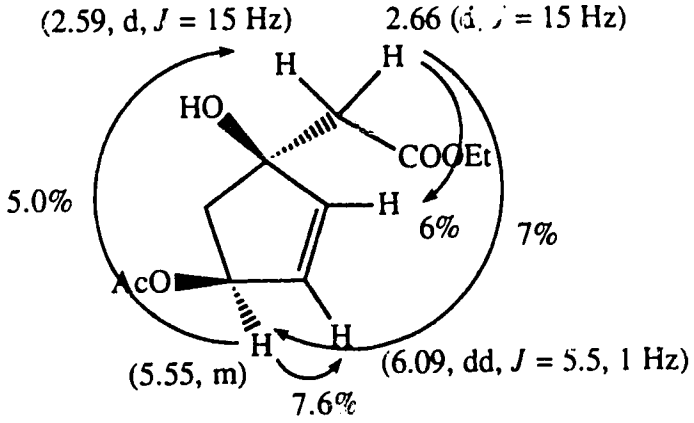
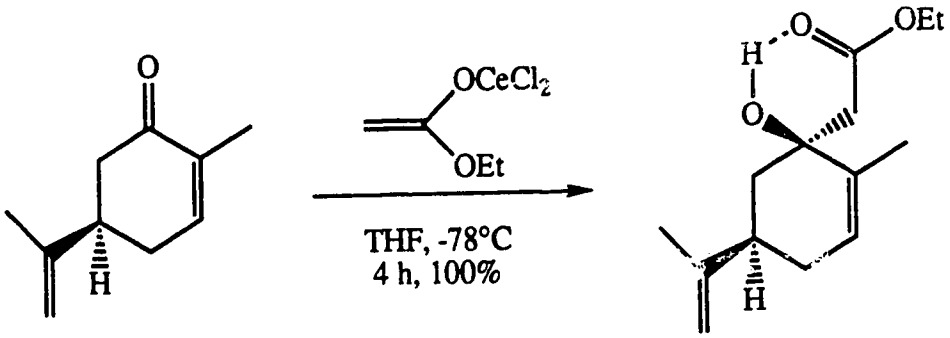


Figure II–2. NOE Data for β–Hydroxy Ester **14a**

The molecular ion peaks were not observed in the high resolution mass spectrum for compounds **14a** and **14b**. However, the peak at m/e 211.0964 corresponding to $(M\text{-}OH)^+$ was observed. The formation of the desired hydroxy esters **14a** and **14b** was also supported by the elemental analysis. The hydroxy esters **14a** and **14b** displayed four infrared absorptions for the hydroxy groups at 3494, 3488, 3479 and 3468 cm^{-1} in the IR spectrum. The ester carbonyl groups exhibited an absorption at 1733 cm^{-1}. The major isomer **14a** showed the following ^1H NMR spectral data. One of the vinylic protons resonated at δ 6.09 as a doublet of doublets (J = 5.5 and 1 Hz); the other was observed at δ 5.93 also as a doublet of doublets (J = 5.5 and 2 Hz). A multiplet centered at δ 5.55 was assigned to the methine proton next to the acetoxy group.

The hydroxy proton appeared at δ 3.84 as a singlet. The methylene protons adjacent to the ester unit resonated at δ 2.66 and 2.59 as a pair of AB doublets (J = 15 Hz). The methylene protons in the five–membered ring appeared at δ 2.55 (J = 14 and 7.5 Hz) and 2.00 (J = 14 and 4 Hz), each as a doublet of doublets. The large coupling constant of 14 Hz was attributed to the geminal AB coupling of these two protons. In the ^{13}C NMR spectrum, two carbonyl carbons appeared at δ 172.22 and 170.84, each as a singlet. The double bond carbons resonated at δ 140.22 (d) and 131.87 (d). The carbon bearing the hydroxy group was observed at δ 80.99 as a singlet, whereas the carbon attached to the acetoxy group resonated at δ 76.97 as a doublet.

The cerium ester enolate **4** showed excellent axial stereoselectivity toward (–)–carvone. Upon treatment of (–)–carvone (**17**) with cerium ester enolate **4** in THF at -78°C for 4 h, the optically active β–hydroxy ester **18** was isolated in quantitative yield. Detailed ^1H NMR analysis revealed strong intramolecular hydrogen bonding between the ester carbonyl and the hydroxy group.



17 18

The high resolution mass spectrum of hydroxy ester **18** showed the molecular ion peak at m/e 238.1570, corresponding to the molecular formula $C_{14}H_{22}O_3$.

The elemental analysis also supported this chemical composition. Its infrared spectrum exhibited an ester carbonyl absorption at 1715 cm^{-1} and hydroxy bands at 3509 and 3505 cm^{-1}. The complete assignments for the ^{1}H NMR and ^{13}C NMR spectral data were made on the basis of spin decoupling experiments, ^{1}H–^{13}C correlation (Figure II–6) and ^{1}H–^{1}H correlation (Figure II–7) NMR spectra.

The assignment of the doublet at δ 39.56 in the ^{13}C APT NMR spectrum was especially important. The only possible carbon which could resonate at δ 39.56 as a doublet is the carbon which bears the isopropenyl group. The ^{13}C–^{1}H correlation NMR experiment indicated that this carbon (δ 39.56, doublet) was connected to the proton whose ^{1}H NMR signal appeared at δ 2.28 as a multiplet. As a result, the signal at δ 2.28 was assigned to the H_d proton (Figure II–5).

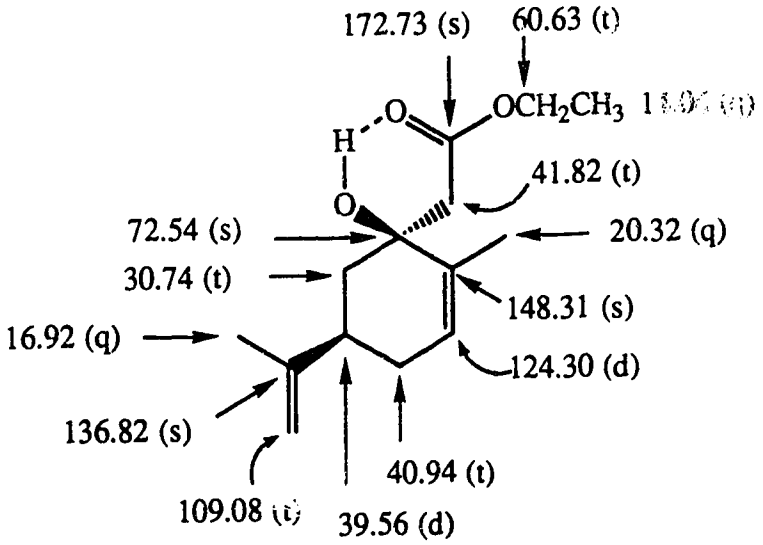


Figure II–3. ^{13}C NMR Data for Alcohol **18**

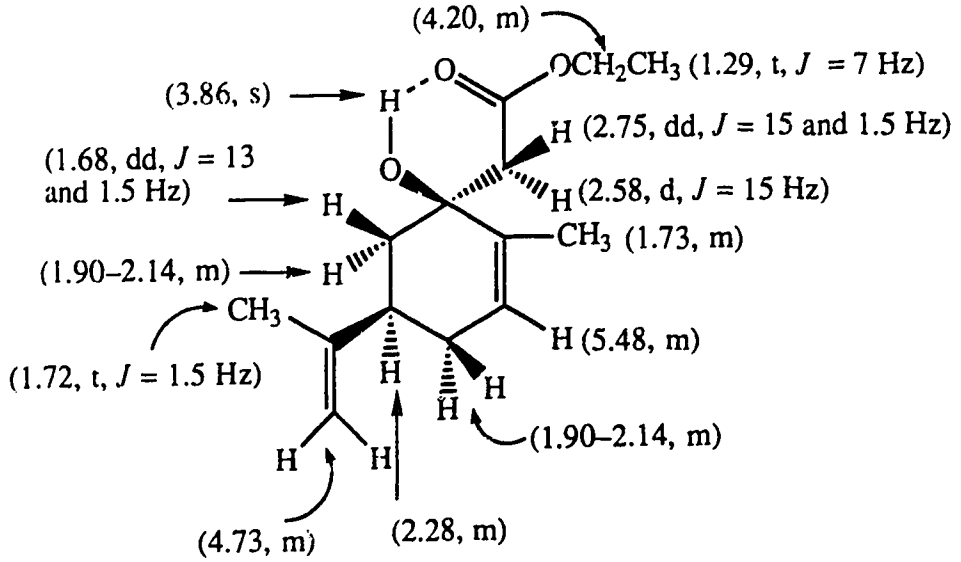


Figure II–4. ^{1}H NMR Data for Alcohol **18**

The absolute stereochemistry at the carbon bearing the hydroxy group was determined to have a *S* configuration by the NOE studies (Figure II–5). Irradiation of the signal at δ 2.58 (H_b, doublet) produced a positive enhancement of 10.9% for the signal at δ 2.28 corresponding to the H_d proton.

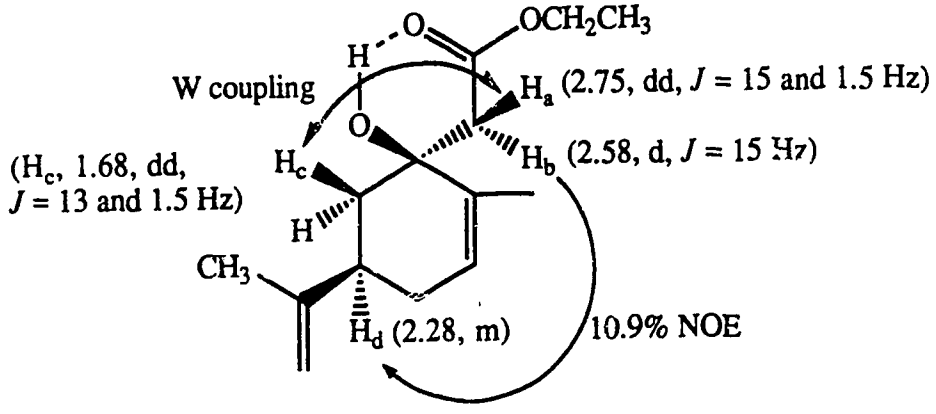
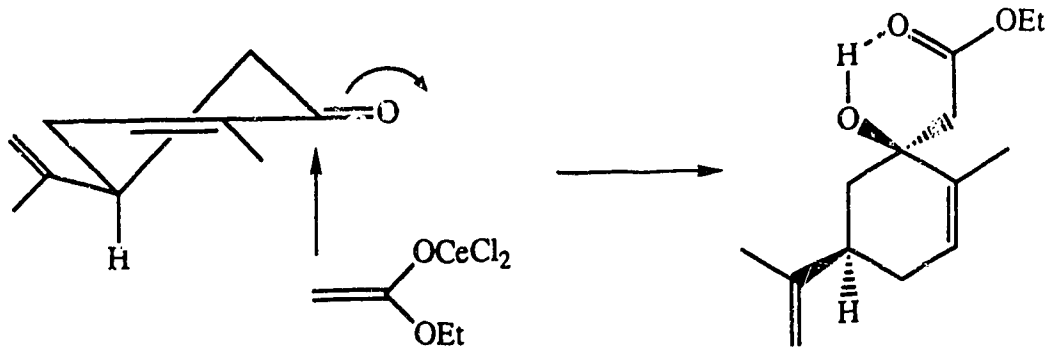


Figure II–5. NOE Data and W Coupling for Alcohol **18**

The presence of the intramolecular hydrogen bonding in alcohol **18** was revealed by the ^1H NMR coupling pattern. It was interesting to find that the H_a proton was split into a doublet of doublets with coupling constants of 15 Hz and 1.5 Hz, whereas the H_b proton resonated as a doublet (J = 15 Hz). The coupling constant of 15 Hz was due to the strong geminal AB coupling of these two protons. The smaller coupling constant of 1.5 Hz for the H_a proton was found to be a W coupling with the H_c proton. This W coupling was confirmed both by the spin decoupling experiment and by the ^1H–^1H correlation NMR spectrum (Figure II–7). Upon irradiation of the signal at δ 2.75, the signals at δ 1.68 (dd) and 2.58 (d) collapsed to a doublet (J = 13 Hz) and a singlet respectively. Similarly, upon irradiation of the H_c signal, the signal at δ 2.75 collapsed to a douolet (J = 15 Hz). The ^1H–^1H correlation NMR also indicated that the protons H_a and H_c were coupled to each other. These results strongly suggested that there existed a fixed conformation for the hydroxy ester unit. That is, the ester unit can not rotate freely, logically, due to hydrogen bonding.

The stereochemical outcome can be explained by the stereoelectronic effect. The ester enolate attacked the carbonyl carbon from the axial direction of the conformationally defined conjugated cyclohexenone to deliver the hydroxy ester **18** as a single substance.



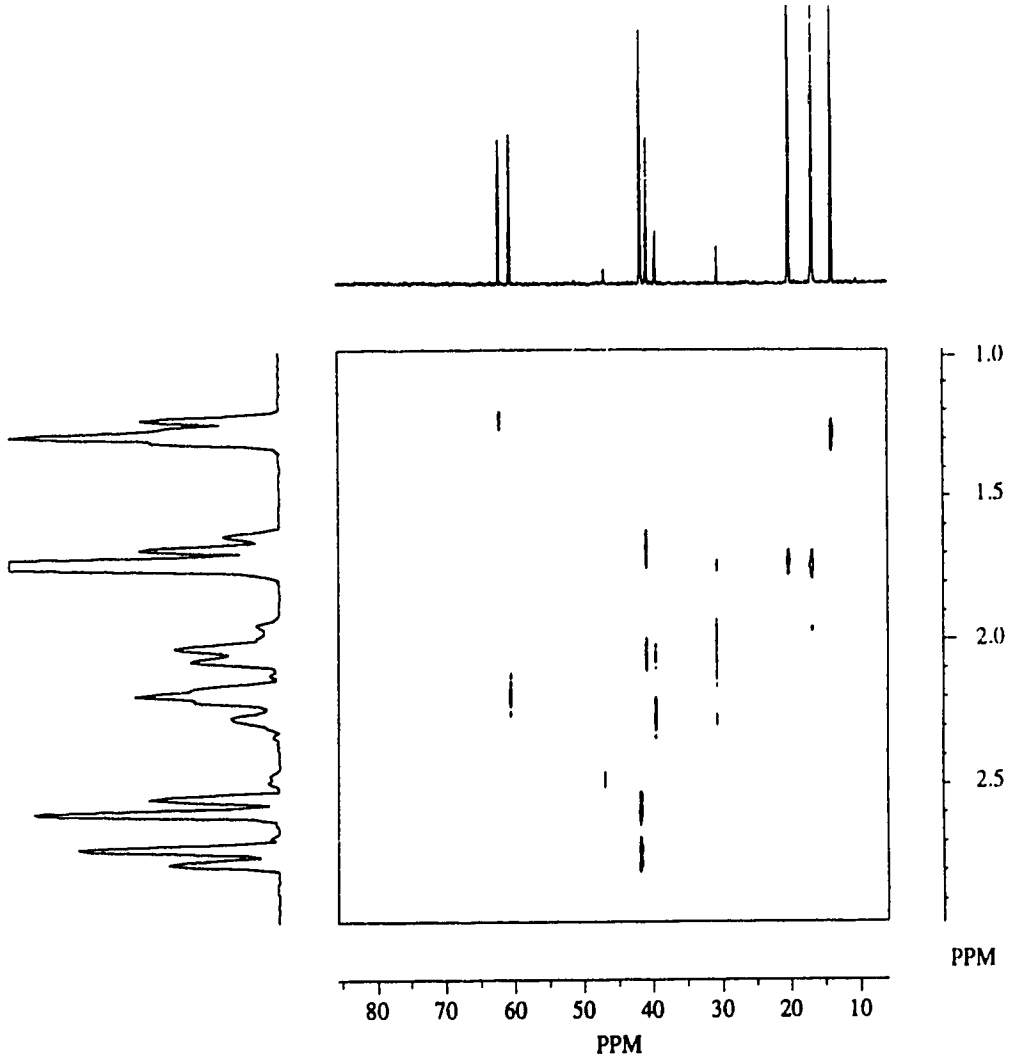


Figure II–6. ^{13}C–^{1}H Correlation Spectrum for Hydroxy–Ester **18**

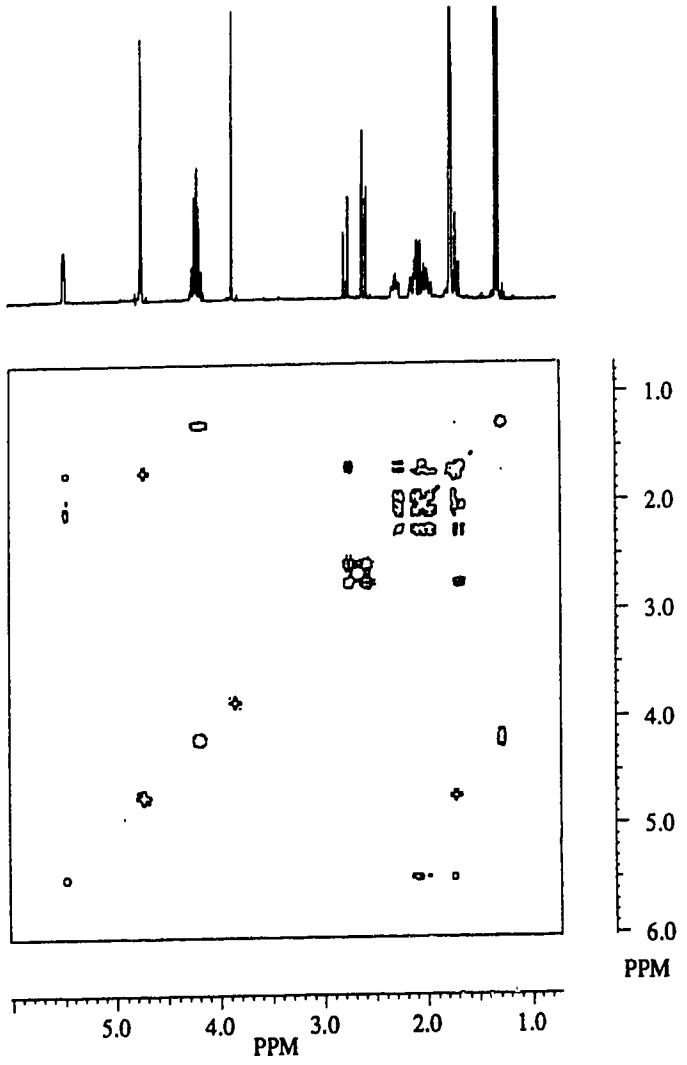


Figure II–7. ^{1}H–^{1}H COSY Spectrum for Hydroxy–Ester **18**

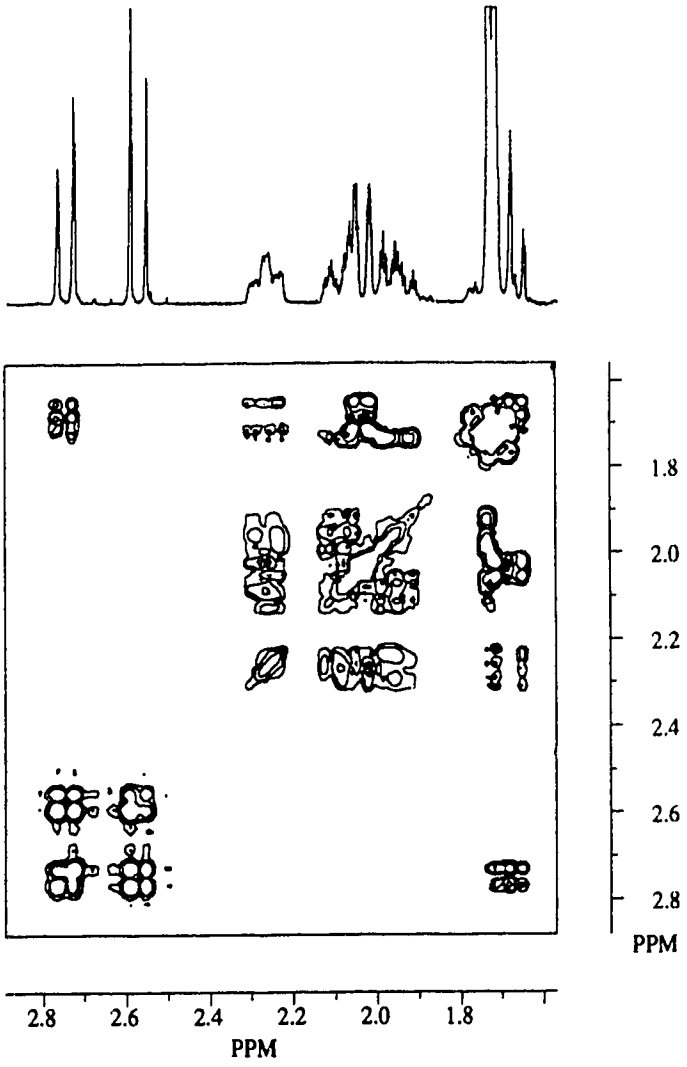
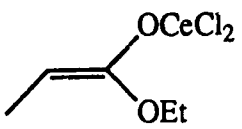
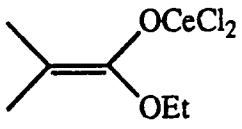


Figure II–8. Expansion for ^{1}H–^{1}H COSY NMR Spectrum of **18**

As mentioned earlier, addition of a lithium ester enolate to a carbonyl group is a reversible process which could afford both 1,2– and 1,4–addition products. The lithium enolates of mono– and disubstituted acetates have greater tendency to undergo 1,4–addition. To examine the reactivity and regioselectivity of substituted cerium ester enolates, cerium ester enolates **19** and **25** were prepared and reacted with carbonyl compounds. The results are shown in Table II–12 and Table II–13. Both **19** and **25** were found to be excellent nucleophiles which added to carbonyl compounds efficiently in THF at -78°C within a short reaction time to yield the β–hydroxy esters in high yields. Moreover, both cerium ester enolates showed an excellent 1,2–regioselectivity. Even the disubstituted cerium enolate **25** always produced the 1,2–addition product.



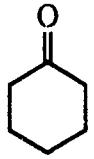
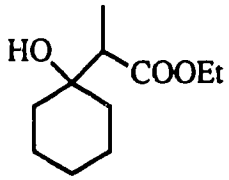
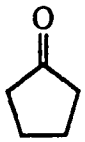
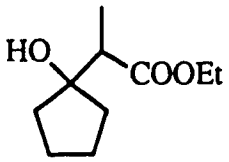
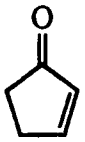
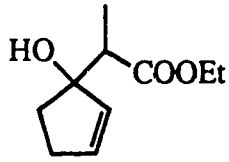
19



25

Treatment of the ketone **20** with cerium enolate **19** in THF at -78°C gave the β–hydroxy ester **21** in 94% yield. The compound **21** has the molecular formula of $C_{11}H_{20}O_3$ as determined by the high resolution mass spectrum. The elemental analysis also supported this chemical composition. Its infrared spectrum showed a strong hydroxy absorption at 3517 cm^{-1} and two bands at 1729 and 1713 cm^{-1} for the ester carbonyl group. The formation of the hydroxy ester was also evident from the ^1H and ^{13}C NMR spectra. In the latter spectrum, the ester carbonyl carbon appeared as a singlet at δ 177.04 and the singlet at δ 71.37 was readily assigned to the carbon bearing the hydroxy group.

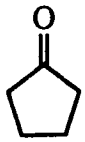
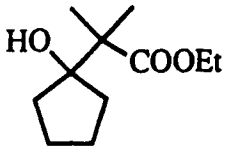
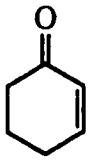
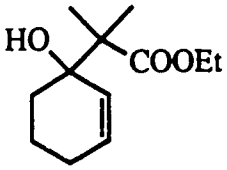
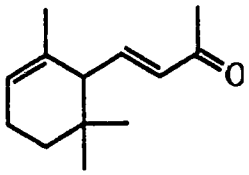
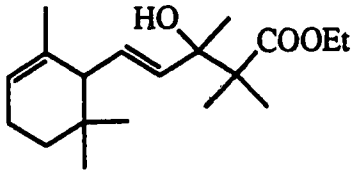
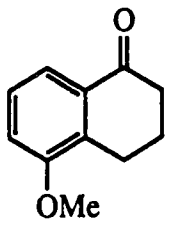
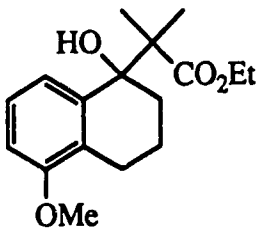
Table II–12. Additions of Cerium Enolate **19** to Carbonyl Compounds

Ketone or Enone	Product(s)	Time (h)	Yield (%)
		8	94
20	21		
		6	97
22	23		
		6	96
5	24		

As shown in Table II–13, cerium ester enolate **25** also reacted with ketones, including highly enolizable ones, readily to afford the desired products in excellent yields. For example, addition of enolate **25** to ketone **30** in THF at -78°C produced the hydroxy ester **31** in excellent yield, although a somewhat longer reaction time was required. The compound **31** displayed a molecular ion peak at m/e 292.1675 in the high resolution mass spectrum, consistent with the molecular formula $C_{17}H_{24}O_4$. Its infrared spectrum exhibited two strong bands at 3480 and 1720 cm^{-1} respectively for the hydroxy and ester groups. The hydroxy proton resonated at δ 4.58 as a singlet in the ^1H NMR spectrum.

The signal for the protons of the methoxy group was observed at δ 3.80 as a singlet.

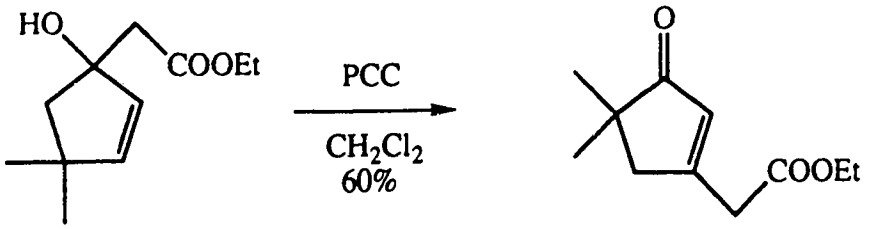
Table II-13. Addition of Cerium Enolate **25** to Carbonyl Compounds

Ketone or Enone	Product	Time (h)	Yield (%)
		7	97
22	26		
		10	92
9	27		
		9	100
28	29		
		15	97
30	31		

The cerium enolate **25** also displayed excellent 1,2–selectivity towards enones. At -78°C, it reacted with enones to produce the corresponding β–hydroxy esters in excellent yields with virtually complete regioselectivity. The reaction of enolate **25** with α-ionone (**28**) afforded the compound **29** in quantitative yield as a mixture of diastereoisomers without isomerizing the double bond in the six–membered ring. The ratio of the mixture was about 50:50 as shown by the ^1H NMR spectrum. The hydroxy ester **29** was determined by the high resolution mass spectrum to have the molecular formula $C_{19}H_{32}O_3$ which was supported by the elemental analysis. Its infrared spectrum showed the hydroxy and ester absorptions at 3500 and 1723 cm^{-1} respectively. There were three vinylic protons in the ^1H NMR spectrum, two of which resonated at δ 5.54 as a multiplet and the other at δ 5.40 as a broad singlet. The ^{13}C NMR spectrum displayed two sets of signals. The ester carbonyl carbons resonated at δ 178.35 and 178.27, each as a singlet. The signals observed at δ 134.36 (d), 134.37 (d), 134.11 (s), 134.01 (s), 130.89 (d), 130.82 (d), 120.99 (d) and 120.94 (d) were attributed to the double bond carbons. The signals for the carbons bearing the hydroxy group were observed at δ 75.55 and 75.50, each as a singlet.

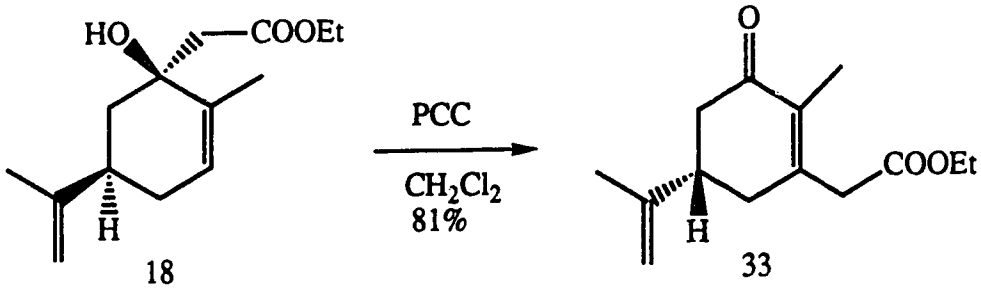
As observed during the course of our synthetic studies towards pentalenolactones (Chapter I), oxidative 1,3–carbonyl transposition of tertiary allylic alcohol **3** with PCC afforded the enone **32** in satisfactory yield. Enone **32** is an important synthetic intermediate, which could not be prepared effectively otherwise, for the construction of bicyclo[3.2.0]heptane ring system in the projected synthesis of pentalenolactone G. With the tertiary allylic alcohols readily available *via* the cerium(III) mediated aldol reaction of cerium ester enolate with enones, the oxidation of these β–hydroxy esters with PCC

was carried out in order. to investigate the generality of this 1,3–carbonyl transposition reaction which, apparently, is of synthetic utility.



3 32

Oxidation of the optically active **18** with PCC afforded the optically active enone **33** in 81% yield. The enone **33** showed a molecular ion peak at m/e 236.1415 in the high resolution mass spectrum, corresponding to the molecular formula $C_{14}H_{20}O_3$. The results of elemental analysis was in agreement with the chemical composition. In the IR spectrum, two bands at 1736 and 1671 cm^{-1} may be attributed to the ester and enone carbonyl groups.



18 33

In the ^{13}C NMR spectrum, the ketone and ester carbonyl carbons resonated at δ 198.99 and 169.63, each as a singlet. The signals at δ 148.92 (s) and 146.51 (s) were due to the β and α carbons of the enone moiety respectively. The other double bond carbons resonated at δ 133.35 and 110.58 respectively as a singlet and a triplet. The carbon bearing the isopropenyl group appeared at δ 41.28 as a doublet. The carbon adjacent to the ester unit resonated at δ 42.51 as a

triplet. The CH_2 carbons in the six–membered ring resonated at δ 40.70 (t) and 36.61 (t). The partial assignment for the ^1H NMR spectrum is shown in Figure II–9. The protons for the external double bond resonated at δ 4.81 and 4.76 as multiplets. A set of AB doublets resonating at δ 3.33 (J = 15 Hz) and 3.28 (J = 15 Hz) were attributed to the methylene protons adjacent to the ester unit. The methine proton H_a appeared at δ 2.68 as a multiplet. The signal at δ 2.60 (ddd, J = 16, 4, 1.5 Hz) was assigned to the equatorial proton H_b which coupled to H_a and H_c (J = 4, 16 Hz). The H_b proton also had a long range coupling with H_d proton (J = 1.5 Hz). The H_c proton in the axial position appeared at δ 2.34 as a doublet of doublets with a large *trans* coupling constant with H_a (J = 13 Hz). Both H_d and H_e protons resonated at δ 2.47 as a multiplet.

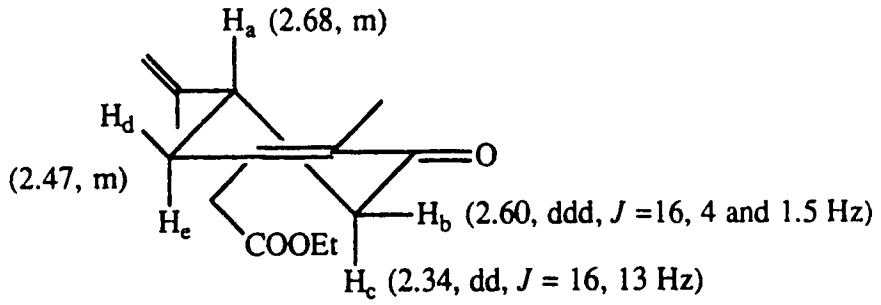
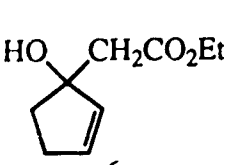
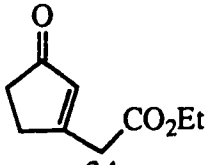
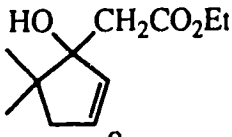
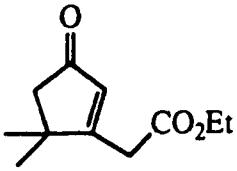
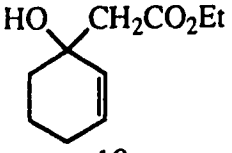
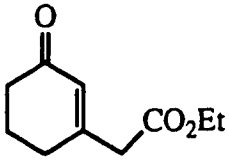
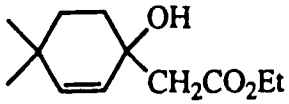
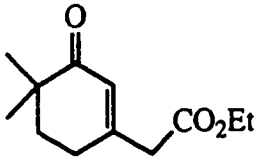
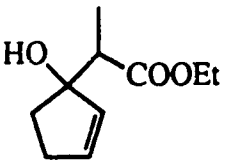
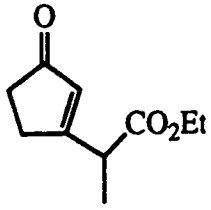
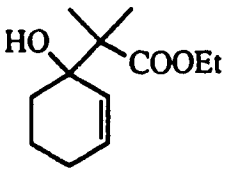
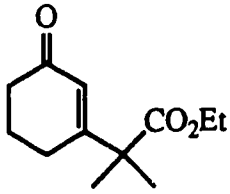


Figure II–9. Partial ^1H NMR Data Assignment for Enone 33

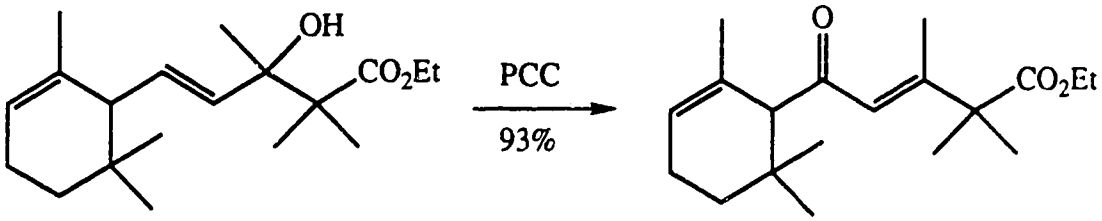
Several additional tertiary allylic alcohols were oxidized by PCC and the results are listed in Table II–14. As shown, every allylic alcohol could undergo oxidative 1,3–carbonyl rearrangement to afford the corresponding enone in good yield. This general 1,3–carbonyl transposition process is of synthetic utility.

Table II–14. Oxidation of Tertiary Allylic Alcohols with PCC

Allylic Alcohol	Product	Time (h)	Yield (%)
 6	 34	2.5	72
 8	 35	15	53
 10	 36	2	74
 16	 37	2	63
 24	 38	6	60
 27	 39	10	90

It is interesting to note that oxidation of **27** with PCC afforded enone **39** in 90% yield despite steric congestion of its hydroxy group. Enone **39** displayed the ester and enone carbonyl absorptions respectively at 1733 and 1674 cm^{-1} in the IR spectrum. In the high resolution mass spectrum, a molecular ion peak at m/e 210.1259 was observed corresponding to the molecular formula $C_{12}H_{18}O_3$. This formula was also proven by the elemental analysis. The vinylic proton was observed to resonate at δ 6.02 as a broad singlet in the ^1H NMR spectrum. In the ^{13}C NMR spectrum, two singlets at δ 199.90 and 174.81 were due to the ketone and ester carbonyl carbons respectively. The α carbon in the enone system resonated at δ 124.46 as a doublet, while the β carbon resonated at δ 166.62 as a singlet. The carbon next to the ester unit resonated at δ 48.58 as a singlet. The geminal dimethyl carbons appeared at δ 23.83 as a quartet.

An open chain tertiary allylic alcohol was also found to undergo oxidative 1,3-carbonyl rearrangement readily. Oxidation of **29** with PCC afforded enone **40** in excellent yield as the only product. Both ^1H and ^{13}C NMR spectral analyses showed the formation of one isomer.



29 40

The enone **40** was determined to have the molecular formula $C_{19}H_{30}O_3$ by the high resolution mass spectrum in which a molecular ion peak at m/e 306.2195

was observed. The results of elemental analysis also supported this chemical composition. In the IR spectrum, absorptions at 1733 and 1682 cm^{-1} were due to the ester and enone carbonyl groups respectively. In the ^{1}H NMR spectrum, the enone proton resonated at δ 6.32 as a broad quartet (J = 1 Hz), while the other vinylic proton appeared at δ 5.61 as a multiplet. The broad singlet at δ 2.69 was assigned to the methine proton in the six–membered ring. A doublet at δ 2.02 (J = 1 Hz) was assigned to the methyl group attached to enone unit. This assignment was further confirmed by the spin decoupling experiment in which irradiation of the signal at δ 6.32 resulted in the collapse of the doublet at δ 2.02 to a singlet. The singlet at δ 1.34, with a integration of six protons, was ascribed to the geminal dimethyl group next to the ester unit. In the ^{13}C NMR spectrum, two singlets at δ 203.97 and 175.44 were assigned to the enone and ester carbonyl carbons respectively. The enone double bond carbons appeared at δ 157.44 and 123.26 respectively as a singlet and a doublet. The other vinylic carbons resonated at δ 131.11 and 122.72, the former as a singlet and the latter as a doublet. The doublet at δ 65.33 was assigned to the carbon next to the enone carbonyl unit. The OCH_2 carbon appeared at δ 60.93 as a triplet. The tertiary carbon adjacent to the ester moiety resonated at δ 50.06 as a singlet.

Its *trans* configuration was determined by a difference NOE experiment. Upon irradiation of the signal at δ 1.34 (geminal dimethyl group next to the ester unit), the signal at δ 6.32 (α proton in the enone system) was enhanced by 6.9% (Figure II–10) in agreement only with the depicted geometry.

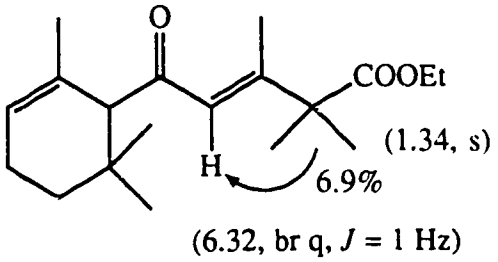


Figure II–10. NOE Data for Enone **40**

This oxidation reaction is mechanistically interesting as only the *trans* isomer was isolated. It was shown that alcohol **29** was a mixture of two diastereoisomers in a ratio of 1:1. If the oxidative rearrangement proceeded in a concerted manner, two enones should have been formed. The unexpected experimental result suggests that oxidation of alcohol **29** might have proceeded with a stepwise mechanism.

In conclusion, we have demonstrated that cerium ester enolate is a much more nucleophilic (towards the ketone carbonyl) and much less basic reagent than the corresponding lithium enolate. It can add to highly enolizable carbonyl compounds to afford the desired products in excellent yields. Another salient feature of cerium ester enolates are their excellent regioselectivity towards the enone system. In every case examined, only the 1,2–addition product was produced, while addition of lithium enolate to enone is often accompanied by 1,4–addition product.

EXPERIMENTAL

General

For a detailed description, see Chapter I, Experimental Section.

All experiments were carried out under an atmosphere of dry argon. Cerium(III) chloride heptahydrate was obtained from Aldrich. All the solvents were dried before use. Other simple chemicals were purchased and purified before use. The following organic materials were prepared according to the procedures in the literature: 5,5–dimethyl–2–cyclopenten–1–one,[49] 4–acetoxy–2–cyclopenten–1–one,[50] and 4,4–dimethyl–2–cyclohexen–1–one.[51]

Optical rotations were obtained on a Perkin–Elmer 24 polarimeter at the sodium D line using a 1.0 dm cell with a total volume of 1 mL. Specific rotation, $[\alpha]_D$, was reported in degrees per decimeter at the specified temperature and the concentration (c) was given in grams per 100 mL in the specified solvent.

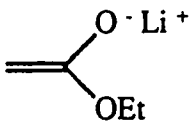
General Procedure for the Addition of Cerium Ester Enolate to Carbonyl Compounds

(a) Anhydrous Cerium(III) Chloride

Cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) (1.36 g, 3.64 mmol) was quickly and finely ground to a powder in a 30 mL round–bottomed flask with a

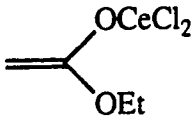
magnetic stirring bar. The flask was heated gradually to 100°C with evacuation (*ca.* 0.1 mmHg) in a Kugelrohr distillation apparatus. After 2 h at 100°C, the oven temperature was gradually increased to 150°C and cerium chloride was heated *in vacuo* for an additional 4–5 h. After the dried cerium chloride was cooled to room temperature under vacuum, argon gas was introduced. Tetrahydrofuran (THF) (12 mL), freshly distilled from sodium and benzophenone, was added all at once with vigorous stirring. The resulting suspension was well stirred for 2 h under argon at room temperature and then used for the preparation of cerium ester enolate.

(b) Preparation of Lithium Ester Enolate **1** of Ethyl Acetate



To a stirred solution of diisopropylamine (405 mg, 4.0 mmol) in dry THF (5 mL), was added *n*–BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol) dropwise at -78°C. The resulting solution was stirred at the same temperature for 20 min under argon. Ethyl acetate (326 mg, 3.7 mmol) in THF (2 mL) was then added to the LDA (1.1 equiv.) solution at -78°C and the mixture was kept stirring for 25 min at -78°C.

(c) Transmetallation of Lithium Ester Enolate **1** with $CeCl_3$ to Generate Cerium Ester Enolate **4** of Ethyl Acetate



The cerium chloride suspension in THF was cooled with stirring to -78°C with a dry ice–acetone bath. The lithium ester enolate prepared from ethyl acetate was quickly transferred to the cerium chloride suspension in THF *via* a cannula. The mixture was vigorously stirred at -78°C for 2 h under an argon atmosphere to ensure the formation of the cerium ester enolate.

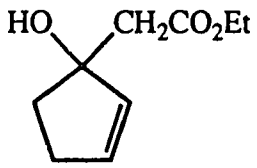
(d) Addition of Cerium Ester Enolate **4** to Carbonyl Compounds

The carbonyl compound (1.80 mmol) dissolved in a small amount of THF was added dropwise to the cerium ester enolate (2.00–2.50 equiv.) by syringe at -78°C and the reaction mixture was stirred at the same temperature for several hours until no starting material was present in the mixture by TLC inspection. The reaction mixture was quenched with saturated NH_4Cl at -78°C and extracted with Et_2O–hexane (1:1) (3 × 15 mL). The combined extracts were washed with H_2O and brine and dried with $MgSO_4$. After evaporation of the solvents, the residue was subjected to flash column chromatography on silica gel (EtOAc in hexane as eluant) or bulb–to–bulb distillation to afford the alcohol(s).

General Procedure for the Addition of Lithium Enolate 1 of Ethyl Acetate to Enones

For the purpose of comparison of cerium enolate with lithium enolate, the reactions of lithium enolate **1** of ethyl acetate with several enones were carried out as follows. The lithio ethyl acetate was prepared according to the procedure described above at -78°C. The enone in dry THF was added and the resulting mixture was stirred at -78°C under an atmosphere of argon for a period of time comparable to that used for the corresponding reaction involving the cerium enolate.

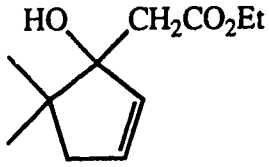
1-(Ethoxycarbonylmethyl)-2-cyclopenten-1-ol (6).



Following the general procedure, 2-cyclopenten-1-one (164 mg, 2.0 mmol) was reacted with cerium enolate **4** (4.0 mmol) for 3.5 h. The adduct **6** was isolated as a colorless oil in 96% yield (326 mg) after purification by flash column chromatography on silica gel (15% EtOAc in hexane as eluant): ^{1}H NMR(300 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 5.5, 2.2 Hz, 1 H, CH=CH), 5.78 (dt, *J* = 5.5, 2.2 Hz, 1 H, CH=CH), 4.20 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 3.61 (s, 1 H, OH), 2.66 (d, *J* = 15 Hz, 1 H, $CHHCO_2Et$), 2.62 (d, *J* = 15 Hz, 1 H, $CHHCO_2Et$), 2.50 (m, 1 H), 2.30 (m, 1 H), 2.00 (m, 2 H), 1.28 (t, *J* = 7 Hz, CH_2CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.72 (s, C=O), 135.07 (d, CH=), 134.13 (d, =CH), 83.15 (s, COH), 60.66 (t, OCH_2), 44.49 (t, CH_2CO_2), 37.76 (t, CH_2), 30.92 (t, CH_2), 14.16 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 3499 (OH), 3478 (OH), 1735 (C=O) cm^{-1}; HRMS M^+ 170.0943 (calcd for $C_9H_{14}O_3$

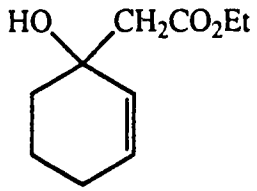
170.0943); Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.36; H, 8.45.

1-(Ethoxycarbonylmethyl)-5,5-dimethyl-2-cyclopenten-1-ol (8).



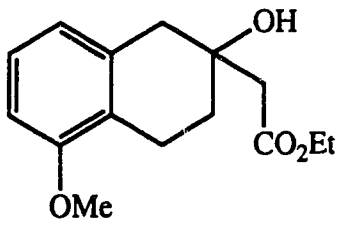
Treatment of 5,5-dimethyl-2-cyclopentenone (334 mg, 3.00 mmol) with cerium enolate **4** (6.7 mmol) in THF for 4 h at -78°C gave alcohol **8** as a colorless oil in 97% yield (576 mg) after purification by flash column chromatography (silica gel, 15% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dt, J = 5.5, 2.2 Hz, 1 H, C**H**=CH), 5.79 (dt, J = 5.5, 2 Hz, 1 H, CH=C**H**), 4.19 (m, 2 H, OCH_2), 3.62 (s, 1 H, OH), 2.58 (d, J = 15.6 Hz, 1 H, C**H**HCO$_2$Et), 2.48 (d, J = 15.6 Hz, 1 H, CH**H**CO$_2$Et), 2.34 (ddd, J = 16, 2, 2 Hz, 1 H, C**H**HCH=), 2.09 (ddd, J = 16, 2, 2 Hz, 1 H, CH**H**CH=), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.1 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 173.52 (s, C=O), 135.40 (d, CH=), 132.77 (d, =CH), 84.08 (s, C-OH), 66.95 (t, OCH_2), 60.73 (t, CH_2CO_2), 46.96 (t, CH_2CH=), 39.78 (s, CMe_2), 24.78 (q, CH_3), 22.98 (q, CH_3), 14.17 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 3500 (OH), 1716 (C=O) cm^{-1}; HRMS M$^+$ 198.1257 (calcd for $C_{11}H_{18}O_3$ 198.1256); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.46; H, 8.95.

1-(Ethoxycarbonylmethyl)-2-cyclohexen-1-ol (10).



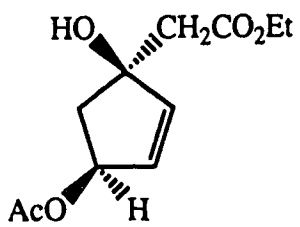
By the above standard procedure, 2–cyclohexen–1–one (196 mg, 2.04 mmol) was reacted with cerium enolate **4** (4.5 mmol) in THF at -78°C for 4 h. The tertiary alcohol **10** was obtained as a colorless oil in 100% yield (376 mg, 2.04 mmol) after bulb–to–bulb distillation (40°C, 0.1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dt, *J* = 10, 4 Hz, 1 H, C**H**=CH), 5.68 (br dt, *J* = 10, 1.3 Hz, 1 H, CH=C**H**), 4.19 (q, *J* = 7 Hz, 2 H, OCH_2), 3.60 (s, 1 H, OH), 2.56 (d, *J* = 16 Hz, 1 H, C**H**HCO_2Et), 2.52 (d, *J* = 16 Hz, 1 H, CH**H**CO_2Et), 1.6–2.1 (m, 6 H, $CH_2CH_2CH_2$), 1.30 (t, *J* = 7 Hz, CH_2CH_3); ^{13}C APT NMR (75 MHZ, $CDCl_3$) δ 172.54 (s, C=O), 131.00 (d, CH=), 130.29 (d, =CH), 68.20 (s, C–OH), 60.66 (t, OCH_2), 45.52 (t, CH_2CO_2Et), 35.78 (t, CH_2), 25.05 (t, CH_2), 18.96 (t, CH_2), 14.21 (q, OCH_2CH_3); FT–IR ($CHCl_3$) 3500 (OH), 1732, 1716 (C=O) cm^{-1}; HRMS M^+ 184.1101 (calcd for $C_{10}H_{16}O_3$ 184.1098); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.09; H, 8.75.

2–(Ethoxycarbonylmethyl)–5–methoxy–1,2,3,4–tetrahydro–2–naphthol (12).

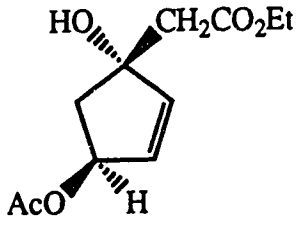


5–Methoxy–2–tetralone (400 mg, 2.27 mmol) was treated with cerium enolate **4** (8 mmol, 3.5 equiv.) in THF at -78°C. TLC analysis showed the complete consumption of the ketone after stirring for 15 h. The alcohol **12** was produced in 92% yield (551 mg, 2.09 mmol) as a white solid whose melting point is 25–30°C after purification by flash column chromatography (silica gel, 20% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8, 8 Hz, 1 H, ArH), 6.68 (d, *J* = 8 Hz, 2 H, ArH), 4.19 (q, *J* = 7 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.74 (s, 1 H, OH), 2.86 (m, 3 H), 2.62–2.70 (m, 1 H), 2.58 (d, *J* = 16 Hz, 1 H, **CH**HCO$_2$Et), 2.54 (d, *J* = 16 Hz, 1 H, CH**H**CO$_2$Et), 1.90–2.00 (m, 1 H), 1.84 (m, 1 H), 1.28 (t, *J* = 7 Hz, 3 H, CH_2CH_3); ^{13}C APT NMR (75 MHz. $CDCl_3$) δ 172.90 (s, C=O), 157.20 (s, Ph), 135.44 (s, Ph), 126.51 (d, Ph), 123.88 (s, Ph), 121.64 (d, Ph), 107.32 (d, Ph), 69.21 (s, C–OH), 60.75 (t, OCH_2), 55.24 (q, OMe), 43.42 (t, CH_2CO_2), 41.81 (t, CH_2), 33.60 (t, CH_2), 20.83 (t, CH_2), 14.22 (q, OCH_2CH_3); FT–IR ($CHCl_3$) 3500 (OH), 1728 (C=O), 1715 (C=O), 1578 (Ph) cm^{-1}; HRMS M$^+$ 264.1366 (calcd for $C_{15}H_{20}O_4$ 264.1362); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 67.92; H, 7.44.

(1*S, 4*S**)–(14a) and (1*R**, 4*S**)–(14b)–4–Acetoxy–1–(ethoxy carbonylmethyl)–2–cyclopenten–1–ol.**



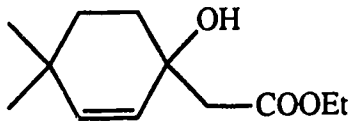
14a



14b

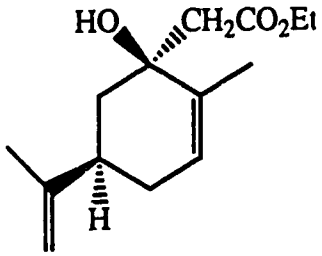
4–Acetoxy–2–cyclopenten–1–one (322 mg, 2.30 mmol) was added to the cerium enolate **4** (8.00 mmol) at -78°C and the reaction mixture was stirred at the same temperature for 7 h. The progress of the reaction was monitored by analytical TLC (silica gel). After the usual work–up and flash column chromatography on silica gel (40% EtOAc in hexane as eluant), an inseparable mixture (9:1) of the diastereoisomeric alcohols **14a** and **14b** was isolated as a colorless oil in 98% yield (514 mg, 2.25 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) major diastereoisomer **14a** δ 6.09 (dd, *J* = 5.5, 1 Hz, 1 H, C**H**=CH), 5.93 (dd, *J* = 5.5, 2 Hz, 1 H, CH=C**H**), 5.55 (m, 1 H, AcOCH), 4.19 (q, 2 H, *J* = 7 Hz, OCH_2), 3.84 (s, 1 H, OH), 2.66 (d, *J* = 15 Hz, 1 H, C**H**HCO_2Et), 2.59 (d, *J* = 15 Hz, 1 H, CH**H**CO_2Et), 2.55 (dd, *J* = 14, 7.5 Hz, 1 H, CHC**H**H), 2.05 (s, 3 H, CH_3COO), 2.00 (dd, *J* = 14, 4 Hz, 1 H, CHCH**H**), 1.28 (t, *J* = 7 Hz, 3 H, CH_2CH_3); minor diastereoisomer **14b** δ 5.96 (dd, *J* = 6, 4.5 Hz, 1 H, C**H**=CH), 5.76 (m, 1 H, AcOCH), 3.89 (s, 1 H, OH), 2.79 (d, *J* = 16 Hz, 1 H, C**H**HCO_2Et), 2.72 (d, *J* = 16 Hz, 1 H, CH**H**CO_2Et), 2.45 (dd, *J* = 12, 7 Hz, 1 H, CHC**H**H), 2.04 (s, 3 H, CH_3COO), (other peaks were overlapped with those of the major diastereoisomer); ^{13}C APT NMR (75 MHz, $CDCl_3$) major diastereoisomer **14a** δ 172.22 (s, C=O), 170.84 (s, C=O), 140.22 (d, CH=), 131.87 (d, =CH), 80.99 (s, C–OH), 76.97 (d, CHOAc), 60.97 (t, OCH_2), 44.99 (t, CH_2CO_2), 44.36 (t, CH_2), 21.44 (q, CH_3COO), 14.15 (q, OCH_2CH_3); minor diastereoisomer **14b** δ 173.80 (s, C=O), 140.94 (d, CH=), 132.13 (d, CH=), 78.32 (d, CHOAc), 45.15 (t, CH_2CO_2), (other peaks were overlapped with those of the major diastereoisomer); FT–IR ($CHCl_3$) 3494, 3488, 3479, 3468 (OH), 1733 (C=O) cm^{-1}; HRMS M^+ was not observed; HRMS $[M–OH]^+$ 211.0964 (calcd for $C_{11}H_{15}O_4$ 211.0970); Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.01. Found: C, 58.30; H, 7.06.

1-(Ethoxycarbonylmethyl)-4,4-dimethyl-2-cyclohexen-1-ol (16).



Enone **15** (250 mg, 2.01 mmol) was treated with cerium enolate **4** (5.60 mmol) at -78°C for 3.5 h, giving the alcohol **16** as a colorless oil in 96% yield (405 mg, 1.93 mmol) after flash column chromatography on silica gel (15% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (s, 2 H, CH=CH), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 3.58 (s, 1 H, OH), 2.56 (d, J = 15 Hz, 1 H, C**H**HCO$_2$Et), 2.54 (d, J = 15 Hz, 1 H, CH**H**CO$_2$Et), 1.6–1.9 (m, 3 H), 1.4–1.5 (m, 1 H), 1.29 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.06 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3); FT-IR ($CHCl_3$) 3500 (OH), 1732 and 1717 (C=O) cm^{-1}; HRMS M$^+$ 212.1413 (calcd for $C_{12}H_{20}O_3$ 212.1413).

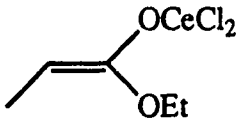
(1*S*, 5*R*)-1-(Ethoxycarbonylmethyl)-2-methyl-5-(1-methyl ethenyl)-2-cyclohexen-1-ol (18).



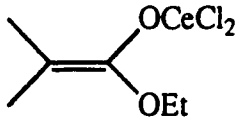
Following the standard procedure, (–)-5*R*-carvone (300 mg, 2.00 mmol) was reacted with cerium enolate **4** in THF at -78°C for 4 h. Analytical TLC indicated the complete disappearance of (–)-carvone after this period of

reaction. After the usual work–up and flash column chromatography on silica gel (10% EtOAc in hexane as eluant), the optically active alcohol **18** was obtained as a colorless oil in 100% yield (476 mg, 2.00 mmol): $[\alpha]_D^{22}$ = -31.40° (c = 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (m, 1 H, CH=C), 4.73 (m, 2 H, CH_2=C), 4.20 (m, 2 H, OCH_2), 3.86 (s, 1 H, OH), 2.75 (dd, *J* = 15, 1.5 Hz, 1 H, **CH**HCO$_2$Et), 2.58 (d, *J* = 15 Hz, 1 H, CH**H**CO$_2$Et), 2.28 (m, 1 H, CH_2**CH**CH_2), 1.90–2.14 (m, 3 H, **CH**H**CH**$_2$), 1.73 (m, 6 H, 2 × CH_3), 1.68 (dd, *J* = 13, 1.5 Hz, 1 H, **CH**H**CH**$_2$), 1.29 (t, *J* = 7 Hz, 3 H, CH_2**CH**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.73 (s, C=O), 148.31 (s, C=CH), 136.82 (s, C=CH_2), 124.30 (d, CH=), 109.08 (t, CH_2=), 72.54 (s, C–OH), 60.63 (t, OCH_2), 41.82 (t, **C**H$_2$CO$_2$), 40.94 (t, CH_2), 39.56 (d, CH_2**C**HCH_2), 30.74 (t, CH_2), 20.32 (q, CH_3), 16.92 (q, CH_3), 14.06 (q, OCH_2**C**H$_3$); FT–IR ($CHCl_3$) 3509 (OH), 3505 (OH), 1715 (C=O), 1645 (C=C) cm^{-1}; HRMS M^+ 238.1570 (calcd for $C_{14}H_{22}O_3$ 238.1569); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.79; H, 9.44.

General Procedure for the Addition of Cerium Enolates 19 and 25 to Carbonyl Compounds



19

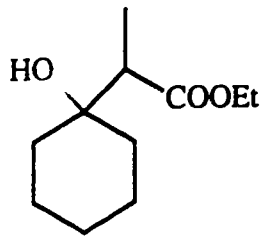


25

The standard procedure previously described for the addition of cerium enolate **4** was followed except that the lithium enolates of ethyl propionate and ethyl isobutyrate were used instead of lithium ethyl acetate. After the usual work–up,

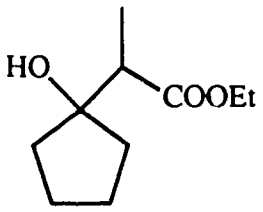
the crude product was purified by flash column chromatography on silica gel (EtOAc in hexane as eluant).

1-(1-Ethoxycarbonylethyl)-1-cyclohexanol (21).



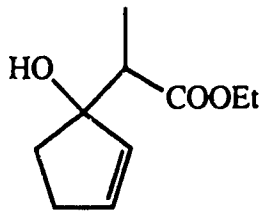
Using the general procedure, cyclohexanone (350 mg, 3.57 mmol) was treated with cerium enolate **19** in THF at -78°C for 8 h and the desired alcohol **21** was formed in 94% yield (671 mg, 3.36 mmol) as a colorless oil (8% EtOAc in hexane as eluant for flash column chromatography on silica gel): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (m, 2 H, OCH_2), 3.07 (s, 1 H, OH), 2.50 (q, J = 7 Hz, 1 H, $CHCO_2$), 1.40–1.70 (m, 10 H, $(CH_2)_5$), 1.29 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.20 (d, J = 7 Hz, CH_3CH); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 177.04 (s, C=O), 71.37 (s, C–OH), 60.52 (t, OCH_2), 47.94 (d, CHMe), 37.13 (t, CH_2), 33.90 (t, CH_2), 25.77 (t, CH_2), 22.00 (t, CH_2), 21.69 (t, CH_2), 14.25 (q, CH_3CH), 11.58 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 3517 (OH), 1729 and 1713 (C=O) cm^{-1}; HRMS M^+ 200.1412 (calcd for $C_{11}H_{20}O_3$ 200.1412); Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.00; H, 10.00. Found: C, 65.94; H, 9.82.

1-(1-Ethoxycarbonylethyl)-1-cyclopentanol (23).



Reaction of cerium enolate **19** (8.00 mmol) with ketone **22** (270 mg, 3.20 mmol) in THF at -78°C for 6 h gave the alcohol **23** as a colorless oil in 97% yield (580 mg, 3.12 mmol) after purification by flash column chromatography on silica gel (8% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (m, 2 H, OCH_2), 3.06 (s, OH), 2.49 (q, J = 7 Hz, 1 H, $CHCO_2$), 1.40–2.00 (m, 8 H, $(CH_2)_4$), 1.29 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.28 (d, J = 7 Hz, 3 H, CH_3CH); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 177.09 (s, C=O), 82.11 (s, C–OH), 60.54 (t, OCH_2), 48.03 (d, CHMe), 39.91 (t, CH_2), 37.27 (t, CH_2), 24.03 (t, CH_2), 23.83 (t, CH_2), 14.24 (q, OCH_2CH_3), 13.30 (q, CH_3); FT–IR ($CHCl_3$) 3525 (OH), 1730 and 1714 (C=O) cm^{-1}; HRMS M$^+$ 186.1255 (calcd for $C_{10}H_{18}O_3$ 186.1256); Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 64.59; H, 9.46.

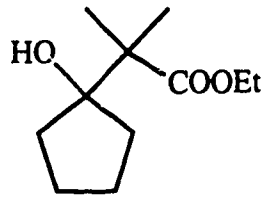
1–(1–Ethoxycarbonylethyl)–2–cyclopenten–1–ol (24).



Following the above standard procedure, treatment of 2–cyclopenten–1–one (270 mg, 3.29 mmol) with cerium enolate **19** (8.00 mmol) in THF at -78°C for 6 h yielded a 6:1 mixture of the diastereoisomeric alcohols **24** (580 mg, 3.15

mmol, 96% yield) as a colorless oil after flash column chromatography on silica gel (15% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) major diastereoisomer δ 5.95 (dt, *J* = 5.5, 1.6 Hz, 1 H, CH=CH), 5.64 (dt, *J* = 5.5, 1.4 Hz, 1 H, CH=CH), 4.20 (q, *J* = 7 Hz, 2 H, OCH_2), 3.38 (s, 1 H, OH), 2.64 (q, *J* = 7 Hz, 1 H, $CHCO_2$), 2.52 (m, 1 H), 2.30 (m, 1 H), 2.06 (m, 1 H), 1.88 (m, 1 H), 1.30 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.22 (d, *J* = 7 Hz, 3 H, CH_3CH); minor diastereoisomer δ 5.80 (dt, *J* = 5.5, 2.2 Hz, 1 H, CH=), 3.28 (s, 1 H, OH), 2.52 (m, 1 H), 2.40 (m, 1 H), (other peaks were overlapped with those of the major diastereoisomer); ^{13}C APT NMR (75 MHz, $CDCl_3$) major diastereoisomer δ 176.18 (s, C=O), 134.81 (d, CH=), 134.48 (d, =CH), 86.18 (s, C–OH), 60.56 (t, OCH_2), 47.38 (d, $CHCO_2$), 34.40 (t, CH_2), 31.16 (t, CH_2), 14.12 (q, CH_3), 12.71 (q, CH_3); minor diastereoisomer δ 175.32 (s, C=O), 135.07 (d, CH=), 133.24 (d, CH=), 86.39 (s, C–OH), 60.47 (t, OCH_2), 48.01 (d, CHCOO), 38.65 (t, CH_2), 34.51 (t, CH_2), 15.85 (q, CH_3), 15.15 (q, CH_3); FT–IR ($CHCl_3$) 3508, 3502 (OH), 1732 and 1710 (C=O) cm^{-1}; HRMS M^+ 184.1103 (calcd for $C_{10}H_{16}O_3$ 184.1099); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.46; H, 8.60.

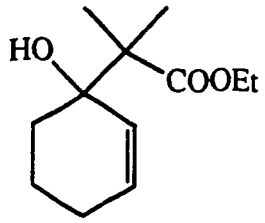
1-(1-Ethoxycarbonyl-1-methylethyl)-1-cyclopentanol (26).



Ketone **22** (270 mg, 3.20 mmol) was treated with cerium enolate **25** (8.0 mmol) in THF at -78°C for 7 h. After flash column chromatography on silica

gel (10% EtOAc in hexane as eluant), the alcohol **26** was isolated as a colorless oil in 97% yield (618 mg, 3.09 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, J = 7 Hz, 2 H, OCH_2), 3.27 (s, 1 H, OH), 1.70–1.90 (m, 4 H), 1.50–1.60 (m, 4 H), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.24 (s, 6 H, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 178.35 (s, C=O), 85.37 (s, C–OH), 60.69 (t, OCH_2), 48.52 (s, CCO_2), 35.68 (t, 2 × CH_2), 24.52 (t, 2 × CH_2), 21.83 (q, 2 × CH_3), 14.11 (q, OCH_2CH_3); FT–IR ($CHCl_3$) 3512 (OH), 1721 and 1705 (C=O) cm^{-1}; HRMS M$^+$ 200.1409 (calcd for $C_{11}H_{20}O_3$ 200.1412); Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.00; H, 10.00. Found: C, 66.29; H, 9.90.

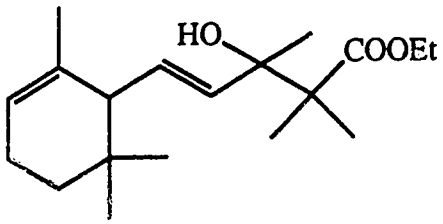
1–(1–Ethoxycarbonyl–1–methylethyl)–2–cyclohexen–1–ol (27).



Addition of cerium enolate **25** (9.00 mmol) to enone **9** (310 mg, 3.23 mmol) took place readily at -78°C but a longer reaction time (10 h) was needed to complete the reaction. The tertiary allylic alcohol **27** (630 mg, 2.97 mmol, 92%) was isolated as a colorless oil after purification by flash column chromatography on silica gel (15%–25% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1 H, CH=), 5.68 (m, 1 H, =CH), 4.19 (m, 2 H, OCH_2), 3.60 (s, 1 H, OH), 1.60–2.10 (m, 6 H, $(CH_2)_3$), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.26 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 178.12 (s, C=O), 131.98 (d, CH=), 128.16 (d, =CH), 72.24 (s, C–OH), 60.81 (t, OCH_2), 49.03 (s, CCO_2), 31.07 (t, CH_2), 25.10 (t, CH_2), 20.89

(q, CH_3), 20.79 (q, CH_3), 18.50 (t, CH_2), 14.09 (q, OCH_2CH_3); FT–IR ($CHCl_3$) 3492 (OH), 1720 and 1700 (C=O) cm^{-1}; HRMS M^+ 212.1413 (calcd for $C_{12}H_{20}O_3$ 212.1412); Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 68.16; H, 9.56.

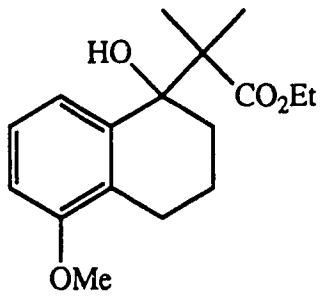
(*E*)–4–Carboethoxy–3,4–dimethyl–1–(2,6,6–trimethyl–2–cyclo hexenyl)penten–3–ol (29).



Following the standard procedure, α–ionone (500 mg, 2.60 mmol) was treated with cerium enolate **25** (8.00 mmol) in THF at -78°C under argon for 9 h. After the usual work–up, the crude product was purified by flash column chromatography on silica gel (5%–10% EtOAc in hexane as eluant), providing a 1:1 mixture of diastereoisomers **29** (803 mg, 2.60 mmol, 100% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (m, 2 H, CH=CH), 5.40 (br s, 1 H, CH=), 4.15 (m, 2 H, OCH_2), 3.92 (s, 1 H, OH), 2.10 (br s, 1 H, =CCHC=), 2.00 (m, 2 H), 1.58 (m, 3 H, CH_3C=), 1.44 (m, 1 H), 1.27 (two sets of triplets, J = 7 Hz, 3 H, OCH_2CH_3), 1.24 (s, 6 H, 2 × CH_3), 1.21 (s, 3 H, CH_3), 0.91 (m, 1 H), 0.89 (two sets of singlets, 3 H, CH_3), 0.80 (two sets of singlets, 3 H, CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 178.35 and 178.27 (s, C=O), 134.46 and 134.37 (d, CH=), 134.11 and 134.01 (s, CH_3C=), 130.89 and 130.82 (d, CH=), 120.99 and 120.94 (d, =CH), 75.55 and 75.50 (s, C–OH), 60.93 (t, OCH_2), 54.30 and 54.13 (d, =CCHCH=), 49.55 (s, Me_2CCO_2), 32.19

and 32.03 (s, CMe_2), 31.62 and 31.58 (t, CH_2), 27.65 and 27.54 (q, CH_3), 27.02 and 27.00 (q, CH_3), 23.69 (q, CH_3), 23.09 (t, CH_2), 22.98 and 22.89 (q, CH_3), 21.46 and 21.32 (q, CH_3), 14.08 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 3500 (OH), 1723 (C=O), 1699 (C=O), 1472 (C=C) cm^{-1}; HRMS M^+ 308.2348 (calcd for $C_{19}H_{32}O_3$ 308.2351); Anal. Calcd for $C_{19}H_{32}O_3$: C, 74.03; H, 10.39. Found: C, 74.32; H, 10.48.

1-(1-Ethoxycarbonyl-1-methylethyl)-5-methoxy-1,2,3,4-tetra hydro-1-naphthol (31).



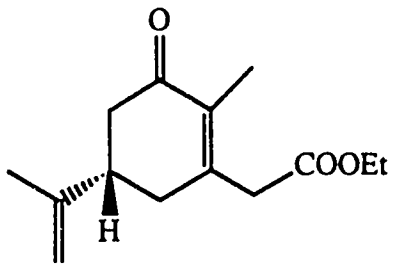
By the standard procedure, cerium enolate **25** (9.00 mmol, 4.0 equiv.) was reacted with 5-methoxy-1-tetralone (400 mg, 2.23 mmol) in THF at -78°C for 20 h. Alcohol **31** was obtained as a colorless viscous oil in 97% yield (632 mg, 2.16 mmol) after flash column chromatography on silica gel (15% EtOAc in hexane as eluant). The product and starting ketone have the same R_f value on analytical TLC. Only after the mixture was stirred for 15 h did ^1H NMR analysis show that the reaction was completed: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 4 Hz, 1 H, ArH), 7.13 (d, J = 4 Hz, 1 H, ArH), 6.72 (dd, J = 4, 4 Hz, 1 H, ArH), 4.58 (s, 1 H, OH), 4.22 (q, J = 7 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 2.99 (dt, J = 17, 4 Hz, 1 H, ArCHH), 2.20 (ddd, J = 17, 11, 5 Hz, 1 H,

ArCHH), 1.98 (m, 2 H), 1.89 (m, 2 H), 1.31 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.26 (s, 3 H), 1.00 (s, 3 H); FT–IR ($CHCl_3$) 3480 (OH), 1720 (C=O), 1691 (C=O), 1583 (Ar) cm^{-1}; HRMS M^+ 292.1675 (calcd for $C_{17}H_{24}O_4$ 292.1675).

General Procedure for the Oxidation of Tertiary Allylic Alcohols with PCC in CH_2Cl_2

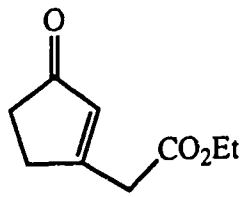
To a magnetically stirred slurry of PCC (2.00 mmol) in CH_2Cl_2 (5–8 mL), was added in one portion a solution of tertiary allylic alcohol (1.00 mmol) in CH_2Cl_2 (2 mL) at room temperature. The resulting dark red–black mixture was stirred for several hours at room temperature under an atmosphere of argon. The progress of the reaction was monitored by the analytical TLC on silica gel. After the complete consumption of the starting material, the reaction mixture was diluted with Et_2O (15 mL). The ethereal solution was decanted from the black resinous residue, which in turn was washed with Et_2O (3 × 10 mL). The combined ethereal solutions were passed through a short column (*ca.* 10 cm) of Florisil to remove any black polar material. The column was washed with diethyl ether (3 × 10 mL) and the combined ethereal solutions were concentrated on a rotatory evaporator. The residue was subjected to flash column chromatography on silica gel (EtOAc in hexane as eluant) to afford the desired enone.

(+)–(5*S*)–3–(Ethoxycarbonylmethyl)–5–(1–methylethenyl)–2–methyl–2–cyclohexen–1–one (33).



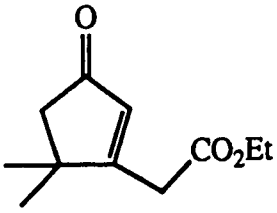
Alcohol **18** (280 mg, 1.17 mmol) was oxidized with PCC (3.53 mmol, 3.0 equiv.) in CH_2Cl_2 (8 mL) for 50 h. Since the oxidation was quite slow, an excess (3.0 equiv.) of PCC was used. After flash column chromatography on silica gel (10% EtOAc in hexane as eluant), the optically active enone **33** was obtained in 81% yield (224 mg, 0.95 mmol) as a colorless oil: $[\alpha]_D^{22}$ = +66.33° (c = 1.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (m, 1 H, C**H**H=), 4.76 (m, 1 H, CH**H**=), 4.19 (q, *J* = 7 Hz, 2 H, OCH_2), 3.33 (d, *J* = 15 Hz, 1 H, C**H**HCO$_2$), 3.28 (d, *J* = 15 Hz, 1 H, CH**H**CO$_2$), 2.68 (m, 1 H), 2.60 (ddd, *J* = 16, 4, 1.5 Hz, 1 H, CHeqHaxC=O), 2.47 (m, 2 H), 2.34 (dd, *J* = 16, 13 Hz, 1 H, CHeq**H**axC=O), 1.81 (br t, *J* = 2 Hz, 3 H, C**H**$_3$C=CH$_2$), 1.76 (br s, 3 H, CH$_3$C=C), 1.28 (t, *J* = 7 Hz, 3 H, OCH$_2$C**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 198.99 (s, C=O, ketone), 169.63 (s, C=O, ester), 148.92 (s, =CCH$_2$COOEt), 146.51 (s, CH$_3$C=C), 133.35 (s, CH$_3$C=CH$_2$), 110.58 (t, CH$_2$=C), 61.18 (t, OCH$_2$), 42.51 (t, CH$_2$CO$_2$Et), 41.28 (d, CH$_2$CHCH$_2$), 40.70 (t, CH$_2$), 36.61 (t, CH$_2$), 20.50 (q, CH$_3$), 14.19 (q, CH$_3$), 11.01 (q, CH$_3$); FT-IR ($CHCl_3$) 1736 (C=O, ester), 1671 (C=O, enone), 1639 (C=C) cm^{-1}; HRMS M^+ 236.1415 (calcd for $C_{14}H_{20}O_3$ 236.1412); Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47. Found: C, 71.35; H, 8.31.

3-Ethoxycarbonylmethyl-2-cyclopenten-1-one (34).



Following the standard procedure, the alcohol **6** (330 mg, 1.94 mmol) was treated with PCC (835 mg, 3.88 mmol) in CH_2Cl_2 (20 mL) at room temperature for 2.5 h. The enone ester **34** was obtained as a light brown oil in 72% yield (235 mg, 1.40 mmol) after flash column chromatography on silica gel (20% EtOAc in hexane as eluant): ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (br s, 1 H, CH=), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 3.47 (br s, 2 H, CH_2CO_2), 2.70 (m, 2 H, CH_2), 2.46 (m, 2 H, CH_2), 1.30 (t, J = 7 Hz, OCH_2CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 209.02 (s, C=O, ketone), 172.55 (s, C=O, ester), 168.59 (s, C=), 132.23 (d, CH=), 61.13 (t, OCH_2), 38.62 (t, CH_2), 35.25 (t, CH_2), 31.41 (t, CH_2), 13.95 (q, CH_3); FT–IR ($CHCl_3$) 1735 (C=O, ester), 1714 (C=O, enone), 1676 (C=C), 1620 (C=C) cm^{-1}; HRMS M^+ 168.0785 (calcd for $C_9H_{12}O_3$ 168.0786); Anal. Calcd for $C_9H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.18; H, 7.17.

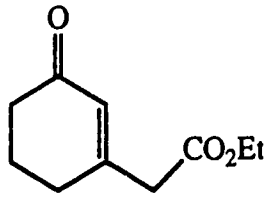
3–Ethoxycarbonylmethyl–4,4–dimethyl–2–cyclopenten–1–one (35).



Treatment of allylic alcohol **8** (210 mg, 1.06 mmol) with PCC (457 mg, 2.12 mmol) in CH_2Cl_2 (10 mL) for 15 h afforded the enone ester **35** in 53% yield

(110 mg, 0.56 mmol) as a light brown oil after purification by flash column chromatography (15% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (br t, J = 1.2 Hz, 1 H, CH=), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 3.33 (d, J = 1.3 Hz, 2 H, CH_2CO_2), 2.32 (s, 2 H, CH_2C=O), 1.29 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.22 (s, 6 H, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 207.05 (s, C=O, ketone), 179.09 (s, C=O, ester), 169.28 (s, C=), 130.35 (d, CH=), 61.32 (t, OCH_2), 51.26 (t, CH_2CO_2), 43.17 (t, O=CCH_2), 33.98 (s, CMe_2), 26.66 (q, 2 × CH_3), 14.07 (q, CH_3); FT-IR ($CHCl_3$) 1739 (C=O, ester), 1718 (C=O, enone), 1693 (C=C), 1618 (C=C) cm^{-1}; HRMS M^+ 196.1101 (calcd for $C_{11}H_{16}O_3$ 196.1100); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.15; H, 8.22.

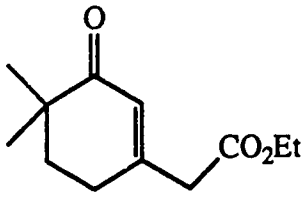
3-Ethoxycarbonylmethyl-2-cyclohexen-1-one (36).



Using the standard procedure, the tertiary allylic alcohol **10** (340 mg, 1.85 mmol) was treated with PCC (997 mmol, 4.63 mmol) in CH_2Cl_2 (10 mL) for 2 h. The crude product was purified by flash column chromatography on silica gel (15% EtOAc in hexane as eluant) to afford the enone ester **36** as a light brown oil in 74% yield (250 mg, 1.37 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (br t, J = 1.2 Hz, 1 H, CH=), 4.19 (q, J = 7 Hz, 2 H, OCH_2), 3.22 (br s, 2 H, CH_2CO_2), 2.40 (m, 4 H), 2.04 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 199.22 (s, C=O, ketone),

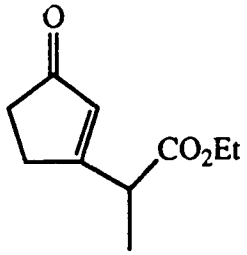
169.28 (s, C=O, ester), 157.18 (s, C=), 128.64 (d, CH=), 61.12 (t, OCH_2), 43.31 (t, CH_2CO_2), 37.03 (t, $O{=}CCH_2$), 29.50 (t, CH_2), 22.46 (t, CH_2), 14.05 (q, CH_3); FT-IR ($CHCl_3$) 1736 (C=O, ester), 1673 (C=O, enone), 1631 (C=C) cm^{-1}; HRMS M^+ 182.0943 (calcd for $C_{10}H_{14}O_3$ 182.0943); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.66; H, 7.89.

3-Ethoxycarbonylmethyl-6,6-dimethyl-2-cyclohexen-1-one (37).



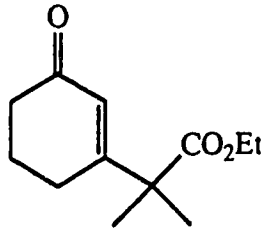
Treatment of alcohol **16** (330 mg, 1.58 mmol) with PCC (850 mg, 3.95 mmol) in CH_2Cl_2 (8 mL) at room temperature for 2 h gave the enone ester **37** as an oil in 63% yield (210 mg, 1.00 mmol) after purification by flash column chromatography on silica gel (5% EtOAc in hexane as eluant): ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (br t, J = 1.2 Hz, 1 H, CH=), 4.18 (q, J = 7 Hz, 2 H, OCH_2), 3.20 (br s, 2 H, CH_2CO_2), 2.42 (br t, J = 6 Hz, 2 H, CH_2), 1.84 (t, J = 6 Hz, 2 H, CH_2), 1.29 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.10 (s, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 204.04 (s, C=O, ketone), 169.46 (s, C=O, ester), 154.90 (s, C=), 127.19 (d, CH=), 61.10 (t, OCH_2), 43.03 (t, CH_2CO_2), 40.37 (s, CC=O), 36.07 (t, $=CCH_2$), 27.04 (t, CH_2), 23.94 (q, 2 × CH_3), 14.09 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 1737 (C=O, ester), 1673 (C=O, enone), 1637 (C=C) cm^{-1}; HRMS M^+ 210.1257 (calcd for $C_{12}H_{18}O_3$ 210.1257); Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.25; H, 8.53.

3-(1-Ethoxycarbonylethyl)-2-cyclopenten-1-one (38).



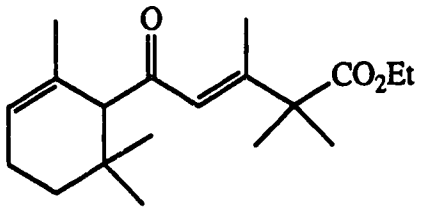
Following the standard procedure, oxidation of allylic alcohol **24** (288 mg, 1.57 mmol) with PCC (1.01 g, 4.70 mmol, 3.0 equiv) in CH_2Cl_2 (7 mL) for 4 h furnished the enone ester **38** as a light brown oil in 56% yield (160 mg, 0.88 mmol) after purification by flash column chromatography on silica gel (30% EtOAc in hexane as eluant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (br q, J = 1 Hz, 1 H, CH=), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 3.56 (br q, J = 7 Hz, 1 H, $CHCO_2$), 2.68 (m, 2 H), 2.44 (t, J = 5 Hz, 2 H), 1.44 (d, J = 7 Hz, 3 H, CH_3CH), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 209.17 (s, C=O, ketone), 178.46 (s, C=O, ester), 171.93 (s, C=), 130.75 (d, CH=), 61.29 (t, OCH_2), 43.54 (d, CHMe), 35.24 (t, $O=CCH_2$), 29.75 (t, CH_2), 15.69 (q, CH_3), 14.10 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 1736 (C=O, ester), 1715 (C=O, enone), 1677 and 1615 (C=C) cm^{-1}; HRMS M^+ 182.0943 (calcd for $C_{10}H_{14}O_3$ 182.0943); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 66.20; H, 7.86.

3-(1-Ethoxycarbonyl-1-methylethyl)-2-cyclohexen-1-one (39).



By the standard procedure, the allylic alcohol **27** (260 mg, 1.23 mmol) was reacted with PCC (793 mg, 3.68 mmol) in CH_2Cl_2 at room temperature for 10 h to give the enone ester **39** (232 mg, 1.10 mmol, 90%) as an oil after flash column chromatography on silica gel (25% EtOAc in hexane as eluant): ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (br s, 1 H, CH=), 4.16 (q, J = 7 Hz, 2 H, OCH_2), 2.40 (t, J = 7 Hz. 2 H), 2.28 (dt, J = 6, 1 Hz, 2 H), 2.00 (quintet, J = 7 Hz, 2 H, $CH_2CH_2CH_2$), 1.38 (s, 6 H, 2 × CH_3), 1.24 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 199.90 (s, C=O, ketone), 174.81 (s, C=O, ester), 166.62 (s, C=), 124.46 (d, CH=), 61.08 (t, OCH_2), 48.58 (s, CMe_2), 37.51 (t, CH_2), 27.10 (t, CH_2), 23.83 (q, 2 × CH_3), 23.10 (t, CH_2), 14.03 (q, OCH_2CH_3); FT-IR ($CHCl_3$) 1733 (C=O, ester), 1674 (C=O, enone), 1621 (C=C) cm^{-1}; HRMS M^+ 210.1259 (calcd for $C_{12}H_{18}O_3$ 210.1256); Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.41; H, 8.47.

(*E*)-4-Carboethoxy-3,4-dimethyl-1-(2,6,6-trimethyl-2-cyclo hexenyl)-2-penten-1-one (40).



Following the standard procedure, alcohol **29** (173 mg, 0.56 mmol) was treated with PCC (602 mg, 2.8 mmol) in CH_2Cl_2 (5 mL) at room temperature for 80 h under an atmosphere of argon. Analysis of the crude product by ^1H NMR and ^{13}C NMR spectra showed that a single diastereoisomer was produced. Flash column chromatography on silica gel (5% EtOAc in hexane as eluant) gave rise to enone **40** as a colorless oil in 93% yield (159 mg, 0.52 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (br q, J = 1 Hz, 1 H, O=CCH=), 5.61 (m, 1 H, CH=), 4.12 (m, 2 H, OCH_2), 2.69 (br s, 1 H, =CCHC=O), 2.11 (m, 2 H), 2.02 (d, J = 1 Hz, 3 H, CH_3C=CHC=O), 1.72 (m, 1 H), 1.60 (br d, J = 2.0 Hz, 3 H, CH_3C=CH), 1.34 (s, 6 H, $(CH_3)_2CCO_2$), 1.21 (t, J = 7 Hz, 3 H, OCH_2CH_3), 0.94 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 203.97 (s, C=O, ketone), 175.44 (s, C=O, ester), 157.44 (s, O=CCH=C), 131.11 (s, MeC=CH), 123.26 (d, CH=CMe), 122.72 (d, O=CCH=), 65.33 (d, CHC=O), 60.93 (t, OCH_2), 50.06 (s, Me_2CCO_2), 32.52 (s), 31.36 (t, CH_2), 28.16 (q, CH_3), 27.66 (q, CH_3), 24.23 (q, CH_3), 24.15 (q, CH_3), 23.35 (q, CH_3), 22.73 (t, CH_2), 16.87 (q, CH_3), 14.05 (q, CH_3); FT–IR ($CHCl_3$) 1733 (C=O, ester), 1682 (C=O, enone), 1610 (C=C) cm^{-1}; HRMS M^+ 306.2195 (calcd for $C_{19}H_{30}O_3$ 306.2190); Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.51; H, 9.80. Found: C, 74.64; H, 9.48.

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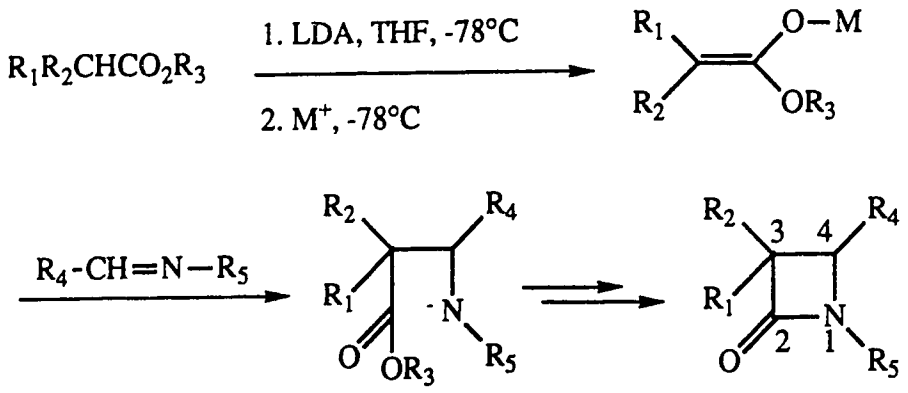
CHAPTER III

CERIUM ESTER ENOLATES IN ORGANIC SYNTHESIS: EFFICIENT SYNTHESIS OF β-LACTAMS

INTRODUCTION

Since the discovery of penicillin, the vast majority of new natural products possessing the β–lactam (2–azetidinone) ring have fallen into the family of compounds known as the β–lactam antibiotics. The β–lactam antibiotics have figured prominently in chemistry due to their desirable medicinal properties as chemotherapeutic agents, their structural novelty, and their attendant–rich chemistry. Thus, considerable efforts have been directed towards the development and utilization of β–lactam forming reactions.[1–4] In recent years, metal ester enolate–imine condensation reactions have been demonstrated to be one of the most promising methods for the construction of β–lactams. The condensation of Reformatsky–type reagents and imines to afford β–lactams was first reported by Gilman and Speeter[5] in 1943. Since this report, considerable attention has been given to the development of new β–lactam syntheses based on this reaction. Because the original reaction was not stereoselective, in most of the later studies zinc was replaced by other metals, *e.g.* lithium, tin, zirconium, titanium, boron, aluminium and magnesium, in order to obtain a stereoselective reaction, although this was not always successful. The general reaction pathway between the enolate of ester and imine is illustrated in Scheme III–1. First, the ester enolate adds to imine to generate the intermediate metal amide ester. In the second step of the β–lactam forming process, the intermediate metal amide acts as a strong nucleophile which attacks the ester functionality to replace the alkoxyl group, giving the azetidinone.

Scheme III-1



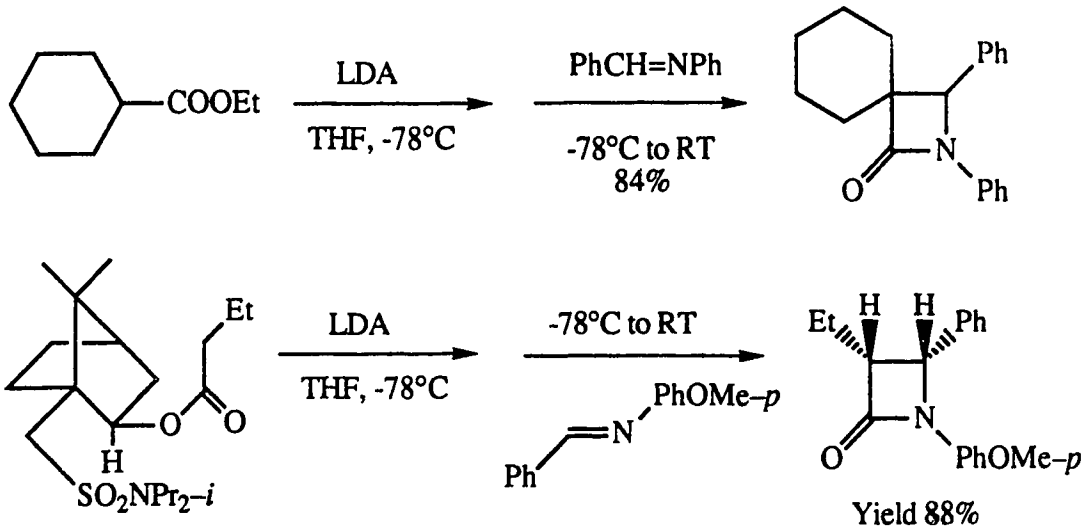
Of these reactions, the lithium ester enolate, aluminium ester enolate and zinc ester enolate were found to condense with imines to give β–lactams directly, while the boron and tin(II) enolates of thiolesters reacted with imines to afford the β–amino thiolesters, without producing β–lactams. In this section, the metal ester enolate–imine condensation reactions will be briefly discussed according to the type of the metal enolate.

(I) Lithium Ester Enolate–Imine Condensation

(a) With Non–Enolizable *N*–Aryl Imines

The condensation of lithium ester enolates with *N*–aryl imines (non–enolizable imines) to afford β–lactams was first reported in 1980 by Newcomb *et al.*[6] The condensation of simple lithium ester enolates with aryl imines was found to produce β–lactams directly in good yields. Excellent *cis* stereoselectivity was observed in the preparation of β–lactams with chiral centers at C–3 and C–4 of the β–lactam ring. When chiral ester enolates were used, asymmetric induction

occurred readily to yield optically active β–lactams with good enantioselectivity (Eq. 1). Hart and Lee[7] applied this methodology to the synthesis of carbapenem antibiotic (+)–PS–5.



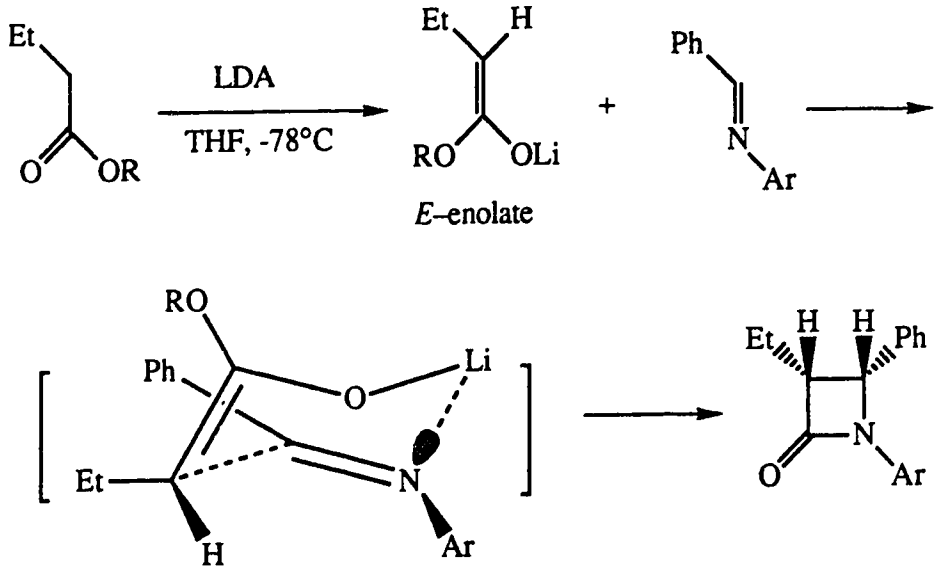
Oppolzer's chiral ester

Yield 88%
de. 99%
ee. 92%

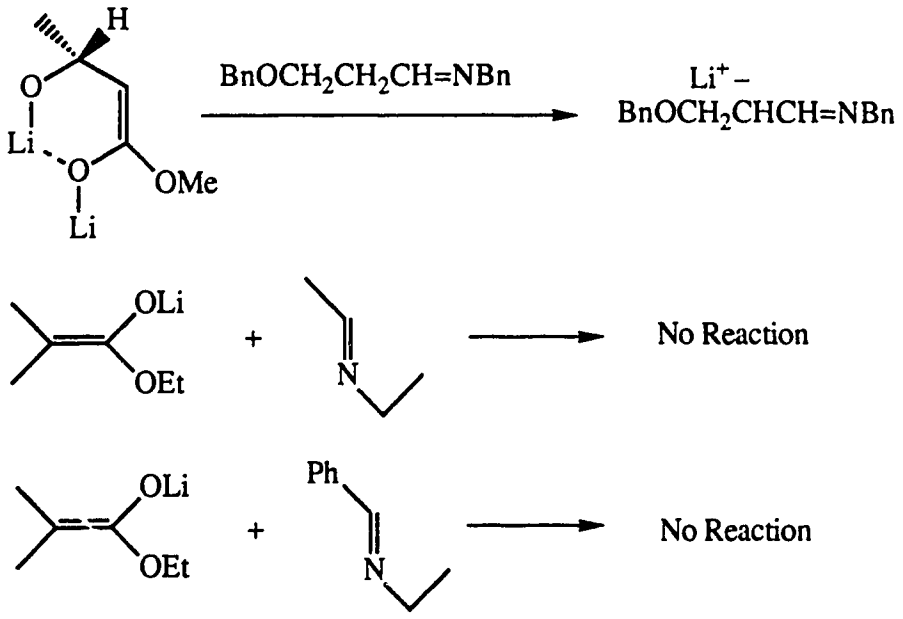
[1]

The *cis* stereochemistry may derive from the rigid six–membered ring chair–like transition state shown in Scheme III–2. Thus, the stereochemistry of the product azetidinone depends not only on the geometries of lithium enolate and imine, but also on the stereoelectronic effect of the lone pair electrons on the nitrogen. It is well established by Ireland[8] and Heathcock[9] that deprotonation of an ester with LDA in THF at -78°C normally gives the *E*–enolate. The nitrogen atom coordinates to the lithium atom *via* the lone pair of electrons.

Scheme III-2

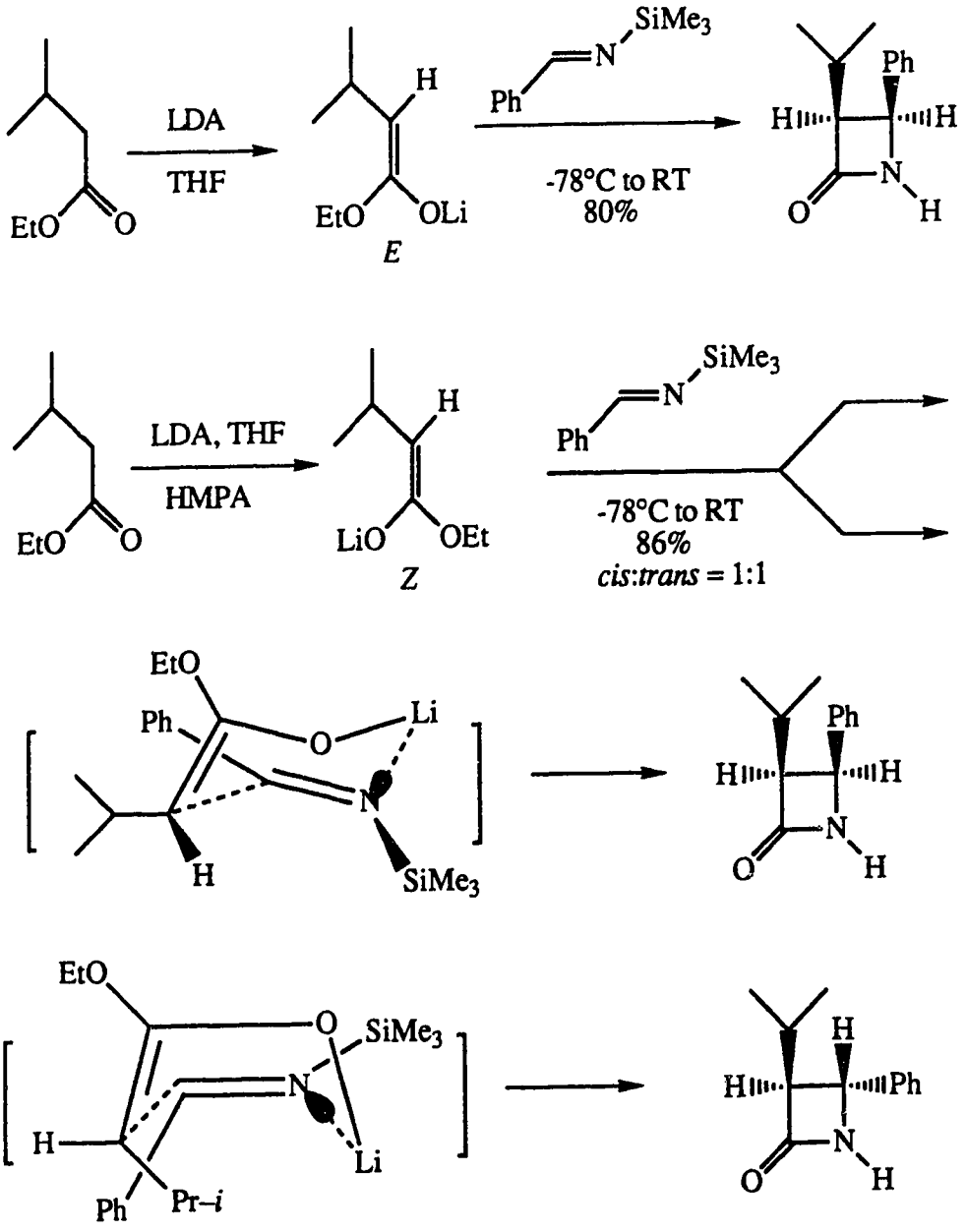


However, lithium enolates failed to react with enolizable imines having a proton α to either the C or N atom. Furthermore, in order to effect the condensation, imines must be electrophilic enough to accept the enolate nucleophile. If an electron–donating group is attached to the C=N bond, no addition of the enolate to the C=N double bond will occur. This is due to the much lower electrophilicity of imine C=N double bond compared with the carbonyl compounds which are more reactive towards organometallic reagents. In these cases, the lithium ester enolate simply deprotonated the imine, resulting in carbanion formation. For example, the condensation of methyl 3–(*R*)–hydroxybutyrate with an appropriately functionalized imine did not afford any desired product probably due to proton exchange[10] as shown in Eq. 2.



(b) With Non–Enolizable *N*–Trimethylsilyl Imines

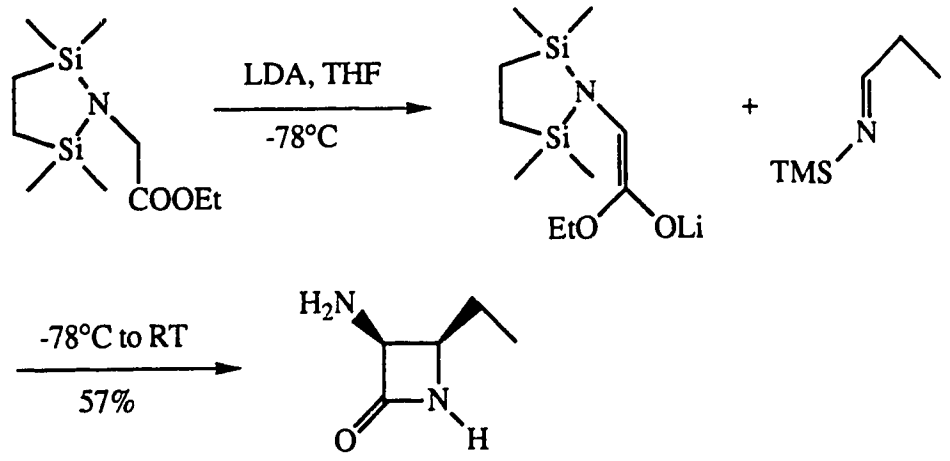
In 1983, Hart *et al.*[11, 12] discovered that non–enolizable *N*–trimethylsilyl imines, readily prepared *in situ* by addition of lithium hexamethyldisilylamide to the corresponding aldehyde, reacted with lithium ester enolates to give *N*–unsubstituted β–lactams directly in good yields. They also found that the condensation reaction proceeded in a stereoselective manner. The stereochemical course of the reaction was shown to be dependent on the lithium ester enolate geometry. The *E*–enolate gave *cis* β–lactam exclusively, while the *Z*–enolate generated by the deprotonation of ester with LDA in THF–HMPA gave nearly equal amounts of *cis* and *trans* β–lactams. These results suggested that the *E*–enolate added to the imine *via* the coordinated chair–like transition state exclusively, whereas the *Z*–enolate added to the imine through both the chair and boat transition states (Eq. 3).



[3]

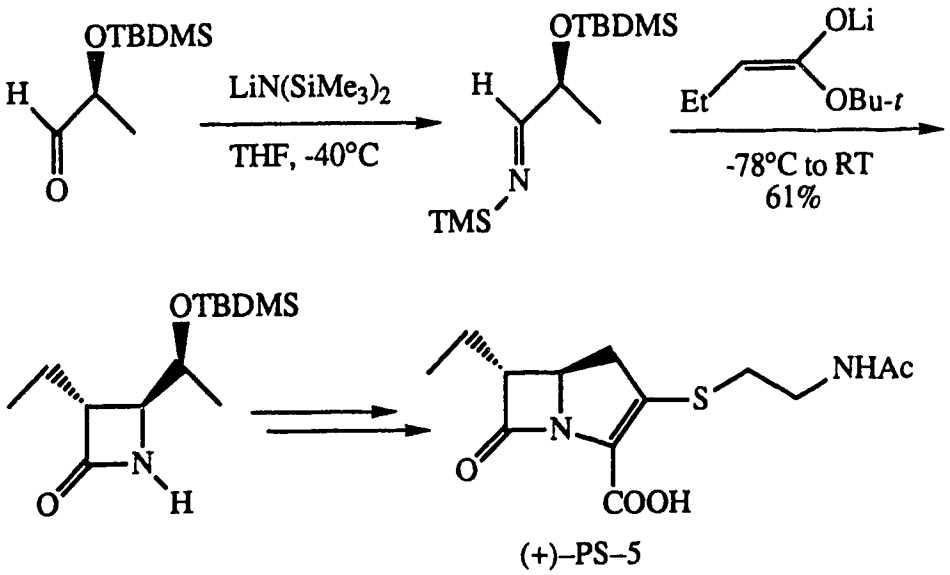
(c) With Enolizable *N*–Trimethylsilyl Imines

In 1987, Cainelli *et al.*[13] found that lithium enolate–*N*–silylimine condensation was also applicable to enolizable *N*–silylimines giving rise to *N*–unsubstituted β–lactams in fairly good yields. These reactions also proceeded with high *cis* stereoselectivity (Eq. 4).



[4]

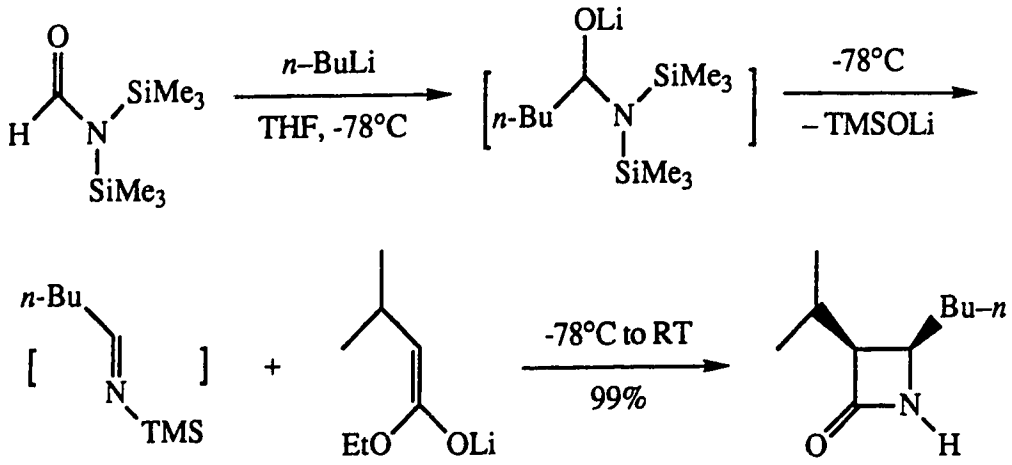
Based on this methodology, Cainelli *et al.*[14] reported in 1988 a new enantioselective total synthesis of carbapenem (+)–PS–5 in which an optically active *N*–silylimine was used for asymmetric induction *via* the ester–imine condensation (Eq. 5). Interestingly, in this reaction, *trans*–azetidinone was formed. No comments were made concerning this unusual stereoselectivity.



[5]

In 1989, Yamamoto *et al.*[15] discovered a new method for the generation of enolizable *N*–silylimines. They also showed that the addition of lithium ester

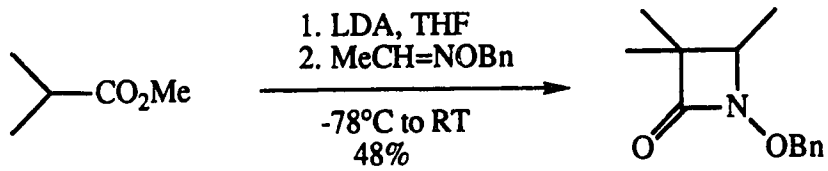
enolate to enolizable *N*–silylimines proceeded readily to give *cis N*–unsubstituted β–lactams in excellent yields (Eq. 6).



[6]

(d) With *N*–Benzyloxy Imines

In 1984, Sekiya and coworkers[16] described the condensation of lithium ester enolate with enolizable *N*–benzyloxy imine to afford the *N*–benzyloxy β–lactam (Eq. 7). However, only α,α–disubstituted ester enolates were found to react with the oxime derivative.

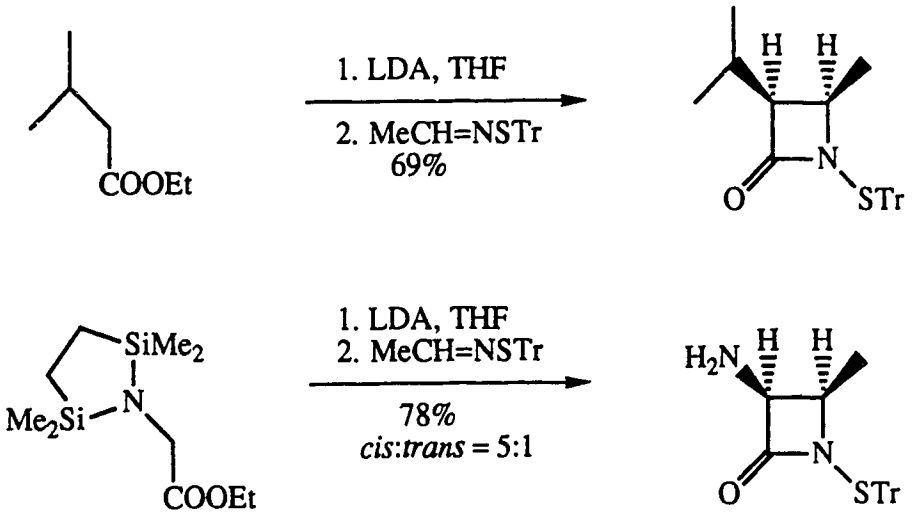


[7]

(e) With *N*–Sulfenimines

In 1986, Hart *et al.*[17] reported that lithium ester enolates reacted with both non–enolizable and enolizable *S*–trityl sulfenimines to give *N*–tritylsulfenyl β–

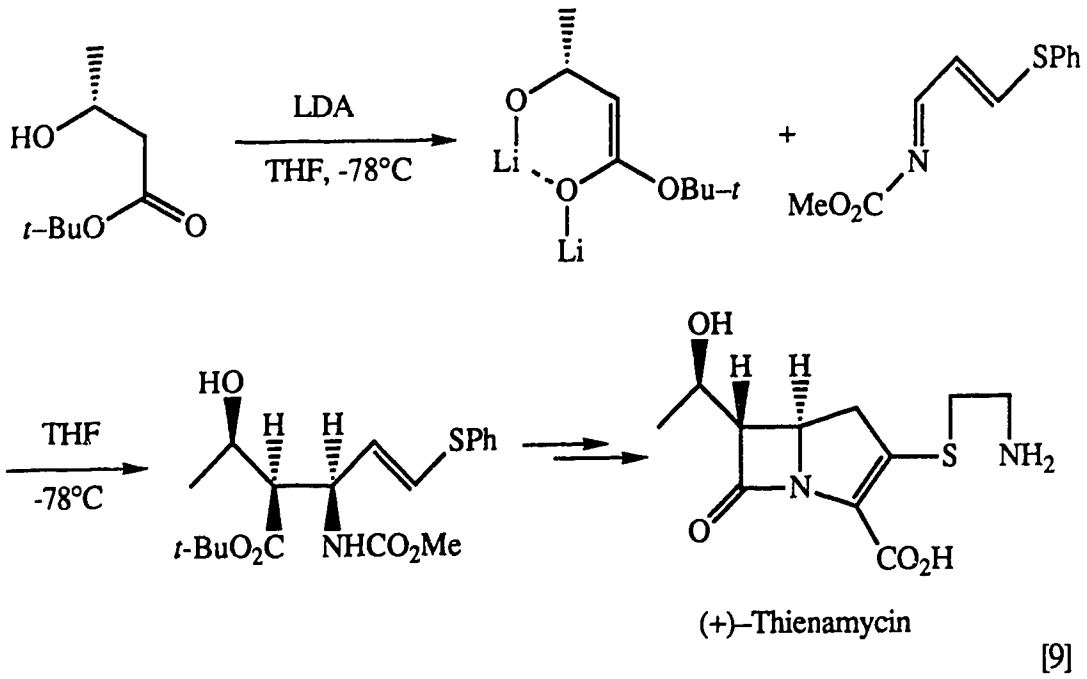
lactams in good yields and with a high degree of *cis* stereoselectivity (Eq. 8). The *N*–tritylsulfenyl β–lactams could be converted to *N*–unsubstituted β–lactams by reductive removal of the sulfenyl group.



[8]

(f) With *N*–Acylaldimines

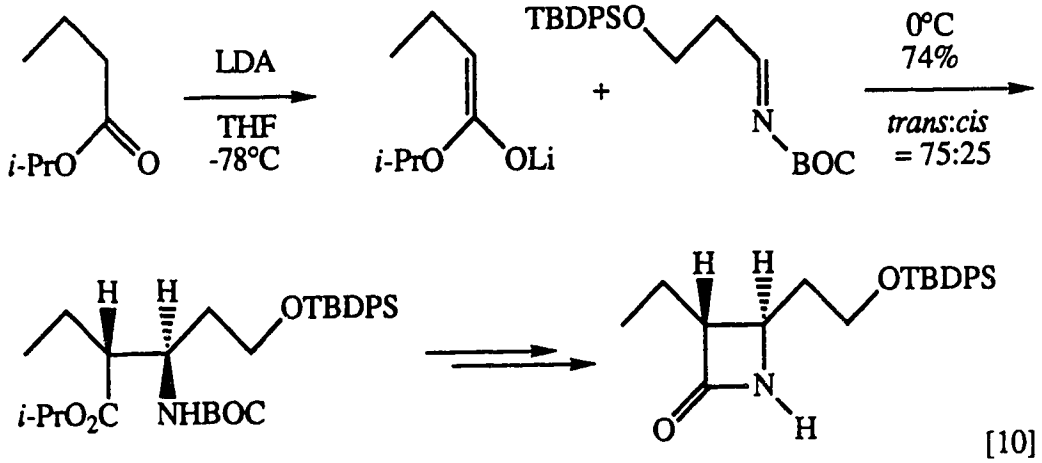
In 1987, Hatanaka and coworker[18] observed that reactions of lithium enolates and *N*–acyl imines took place readily to afford high yields of β–amino esters. According to this methodology, the β–lactam antibiotic (+)–thienamycin was stereoselectively synthesized (Eq. 9).



(+)–Thienamycin

[9]

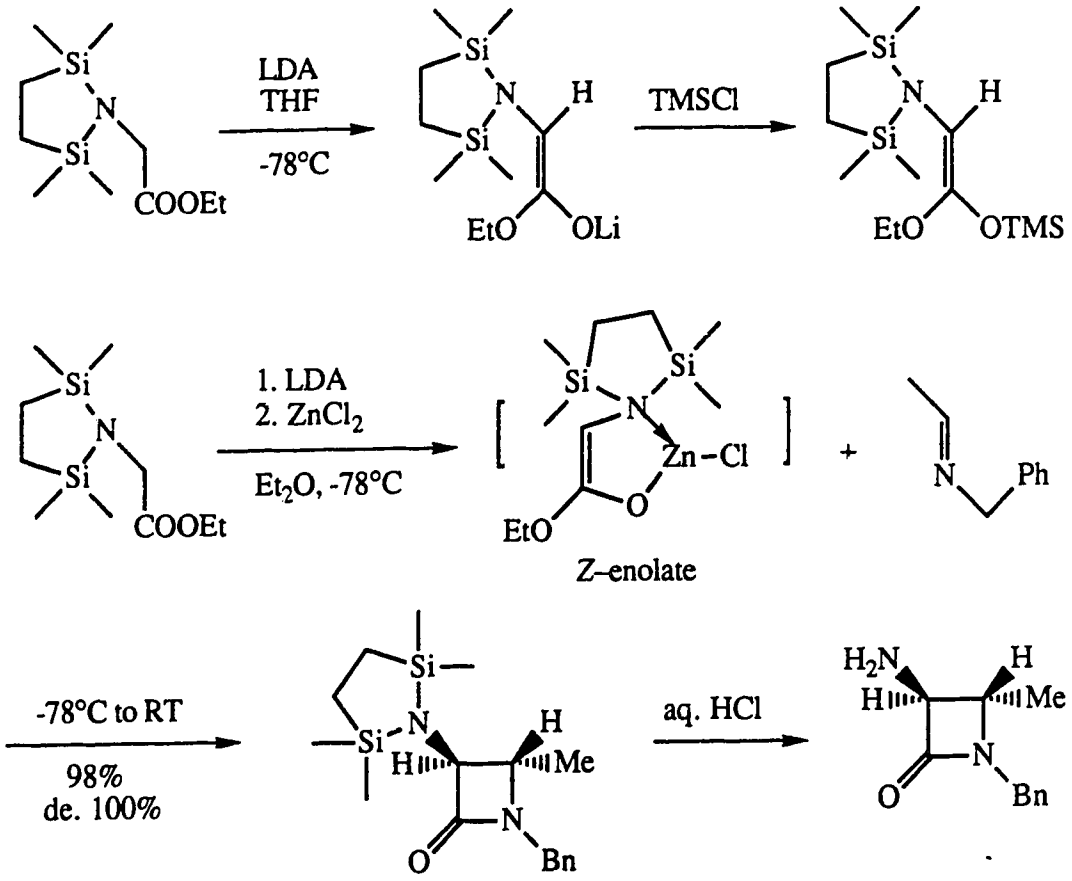
Later, Shono *et al.*[19, 20] reported a similar reaction (Eq. 10). Interestingly, it gave rise to the *trans* β–lactam as the predominant product.



[10]

(II) Zinc Ester Enolate–Imine Condensation

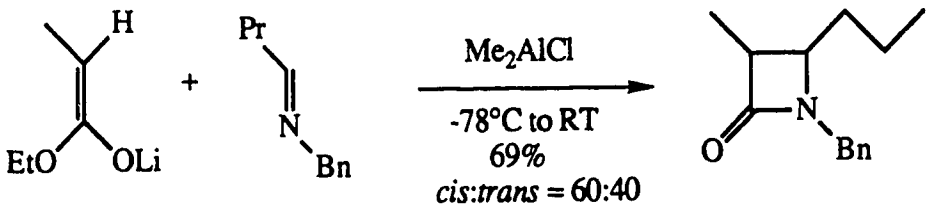
The preparation of β–lactams by the reaction of Reformatsky reagents with imines was first reported in 1943 by Gilman and Speeter.[5] Enolizable imines were also found to react with Reformatsky reagents, however no stereoselectivity was observed.[21, 22] In 1988, Koten and his collaborators[23, 24] prepared the zinc ester enolates of glycine ester derivatives which were shown to react with enolizable imines to afford β–lactams in good yields with high *trans*–stereoselectivity. The zinc ester enolate was prepared from the corresponding lithium enolate *via* transmetallation using one equivalent of zinc chloride. The zinc enolate of disilyl protected glycine ethyl ester existed exclusively in the *Z* configuration through intramolecular coordination of the nitrogen atom to the zinc atom, resulting in the chelate bonding of the enolate ion. The *Z* configuration of the zinc enolate was confirmed by the isolation of Z–trimethylsilylketene ketal upon trapping the zinc enolate with TMSCl. The reactions of *Z*-enolate with *E*–imines proceeded *via* a chair–like transition state to afford *trans* β–lactams. On the other hand, kinetic deprotonation of the protected glycine ester with LDA in THF at -78°C was shown to proceed with high selectivity to yield the *E*–enolate[25] which was confirmed by trapping with Me_3SiCl. The *E*–enolate showed high *cis* stereoselectivity towards the *E*–imine. From these results, it was concluded that the geometry of the ester enolate was changed from *E* to *Z* during the metal exchange with $ZnCl_2$. This zinc enolate–imine condensation reaction provides a convenient route for the stereoselective synthesis of *trans*–3–amino–β–lactams which are useful intermediates for the synthesis of monobactams.[25] An example is shown in Eq. 11.



[11]

(III) Aluminium Ester Enolate–Imine Condensation

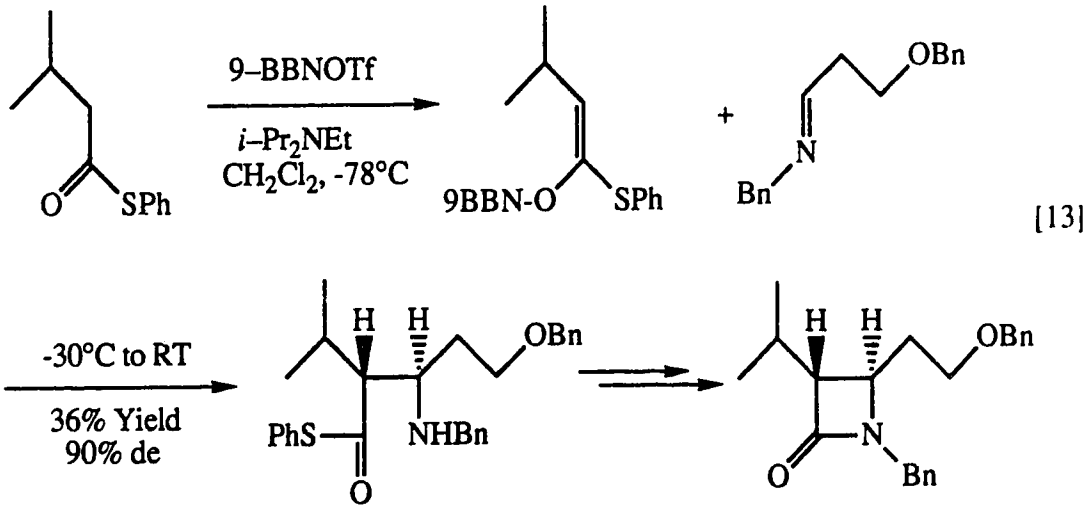
In 1987, Akiba[26] and Shibasaki[27] independently reported that lithium ester enolates and lithium thiolester enolates reacted with enolizable aldimines in the presence of alkylaluminium chloride to afford β–lactams in good yields. However, low *cis/trans* stereoselectivity was observed (Eq. 12).



[12]

(IV) Boron Enolate–Imine Condensation

The addition of boron enolate to C=N double bonds (enolizable or non-enolizable) is a useful procedure for the stereoselective synthesis of β–amino thiolesters (Eq. 13).[10, 28, 29] The resulting β–amino thiolesters could be cyclized to β–lactams by suitable β–lactam forming reactions.[30] Unlike lithium ester enolates (*E* configuration) which gave *cis* β–lactams upon treatment with imines, boron enolates derived from thiolesters and 9–BBNOTf existed in the Z–enolate form. As a result, boron enolates reacted with imines *via* a chair–like transition state to afford *trans* β–lactams after the resulting β–amino thiolesters were cyclized.

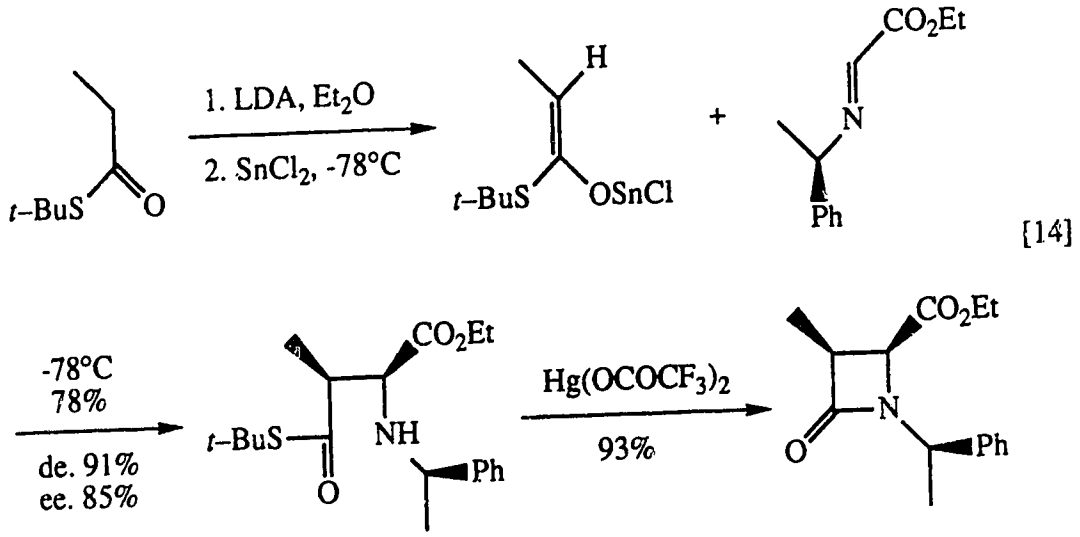


[13]

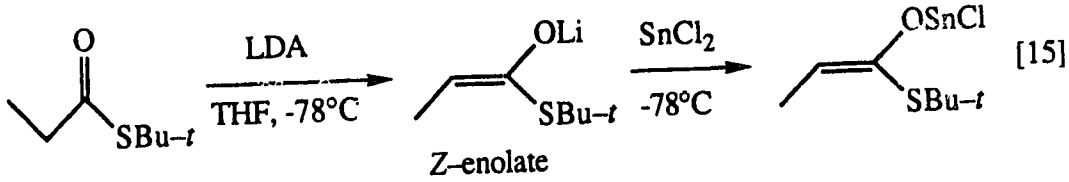
This stereoselective boron enolate–imine condensation reaction was later utilized by Shibasaki *et al.*[31] in the asymmetric synthesis of the carbapenem antibiotic (+)–PS–5 using a chiral imine to achieve asymmetric induction.

(V) Tin Enolate–Imine Condensation

Tin(II) has considerable affinity towards the nitrogen atom. It was found that Sn(II) enolate derived from a thiolester efficiently activated the imino group and added to an imine in a highly stereoselective manner to afford *syn*–β–amino thiolester which could be subsequently converted to the corresponding *cis*–β–lactam.[32, 33] When chiral imines having a chiral auxiliary on the nitrogen atom were used, high enantioselectivity was achieved and optically active *cis* β–lactams were obtained (Eq. 14).

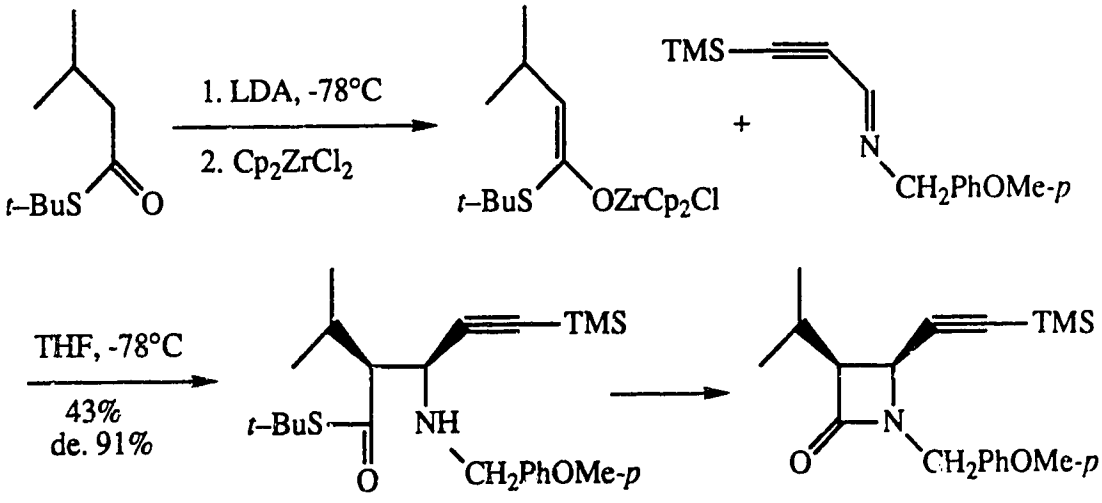


It was also shown that deprotonation of thiolesters with LDA in THF gave the (Z)–enolates[34] predominantly and this configuration was retained after the metal exchange to give the corresponding Sn(II) enolate (Eq. 15).



(VI) Zirconium Enolate–Imine Condensation

Shibasaki *et al.*[27] investigated the application of zirconium thiolester enolates to β–lactam synthesis. Its addition to imines was found to proceed smoothly to give *syn*–β–amino thiolesters in good yields and with high diastereoselectivity. The zirconium enolate was conveniently prepared from the corresponding lithium enolate by ligand exchange with Cp_2ZrCl_2. Loss of enolate geometry was not significant during the lithium–zirconium exchange. The stereochemistry of the zirconium enolate derived from thiolester was determined to be *Z* predominantly (*Z* : *E* = 9 : 1) by Evans *et al.*[34] The zirconium enolate reacted with the *E*–imine preferentially *via* a chair–like transition state, resulting in the formation of the *syn*–adduct (Eq. 16).



[16]

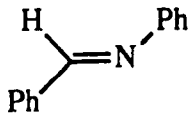
In conclusion, both *cis* and *trans* β–lactams may be prepared from thiolesters depending on the geometry of metal enolate. Boron enolates of thiolesters give *trans* products, whereas Sn(II) and zirconium enolates of thiolesters afford the *cis* β–lactams after the cyclization of the resulting β–amino thiolesters. Both tin and boron enolates can react with enolizable imines. Lithium ester enolates

only react with non–enolizable imines with the exception of *N*–silylimines to give *cis* β–lactams. Aluminium ester enolate can react with enolizable imines, but the reactions proceed without stereoselectivity.

Even though numerous methods have been developed for the synthesis of β–lactams, direct, efficient, stereoselective and general procedures are in constant demand in order to facilitate the preparation of this class of important compounds. The ester enolate–imine condensation reaction discussed earlier is potentially the most useful method for the synthesis of β–lactams. However, most existing procedures lack generality and/or stereoselectivity. Accordingly, there is room for further improvement. We have shown previously (see Chapter II) that cerium(III) ester enolate is much more nucleophilic than the corresponding lithium enolate towards carbonyl compounds. This superior nucleophilicity combined with the low basicity make possible the addition of cerium ester enolates to even highly enolizable or sterically hindered ketones. In light of this, we anticipated that cerium ester enolates would react with imines to produce β–lactams with high efficiency. An investigation has been undertaken, cumulating in the development of an improved general procedure for β–lactam synthesis. Results are described in this chapter.

RESULTS and DISCUSSION

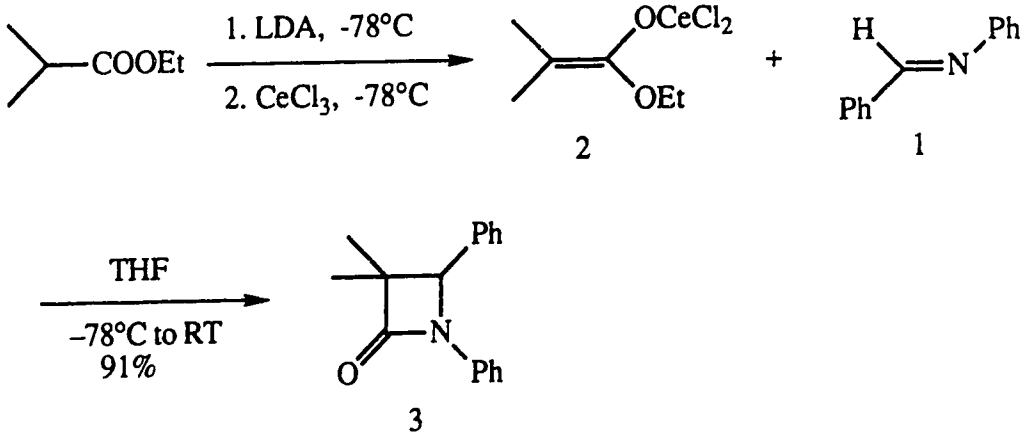
In order to determine the applicability of cerium ester enolate to β–lactam synthesis, the reaction of imine **1** and enolate **2** was selected as a model. Imine **1**, readily available from the condensation of benzaldehyde and aniline,[35] displayed the molecular ion peak at m/e 181.0886. The C=N double bond has an infrared absorption at 1628 cm^{-1}. The vinylic proton resonated at δ 8.45 as a singlet in its ^{1}H NMR spectrum. The ^{13}C APT spectrum showed the C=N double bond resonance signal at δ 160.40 as a doublet.



1

Reaction of one equivalent of cerium enolate **2**, prepared by transmetallation of the corresponding lithium enolate with $CeCl_3$, with imine **1** in THF at temperatures ranging from -78°C to room temperature proceeded readily to afford the desired β–lactam **3**[6] directly in 91% yield. In a parallel experiment, treatment of **1** with the lithium enolate in the absence of $CeCl_3$ gave the β–lactam **3** in a considerably poorer yield of 75%. The high resolution mass spectrum of **3** showed the molecular ion peak at m/e 251.1306 consistent with the molecular formula $C_{17}H_{17}NO$. The formation of the β–lactam ring was supported by the infrared spectrum which showed an absorption band at 1744 cm^{-1}, characteristic for the β–lactam carbonyl. In the ^{1}H NMR spectrum, the proton at C–4 resonated at δ 4.82 as a singlet. The signals for the geminal dimethyl group were observed at δ 1.53 and 0.85 as singlets. The carbonyl

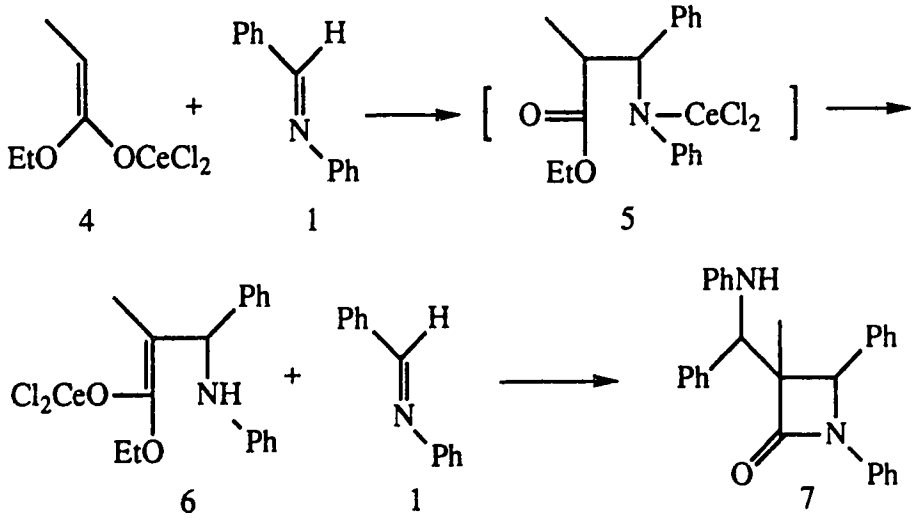
carbon resonated in the ^{13}C APT spectrum at δ 171.50 as a singlet. The C–4 resonance signal was observed at δ 66.56 as a doublet.



Cerium enolates **4** and **8** were also prepared and their reactions with imine **1** were examined. It was shown[6] that the reaction of the lithium enolates of ethyl acetate and ethyl propionate with imine **1** did not occur at temperatures below 0°C. At higher temperatures, these enolates were found to decompose. Interestingly, addition of one equivalent of enolate **4** to imine **1** in THF at a temperature range of -78–25°C afforded the unexpected β–lactam **7**[36] as the only product in 55% yield. Its molecular formula was determined to be $C_{29}H_{26}N_2O$ by the high resolution mass spectrum. In the infrared spectrum, the band at 3400 cm^{-1} indicated the presence of the secondary amino group. The β–lactam carbonyl absorption was observed at 1740 cm^{-1}. Both ^1H NMR and ^{13}C APT spectra also supported the structural assignment. There were 20 protons in the aromatic range in the ^1H NMR spectrum, indicating two equivalents of imine **1** had been introduced. The signal of the H–4 proton was observed at δ 5.30 as a singlet. The signal at δ 4.76 (2 H, broad singlet) could be attributed to the NH proton and the proton adjacent to this group. There was

only one carbonyl carbon resonance observed in the ^{13}C spectrum at δ 169.55 as a singlet. The doublets at δ 63.91 and 62.82 were readily assigned to the C–4 and the carbon bearing the NHPh group respectively. The carbon adjacent to the carbonyl unit was observed at δ 62.31 as a singlet.

The formation of **7** can be explained by the following mechanism. Addition of cerium enolate **4** to **1** produced the intermediate cerium amide **5** which acted as a base to remove the proton α to the carbonyl group, generating the ester enolate **6**. Reaction of cerium ester enolate **6** with one more equivalent of imine **1** gave the β–lactam **7** after cyclization.

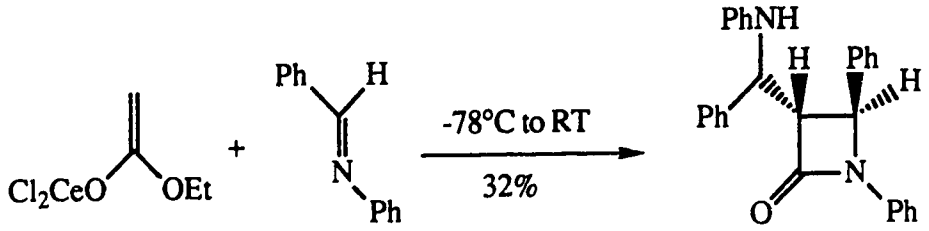


4 1 5 6 1 7

Similarly, cerium enolate **8** also reacted with imine **1** to provide *trans* β–lactam **9** in 32% yield as the only diastereoisomer. The high resolution mass spectrum of **9** suggested the molecular formula $C_{28}H_{24}N_2O$ which indicated two equivalents of imine **1** were involved in this reaction. The infrared absorption bands at 3400 (NH) and 1745 (C=O) cm^{-1} also supported the formation of **9**. The proton at C–4 resonated at δ 4.80 as a doublet (J = 2 Hz) coupled with the

proton at C–3 which in turn appeared at δ 3.60 as a doublet of doublets (J = 6.5, 2 Hz). The NH proton resonated at δ 4.68 as a doublet (J = 7 Hz) coupled with its neighboring proton which in turn was split into a triplet at δ 4.94. Its ^{13}C APT spectrum showed one carbonyl carbon resonance at δ 164.92 as a singlet. The C–3 and C–4 resonance signals were observed at δ 65.15 and 56.99 as doublets respectively.

The *trans* stereochemistry of β–lactam **9** at C–3 and C–4 was assigned on the basis of the coupling constant (J = 2 Hz) of H–3 and H–4. In the β–lactam ring system, *trans* vicinal protons normally have a coupling constant of 2 Hz (J_{trans} = 2 Hz), whereas *cis* vicinal protons have a coupling constant of about 6 Hz (J_{cis} = 6 Hz).

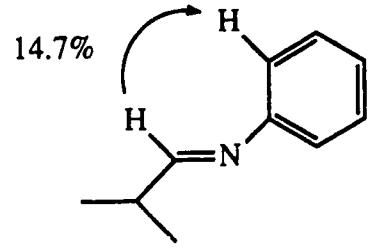


8 1 9

The above results clearly indicated the feasibility of using cerium ester enolate–imine condensation for the direct formation of the β–lactam ring system and prompted us to carry out further studies using enolizable imines. Accordingly, the enolizable imine **10** was prepared in nearly quantitative yield by reaction of isobutyraldehyde and aniline at 0°C. Imine **10** was not stable at room temperature and had to be kept in an acid free container below 0°C and used as soon as possible. The molecular ion peak was observed at m/e 147.1045 in the high resolution mass spectrum, corresponding to the molecular formula

$C_{10}H_{13}N$. Its infrared absorption for the C=N bond was observed at 1667 cm^{-1} in the IR spectrum. The proton attached to the C=N double bond resonated at δ 7.71 as a doublet (J = 4.5 Hz). The geminal methyl protons resonated at δ 1.19 as a doublet (J = 7 Hz). The C=N carbon appeared at δ 170.62 as a doublet in the ^{13}C NMR spectrum.

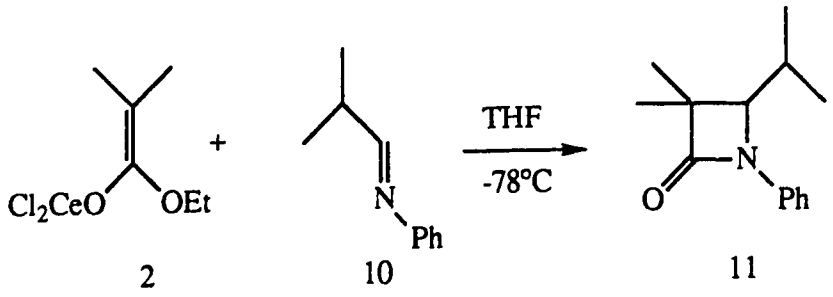
The *E*–configuration of imine **10** was determined by the NOE experiment (Figure III–1). Upon irradiation of the signal at δ 7.71, a 14.7% enhancement was observed for the aromatic protons *ortho* to the substituent.



10

Figure III–1. NOE Data for Imine **10**

With the desired enolizable imine **10** in hand, its reaction with the cerium ester enolate **2** was examined. Treatment of one equivalent of cerium enolate **2** with **10** gave the desired β–lactam **11** in about 40% yield after 24 h at -78°C. Increasing the temperature to 25°C did not improve the yield. After some experimentation, it was recognized that an excess of the cerium enolate was required in order to improve the yield of the product. Thus, when two equivalents of **2** were used, a 90% yield of **11** was realized after 10 h at -78°C.



2 10 11

The β–lactam **11** showed the molecular ion peak at m/e 217.1467 in agreement with the required molecular formula $C_{14}H_{19}NO$. The elemental analysis also supported this composition. In the IR spectrum, the typical β–lactam carbonyl absorption was observed at 1752 cm^{-1}. In the ^1H NMR spectrum, H–4 resonated at δ 3.60 as a doublet (J = 9 Hz). The geminal methyl groups at C–3 appeared at δ 1.38 and 1.35 as singlets. The ^{13}C NMR spectrum showed the carbonyl carbon resonance at δ 172.88 as a singlet. The C–3 and C–4 resonance signals were observed as a singlet at δ 52.37 and a doublet at δ 69.42 respectively.

Having established that cerium ester enolate can react with enolizable imine, we then turned our attention to the generality and stereoselectivity of the cerium enolate–imine condensation process. All reactions were carried out under the following conditions using two equivalents of cerium enolate, and the progress of the reaction was monitored by TLC analysis. Normally, the reaction mixture was stirred for several hours at -78°C and if TLC showed the presence of the imine, the mixture was gradually warmed up to 0°C or room temperature and further stirred for several hours.

First, several α,α–dialkyl esters were prepared and their cerium enolates were treated individually with imine **10** under the standard conditions. The

experimental results are summarized in Table III–1. As shown in Table III–1, in all the cases, the β–lactams were obtained in excellent yields without any exception. Although TLC analysis indicated that all addition reactions took place readily at -78°C, the reaction temperature in each case must be raised to 25°C in order to complete the reaction.

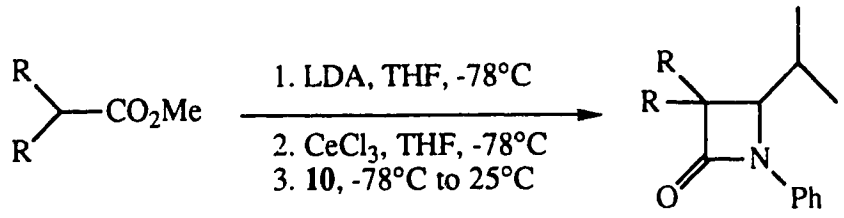
β–Azetidinone **14**, for example, was isolated in 94% yield as a white crystal (mp 67–68°C). The molecular formula of compound **14** was determined to be $C_{16}H_{23}NO$ by the high resolution mass spectrum which displayed the molecular ion peak at m/e 245.1781. This molecular formula was further confirmed by the elemental analysis. The IR spectrum of **14** showed a strong absorption at 1745 cm^{-1} for the β–lactam carbonyl group. The H–4 proton resonated at δ 3.64 as a doublet (J = 8 Hz) in the ^1H NMR spectrum. In the ^{13}C NMR spectrum, the carbonyl carbon was observed at δ 172.31 as a singlet. The C–4 carbon appeared at δ 67.18 as a doublet, whereas the C–3 singlet was observed at δ 60.03.

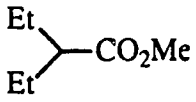
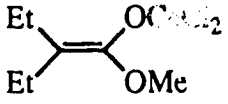
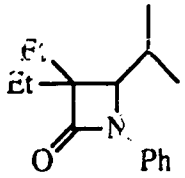
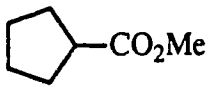
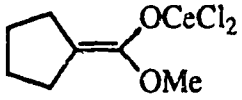
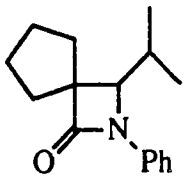
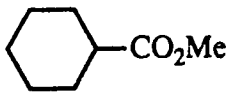
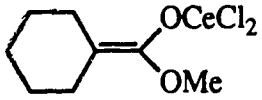
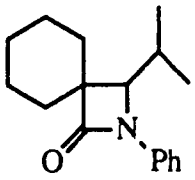
Both spiro β–lactams **17** and **20** were also formed in excellent yields. The former compound showed the molecular ion peak at m/e 243.1620 in the high resolution mass spectrum, in agreement with the molecular formula $C_{16}H_{21}NO$. The elemental analysis further confirmed the composition. In the IR spectrum, the amide carbonyl absorption was observed at 1748 cm^{-1}. In the ^1H NMR spectrum, the H–4 proton resonated at δ 3.78 as a doublet (J = 7 Hz). The carbonyl carbon appeared at δ 173.09 as a singlet in the ^{13}C NMR spectrum. The C–3 and C–4 carbons resonated as a singlet at δ 62.13 and as a doublet at δ 68.26 respectively.

The azetidinone **20** was determined by the high resolution mass spectrum to have the molecular formula $C_{17}H_{23}NO$ which was also confirmed by the elemental analysis. Its amide carbonyl absorption was observed at 1741 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum, the H–4 proton resonated at δ 3.48 as a doublet (J = 8 Hz). The ^{13}C NMR spectrum also indicated the formation of the β–lactam bond displaying a singlet at δ 172.54 for the carbonyl carbon. The C–4 resonance signal was observed at δ 68.88 as a doublet.

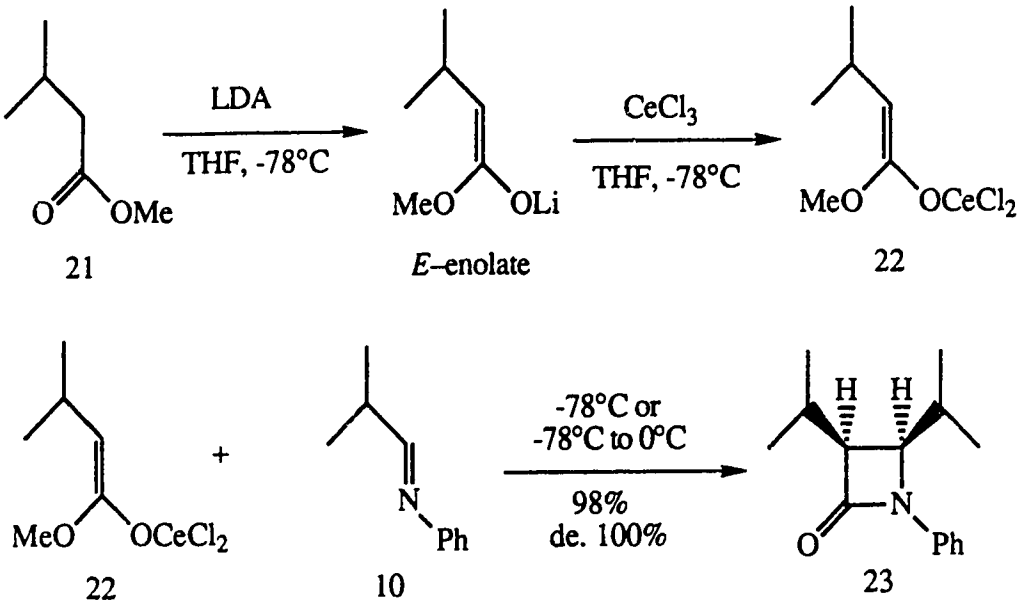
The addition of the lithium enolate of ester **18** to imine **10** was also examined in order to compare the reactivity of lithium enolate and cerium enolate. Under the same conditions, the azetidinone **20** was obtained only in 20% yield when the lithium enolate was employed. Clearly, the addition of the cerium enolate **19** to imine **10** is by far more efficient than that involving the corresponding lithium enolate.

Table III–1. Preparation of β–Lactams by Cerium Enolate–Enolizable Imine Condensation



Ester	Cerium Enolate	β–Lactam	Yield (%)
			94
12	13	14	
			100
15	16	17	
			93
18	19	20	

In order to examine the stereoselectivity of the cerium enolate–imine condensation, several cerium enolates were prepared from the monosubstituted acetates and their additions to imine **10** examined. The cerium enolate **22** of ester **21** was conveniently formed by transmetallation of lithium enolate with $CeCl_3$ at -78°C. Treatment of cerium enolate **22** with enolizable imine **10** in THF at -78°C for 4 h gave rise to the *cis* azetidinone **23** in nearly quantitative yield with 100% diastereoselectivity.



The β–lactam **23** was obtained as a white crystal (mp 91–92°C). Its molecular ion peak was displayed by the high resolution mass spectrum at m/e 231.1622 corresponding to the molecular formula $C_{15}H_{21}NO$. This formula was confirmed by the elemental analysis. Quite interestingly, its amide carbonyl absorption was observed at 1725 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum, the H–4 proton resonated at δ 4.12 as a doublet of doublets (J = 6 and 4.2 Hz) coupled with H–3 by 6 Hz. The H–3 proton was observed at δ 3.10 also as a doublet of doublets (J = 9.4 and 6 Hz). In the ^{13}C NMR spectrum, the

amide carbonyl carbon resonance signal was observed at δ 168.28 as a singlet. The C–3 and C–4 carbons resonated at δ 60.59 (d) and 59.18 (d).

The *cis* stereochemistry regarding C–3 and C–4 was assigned on the basis of the coupling constant of H–3 and H–4 and the NOE study (Figure III–3). The coupling constant of $J_{3,4}$ = 6 Hz indicated that they were *cis* related to each other. An NOE experiment also supported this assignment. Upon irradiation of the signal at δ 4.12 (H–4), the signal at δ 3.10 (H–3) was enhanced by 18.2% confirming the *cis* relationship between H–3 and H–4.

As far as the stereoselectivity is concerned, the cerium enolate–imine condensation presumably proceeded in a manner similar to the aldol condensation *via* a six–membered ring chair–like transition state. Thus, both the stereochemistry of cerium enolate and imine geometry played an important role in determining the stereochemical outcome. It was well established by Ireland *et al.*[8, 9] that deprotonation of normal α–alkyl esters with LDA in THF at -78°C afforded predominantly the *E*–enolates. We suspected that transmetallation of lithium enolate with $CeCl_3$ in THF at -78°C did not alter the configuration of the enolate, based on the fact that the stereochemistry of many metal enolates, derived from the corresponding lithium enolate by metal exchange, remained unchanged. The geometry of the imine **10** has been established as the *E* isomer by NOE measurement (Figure III–1). Due to the stereoelectronic effect[37, 38] of the lone pair on the nitrogen which was coordinated to the cerium atom, the chair–like transition state shown in Figure III–2 was proposed to give *cis* β–lactams.

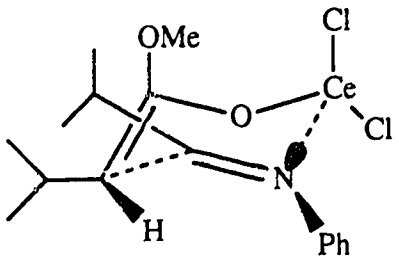


Figure III–2. Transition State for the Formation of β–lactam **23**

The additions of several other monosubstituted cerium ester enolates to imine **10** were also examined under the same conditions. The results are summarized in Table III–2. As shown in Table III–2, in all the cases examined, the addition of cerium enolate with imine **10** proceeded smoothly at -78°C to afford the corresponding azetidinone in excellent yield. Moreover, all the condensation reactions showed remarkable diastereoselectivity (de. 100%) and *cis* β–lactams were obtained as the only products without exception. The stereochemical assignments of all the azetidinones were similarly confirmed by NOE experiments (Figure III–3) in addition to the observed *cis* vicinal coupling constants ($J_{3,4}$ = 6.0 Hz) in the ^{1}H NMR spectra.

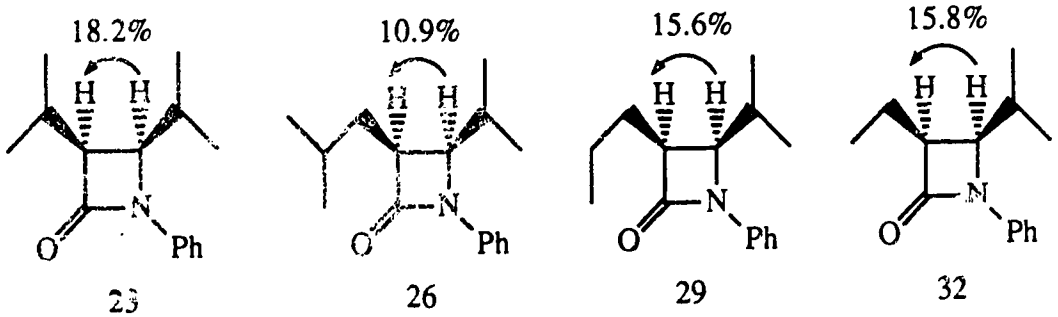
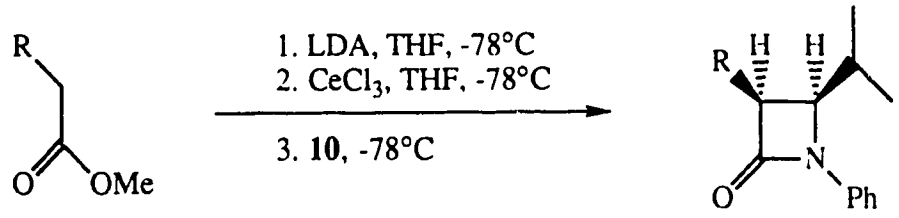
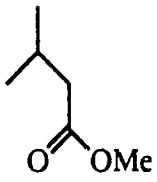
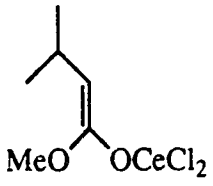
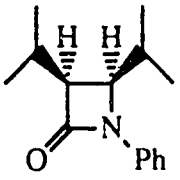
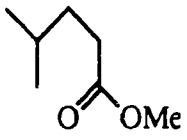
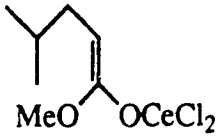
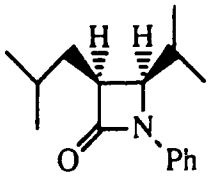
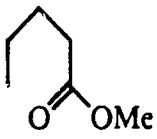
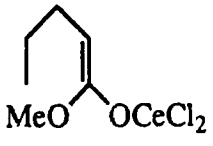
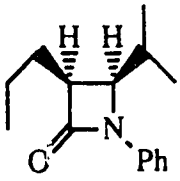
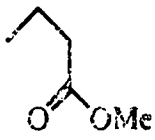
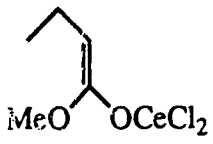
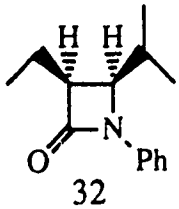


Figure III–3. NOE Data for Azetidinones **23**, **26**, **29** and **32**

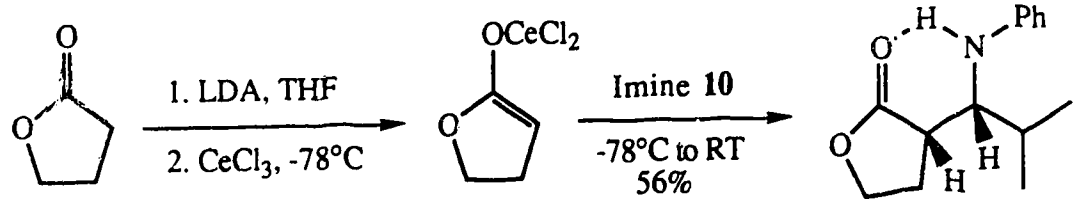
Table III–2. Stereoselective Synthesis of *cis* β–Lactams by Addition of Monosubstituted Cerium Enolates to Imine **10**



Ester	Cerium Enolate	β–Lactam	Yield (%)
			98
21	22	23	
			94
24	25	26	
			92
27	28	29	
			95
30	31	32	

On the basis of the transition state shown in Figure III–2, the stereochemical outcome of the β–lactam formation could be predicted if the stereochemically defined cerium enolate could be prepared. Having this idea in mind, we subsequently carried out a series of stereochemical studies.

γ–Lactone **33** was deprotonated with LDA in THF at -78°C to generate the stereochemically defined lithium enolate (*E*–configuration) which should undergo transmetallation with $CeCl_3$ to provide cerium enolate **34** with the clearly defined geometry. However, reaction of cerium enolate **34** with imine **10** at temperatures ranging from -78°C to room temperature afforded only the β–amino lactone **35** in 56% yield without further ring closure.



33 **34** **35**

The β–amino lactone **35** was obtained as a white crystalline compound (mp 105–106°C). The high resolution mass spectrum of **35** showed the molecular ion peak at m/e 233.1415, corresponding to the molecular formula $C_{14}H_{19}NO_2$ which was also confirmed by the elemental analysis. Compound **35** showed the amino absorption at 3350 cm^{-1} in the IR spectrum. The absorption band at 1759 cm^{-1}, typical for the γ–lactone carbonyl group, was also observed. Each of the methylene protons next to the oxygen atom appeared, in the ^1H NMR spectrum, as a doublet of doublets of doublets with a geminal coupling constant of 8.0 Hz; one at δ 4.30 (J = 8.0, 8.0, 4.0 Hz) and the other at δ 4.20 (J = 8.0,

8.0, 7.0 Hz). The protons of the other methylene group appeared at δ 2.20–2.30 as multiple peaks. The methine proton α to the lactone carbonyl resonated at δ 2.85 as a doublet of triplets (J = 3.5, 9.5 Hz). The methine proton next to nitrogen atom resonated at δ 3.80 (m). By conducting the spin decoupling experiments (Table III–3), it was found that these methine protons were coupled to each other by 3.5 Hz. This coupling constant was of use in determining the relative stereochemistry of the β–amino lactone **35**. In the ^{13}C NMR spectrum, a singlet at δ 178.76 was assigned to the carbonyl carbon. The carbon α to the carbonyl unit and the carbon bearing the amino group appeared at δ 42.45 (d) and 66.71 (d).

Table III–3. Spin Decoupling Data for β–Amino γ–Lactone **35**

Signal Irradiated (δ)	Signal Decoupled (δ)
4.30 (OCHa)	4.20 (OCHb) and 2.25 (OCH_2CH_2)
4.20 (OCHb)	4.30 (OCHa) and 2.25 (OCH_2CH_2)
3.80 (CHNH)	2.85 (O=CCH, dt → t, 9.5 Hz) 3.45 (NH) and 1.90 ($CHMe_2$)
2.25 (OCH_2CH_2)	4.30 (OCHa, ddd → d, 8.0 Hz) 4.20 (OCHb, ddd → d, 8.0 Hz) 2.85 (O=CCH, dt → d, 3.5 Hz)

β–Amino lactone **35** is expected to exert strong intramolecular hydrogen bonding as depicted and the small coupling constant of 3.5 Hz observed for the two neighboring methine protons strongly suggested a *cis* relationship. This stereochemical outcome lent support to the proposed transition state shown in Figure III–2.

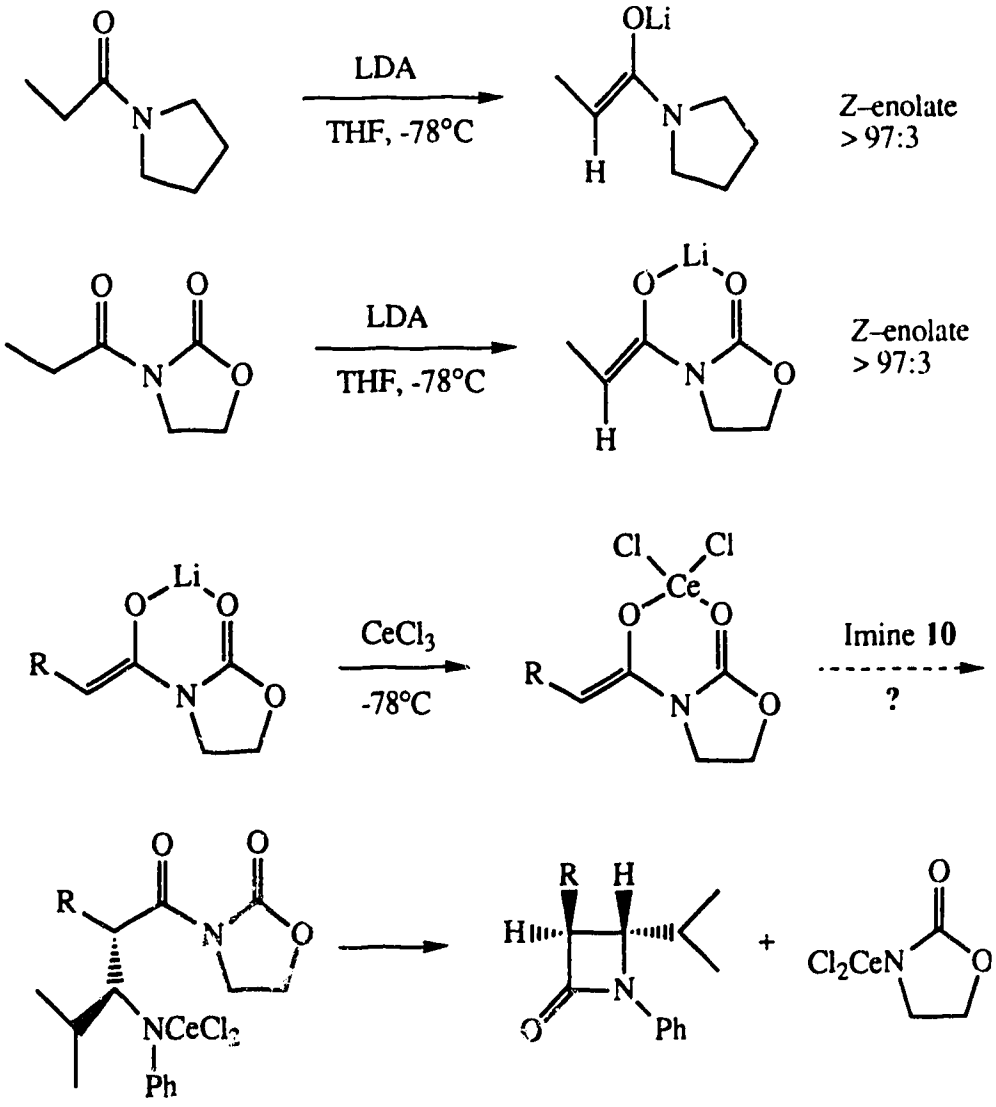
It was concluded that the stereochemical results depended on both the stereochemistry of the enolate and the geometry of the imine. An *E*–cerium enolate would react with a *trans* imine to afford the *cis* azetidinone. If the stereochemistry of the cerium enolate could be controlled in the *Z* form, a *trans* azetidinone should result from its addition to a *trans* imine *via* the postulated chair–like transition state. At present, there are two methods available for the preparation of *Z*–enolates. The most widely used method is based on Evans' amide and related compounds. Deprotonation of these amides with LDA in THF at -78°C gave predominantly the *Z*-enolates. The other useful methodology was developed by Ireland and coworkers who used the THF–HMPA solvent system to facilitate the formation of *Z*–enolates from esters.

Evans and his coworkers[39, 40] have shown that kinetic deprotonation of the amido compounds with LDA in THF at -78°C gave rise to the corresponding *Z*–enolates (Scheme III–3).

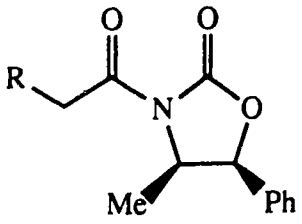
We chose the 2–oxazolidinone derivative as the precursor of the *Z*–enolate on the basis of the following considerations. First, deprotonation of 2–oxazolidinone with LDA is known to give the *Z*–enolate. Subsequent transmetallation with $CeCl_3$ should give the desired *Z* cerium amide enolate,

which is expected to react with the *E*–imine **10** *via* a chair–like transition state to afford the *trans* β–lactam (Scheme III–3). Secondly, 2–oxazolidone is an excellent leaving group. Normally, an alkoxide can replace this group very readily at 0°C. Thus, the intermediate resulting from the addition of the *Z*–enolate to imine **10** could, in principle, undergo cyclization with ease to provide the desired *trans* azetidinone.

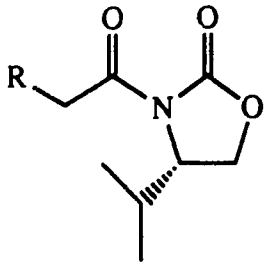
Scheme III–3



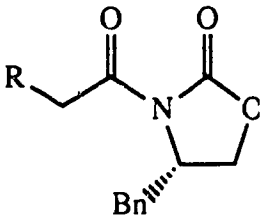
Thirdly, it had been demonstrated by Evans *et al.*[40] that chiral 2–oxazolidinones such as **36**, **37** and **38** are excellent chiral starting materials to effect asymmetric induction. Hence, the reaction of cerium enolates, prepared from chiral 2–oxazolidinones, with imine **10** should lead to optically active azetidinones.



36

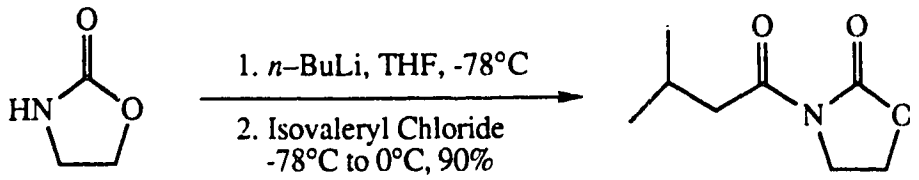


37



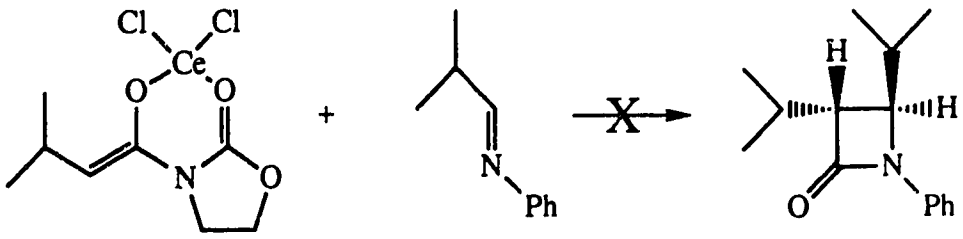
38

The 2–oxazolidinone **39** was prepared in 90% yield by the treatment of the lithium salt of 2–oxazolidone with isovaleryl chloride at 0°C. The high resolution mass spectrum of compound **39** exhibited the molecular ion peak at m/e 171.0895 corresponding to the molecular formula $C_8H_{13}NO_3$. This molecular formula was also supported by the elemental analysis. In the IR spectrum, absorptions at 1778 and 1698 cm^{-1} were observed for the carbonyl groups. In the ^1H NMR spectrum, the methylene protons in the oxazolidone ring resonated at δ 4.40 (t, J = 8 Hz) and δ 4.02 (t, J = 8 Hz), whereas those adjacent to the amide carbonyl appeared at δ 2.81 as a doublet (J = 7 Hz). In the ^{13}C NMR spectrum, two singlets at δ 172.87 and 153.55 were ascribed to the carbonyl carbons. The methylene carbons bearing hetero atoms resonated at δ 61.95 (t) and 43.58 (t).



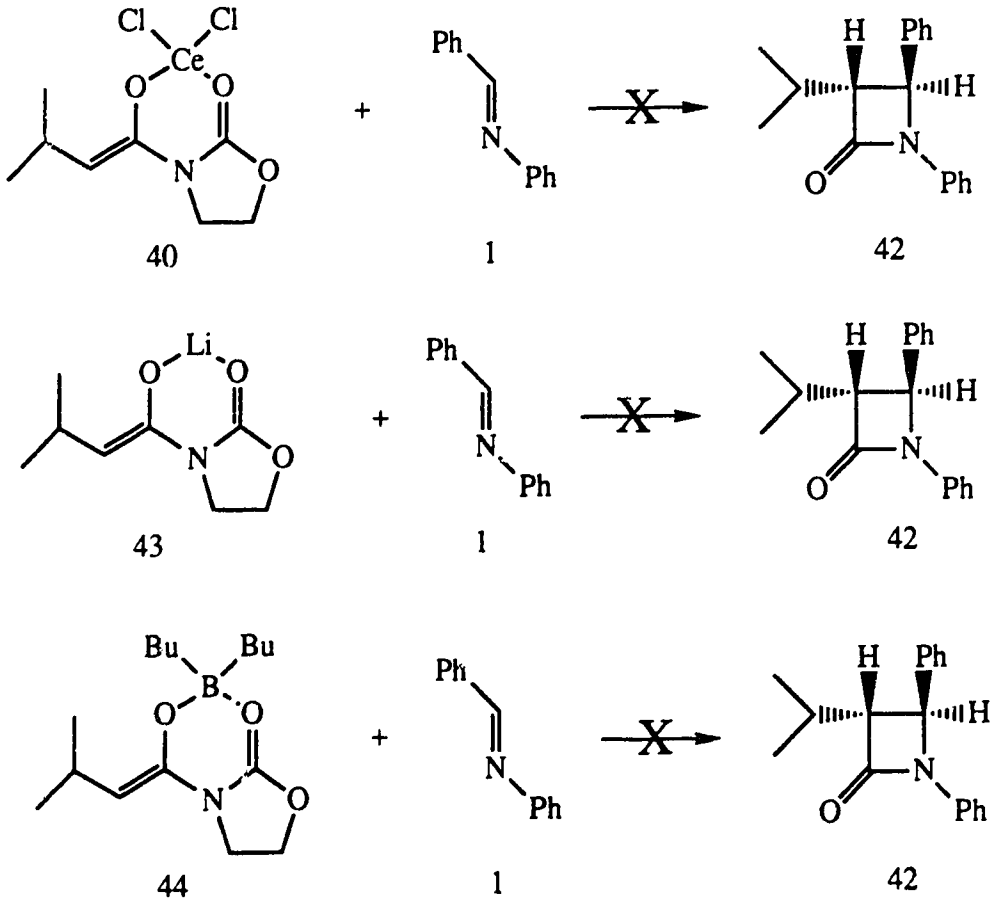
39

With the desired amide **39** in hand, the reaction of its cerium enolate **40** with imine **10** was attempted. However, under various conditions, no reaction was observed. In every case tried, only the starting imine and decomposed 2–oxazolidinone were obtained. These results are due to the lower nucleophilicity of 2–oxazolidinone enolate than that of the ester enolate. The low nucleophilicity of the enolate of 2–oxazolidinone was also observed by Evans.[40] For example, normal lithium ester enolates can react with aldehydes even at -78°C, whereas the lithium enolate of 2–oxazolidinone only reacted with aldehydes at 0°C. Generally, the lithium enolate of 2–oxazolidinone undergoes decomposition reaction above 0°C.

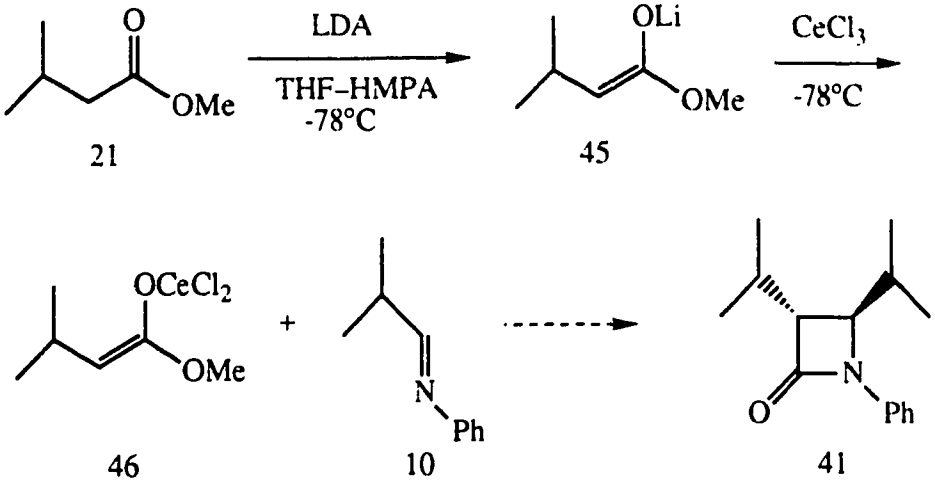


40 10 41

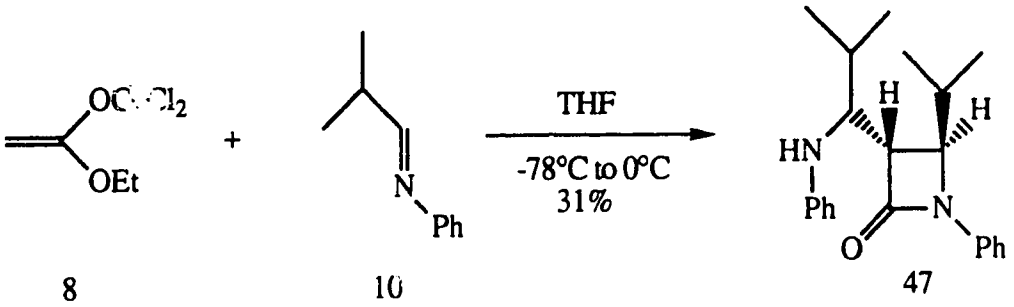
Additions of the cerium (**40**), lithium (**43**) and boron (**44**)[40] enolates with nonenolizable imine **1** were also attempted, but all failed to react with imine **1**; only starting imine **1** was recovered after the reactions. Obviously, the enolates of 2–oxazolidinones are much less nucleophilic than the ester enolates.



Another possibility for obtaining the *Z*-enolate is to deprotonate the ester with LDA in THF–HMPA solvent system (about 20% of HMPA) developed by Ireland[8] in 1976. For example, deprotonation of ester **21** with LDA in THF–HMPA at -78°C generated the corresponding *Z*–enolate **45** predominantly which could, in principle, be converted to *Z*–cerium enolate **46** by transmetallation with $CeCl_3$ at -78°C. Reaction of cerium enolate **46** with imine **10** is expected to give rise to *trans* β–lactam **41**. This idea remains to be tested.



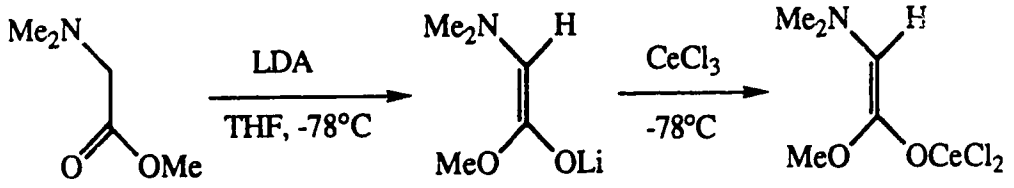
Having examined the cerium enolates of disubstituted and monosubstituted acetates with imines, we turned to investigate the reaction of the simplest cerium enolate **8** with imine **10**. Treatment of the imine **10** with two equivalents of cerium enolate **8** at -78°C for 3 h and then at 0°C for 2 h afforded *trans* azetidinone **47** as white crystals in 31% yield after recrystallization from hexane and ethyl acetate.



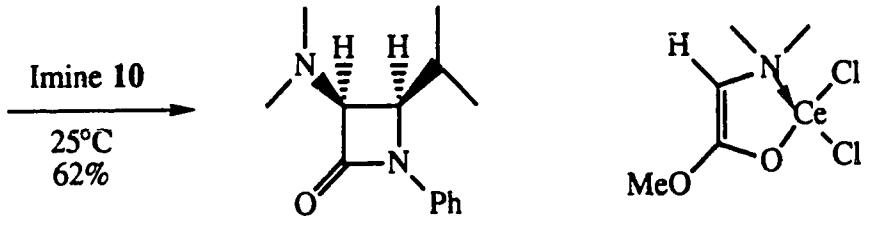
The high resolution mass spectrum of azetidinone **47** showed the molecular ion peak at m/e 336.2203 corresponding to the molecular formula $C_{22}H_{28}N_2O$. This molecular formula was also confirmed by the elemental analysis. Azetidinone **47** exhibited the amino and carbonyl absorptions at 3360 and 1732 cm^{-1} respectively in the IR spectrum. The ^1H NMR spectrum displayed a

doublet of doublets (J = 4, 2 Hz) at δ 3.94 due to the H–4 proton which coupled to the H–3 proton by 2 Hz. The H–3 proton resonating at δ 3.16 was also observed as a doublet of doublets (J = 10, 2 Hz). The coupling constant of 2 Hz for H–3 and H–4 indicated a *trans* relationship between these protons. In the ^{13}C NMR spectrum, the singlet at δ 165.80 was assigned to the C=O carbon. The C–3 and C–4 carbons resonated at δ 53.49 (d) and 60.79 (d) respectively.

Synthesis of 3–amino β–lactams is very important in β–lactam chemistry.[3] In light of this, the addition of the cerium enolate **49**, prepared from the α–amino ester **48** to imine **10**, was examined. This reaction was found to occur at room temperature to afford the *cis* azetidinone **50** as the only isolated product in 62% yield. The progress of the reaction was monitored by TLC analysis. No addition was observed at -78°C. Only when the temperature was brought to 25°C, did the addition of cerium enolate **49** to imine **10** occur.



48 49



50 Z–enolate 51

The azetidinone **50**, obtained as a white solid, showed a strong amide carbonyl absorption at 1745 cm^{-1} in the IR spectrum. Its high resolution mass spectrum exhibited the molecular ion peak at m/e 232.1573 consistent with the molecular formula $C_{14}H_{20}N_2O$. The elemental analysis also supported this molecular formula. In the ^1H NMR spectrum, the H–4 proton resonated at δ 4.00 (dd, J = 5.5, 5.5 Hz), whereas the H–3 proton appeared at δ 3.84 as a doublet ($J_{3,4}$ = 5.5 Hz). In the ^{13}C NMR spectrum the carbonyl carbon resonated at δ 166.16 as a singlet. The resonance signals at δ 73.38 (d) and 63.06 (d) were assigned to the C–3 and C–4 carbons respectively.

The *cis* stereochemistry was assigned on the basis of the coupling constant of H–3 and H–4 ($J_{3,4}$ = 5.5 Hz) as well as the NOE experiment. Upon irradiation of the doublet at δ 3.84 (H–3), a 8.2% enhancement was observed for the signal at δ 4.00 corresponding to H–4 proton. Other results obtained from the NOE experiment are outlined in Figure III–4.

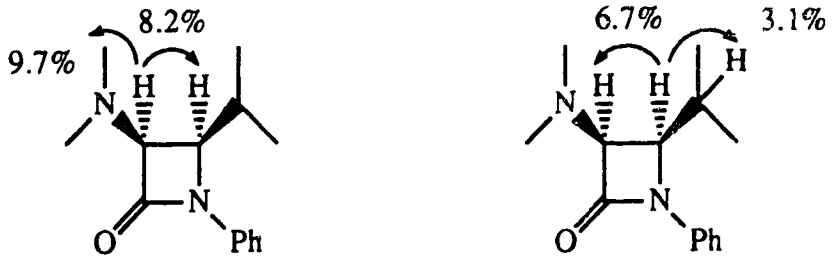
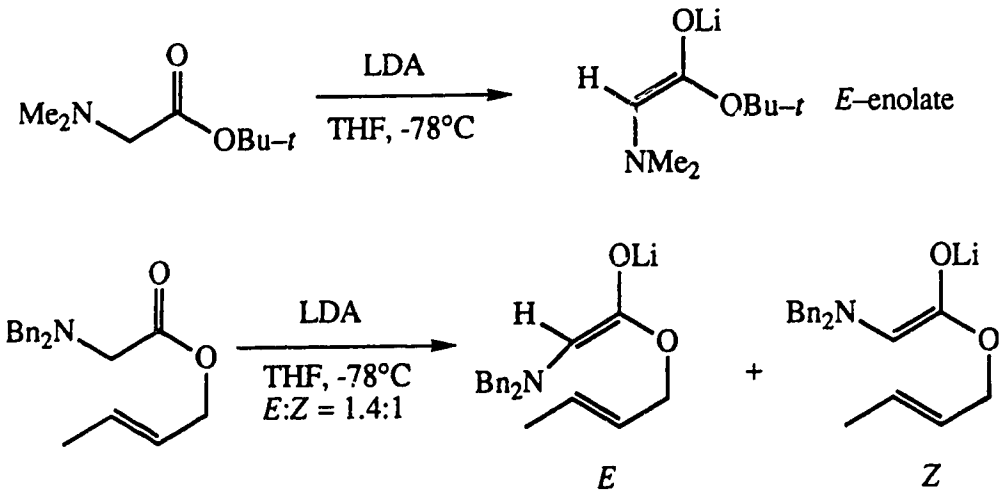


Figure III–4. NOE Data for Azetidinone **50**

To the best of our knowledge, the geometry of the lithium enolate of the α–amino ester, generated by kinetic deprotonation with LDA in THF at -78°C, has yet to be fully established. Only a few examples[40] exist, which showed that

deprotonation of an α–amino ester with LDA in THF at -78°C led to the *E*–enolate in modest selectivity (Scheme III–4).

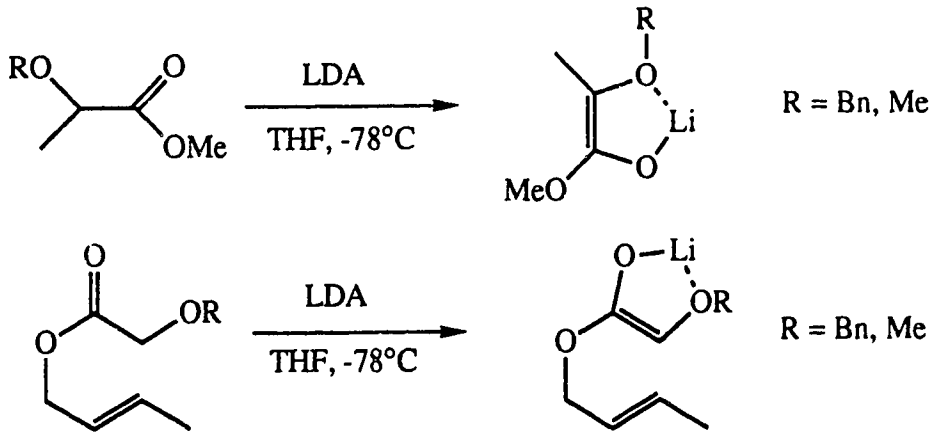
Scheme III–4



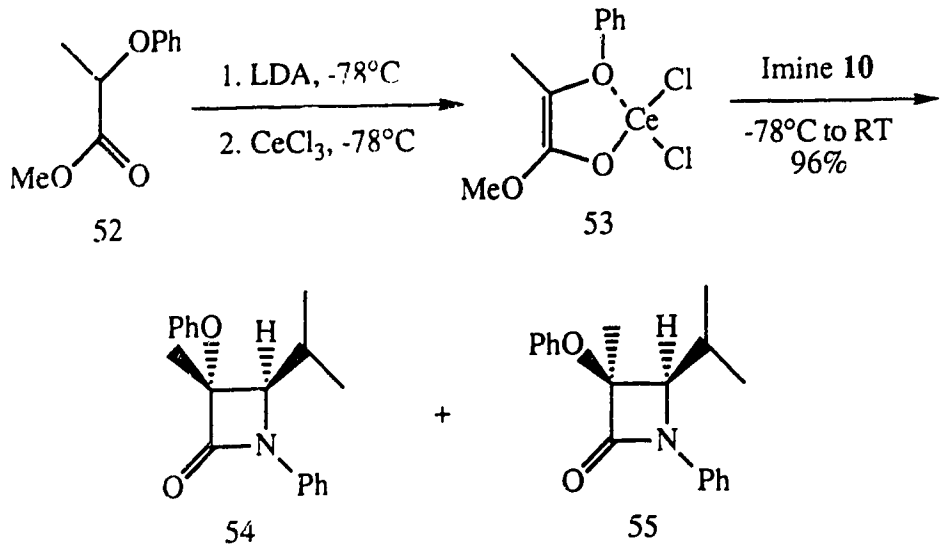
From the stereochemical outcome and with the assumption that the reaction proceeded *via* a chair–like transition state, it appears that deprotonation of α–amino ester **48** under the described conditions gave preferentially the *E* enolate. Subsequent transmetallation with $CeCl_3$ proceeded with retention of stereochemistry to afford the *E* cerium enolate **49**. Likely, it was this *E* enolate and not the chelated *Z*–enolate **51** that was involved in this reaction. This result was in sharp contrast with that obtained for the zinc enolate of α–amino ester by Koten.[23, 24] The latter was shown to exist mainly in the chelated *Z*–form which gave *trans* β–lactam with *trans* imine. Thus, the cerium enolate and zinc enolate of α–amino ester could provide complimentary routes to either *cis* or *trans* azetidinones.

Unlike the α–amino ester, it was well established that deprotonation of α–alkoxy ester with LDA in THF at -78°C gave predominantly the chelated enolate (*Z*–enolate)[40–45] (Scheme III–5). This process has been widely utilized in the total synthesis of natural products. We anticipated that the *Z*–cerium enolate (chelation form) of α–alkoxy ester would be generated from the corresponding lithium enolate *via* transmetallation with $CeCl_3$. Its condensation with a *trans* imine could then result in the formation of the alkoxyl substituted *trans* β–lactam system *via* the proposed chair–like transition state.

Scheme III–5



With this idea in mind, we prepared the cerium enolate **53** from ester **52** and carried out its addition with imine **10**. As expected, the *trans* azetidinone **54** was produced as the major product (83%) along with a small amount of *cis* isomer **55** (13%).



52 53 54 55

The more polar isomer **54** showed strong amide carbonyl absorptions at 1756 and 1750 cm^{-1} in the IR spectrum. The presence of the β–lactam moiety was also evident from the ^{13}C NMR spectrum in which a singlet was observed at δ 167.43 for the carbonyl carbon. Its high resolution mass spectrum exhibited the molecular ion peak at m/e 295.1574 corresponding to the molecular formula $C_{19}H_{21}NO_2$ which was also confirmed by the elemental analysis. In the ^1H NMR spectrum, the H–4 proton appeared at an abnormally low field of δ 4.14 (d, J = 7.5 Hz), apparently due to the deshielding effect of the phenoxy group. The singlet at δ 1.70, integrating to three protons, was assigned to the methyl group attached to the β–lactam ring. The C–3 carbon was observed at δ 89.85 as a singlet and the C–4 carbon at δ 68.14 as a doublet in the ^{13}C NMR spectrum.

The less polar compound **55** showed, in the IR spectrum, an amide carbonyl absorption at 1751 cm^{-1}. Its molecular formula was determined to be $C_{19}H_{21}NO_2$ by the high resolution mass spectrum which displayed a molecular ion peak at 295.1576. The H–4 proton resonance signal was observed at δ

3.94 as a doublet (J = 7 Hz) in the ^{1}H NMR spectrum. The methyl group attached to C–3 resonated at δ 1.62 as a singlet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 166.79 as a singlet. The C–3 and C–4 carbons were found at δ 87.06 (s) and 70.10 (d) respectively.

The stereochemistry of the isomeric azetidinones **54** and **55** was assigned based on the NOE experiments. For azetidinone **54**, irradiation of the signal at δ 1.70 brought about 4% of enhancement for the signal at δ 2.20 (C**H**Me$_2$). This finding indicated that the methyl and isopropyl groups were spatially close to each other. In the case of **55**, upon irradiation of the doublet at δ 3.94 (H–4), the singlet at δ 1.62 (C–3 methyl) was enhanced by 15%. The relative stereochemistry was thus established as shown in Figure III–5.

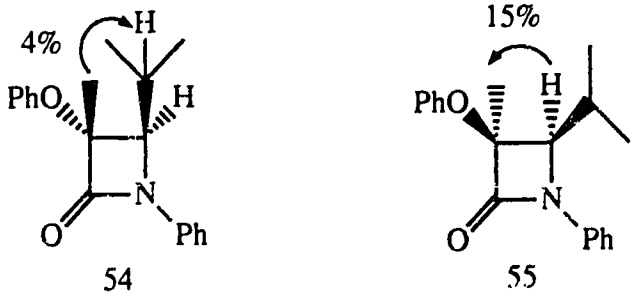
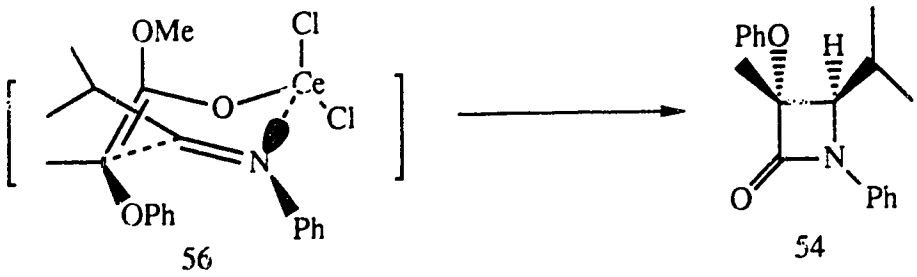


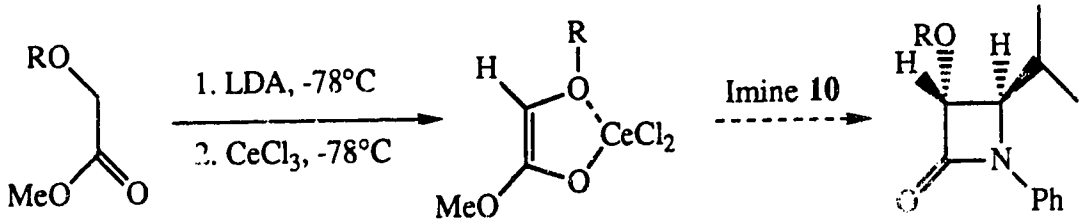
Figure III–5. NOE Data for Azetidinones **54** and **55**

The formation of the isomer **54** as the major product could be rationalized by invoking an addition of chelated enolate **53** to imine **10** *via* a chair–like transition state **56**. The azetidinone **55** might have been derived from the corresponding boat transition state.



56 54

We also examined the addition of cerium enolates **60**, **61** and **62**, prepared from the α–alkoxyl monosubstituted acetates **57**, **58** and **59** by treatment with LDA in THF at -78°C followed by transmetallation with $CeCl_3$, to imine **10**. However, all attempts to effect the addition of enolates **60**, **61** and **62** to imine **10** failed. Only decomposed ester and imine were obtained after the usual work–up of the reaction mixture. This negative result could be explained by the low nucleophilicity and relatively low stabilities of the cerium enolates of α–alkoxyl monosubstituted acetates under the reaction conditions (25°C).



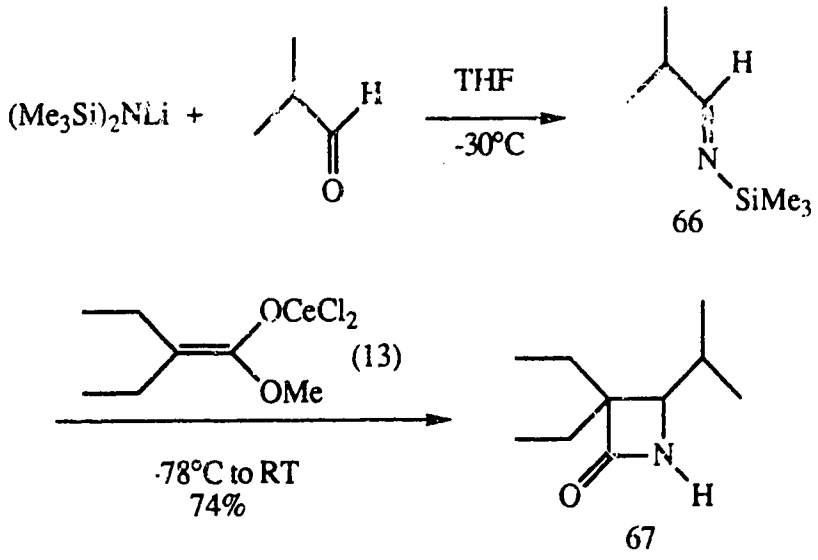
R = Ph, 57;
Bn, 58;
Me, 59

R = Ph, 60;
Bn, 61;
Me, 62

R = Ph, 63;
Bn, 64;
Me, 65

As discussed in the Introduction Section, the preparation of *N*–unsubstituted azetidinones is of importance to β–lactam chemistry. Many natural β–lactam antibiotics have been synthesized from *N*–unsubstituted β–lactams. With this purpose in mind, we examined the addition of the cerium ester enolate to enolizable *N*–silyl imines. The *N*–silyl imine **66** was prepared *in situ* by addition of lithium bis(trimethylsilyl)amide to isobutyraldehyde at -35°C

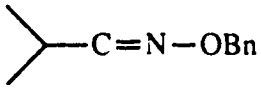
followed by Peterson elimination at this temperature. *N*–Silyl imine **66** was a very noxious smelling compound which deteriorated rapidly at higher temperatures. Treatment of two equivalents of cerium enolate **13** with freshly prepared *N*–silyl imine **66** at a temperature range of -78°C to 25°C gave the *N*–unsubstituted azetidinone **67** directly in 74% yield. By monitoring the reaction with analytical TLC, it was shown that no addition occurred below room temperature. When one equivalent of cerium enolate was employed, only about 48% yield of **67** was obtained. When lithium ester enolate (one equivalent) of ester **12** was used alone without $CeCl_3$, a 65% yield of azetidinone **67** was isolated.



The azetidinone **67** was isolated as white crystals (mp 67°C). The high resolution mass spectrum did not show the molecular ion peak; only the $(M-CONH)^+$ ion peak was observed. However, the elemental analysis confirmed the chemical composition of the molecular formula $C_{10}H_{19}NO$. This was supported by the low resolution mass spectrum (EI method) which showed the

molecular ion peak at m/e 169. Its infrared absorptions for the NH and amide carbonyl groups were observed at 3208 and 1760 cm^{-1} respectively. The NH proton resonated at δ 5.90 as a broad singlet in the ^1H NMR spectrum. The H–4 proton was observed at δ 2.93 as a doublet (J = 10 Hz). The ^{13}C NMR spectrum showed the carbonyl carbon at δ 174.68 as a singlet. The C–4 and C–3 carbons resonated at δ 65.14 (d) and 61.01 (s) respectively.

The other commonly used methods for the preparation of *N*–unsubstituted azetidinones involve the formation of the *N*–substituted β–lactam first, followed by removal of the substituent on the nitrogen. *N*–Benzyloxy β–lactams were shown to be useful precursors of *N*–unsubstituted β–lactams. Bearing this purpose in mind, we prepared the *N*–benzyloxy imine **68** in 96% yield by treatment of isobutyraldehyde with *O*–benzylhydroxyamine hydrochloride in refluxing pyridine. The *N*–benzyloxy imine **68** was obtained as a mixture of *trans* and *cis* isomers (*trans*:*cis* = 70:30) as determined by the ^1H NMR analysis. The high resolution mass spectrum of **68** exhibited a molecular ion peak at m/e 177.1154 corresponding to the molecular formula $C_{11}H_{15}NO$. The compound **68** showed an absorption band at 1454 cm^{-1} in the IR spectrum for the C=N double bond. In the ^1H NMR spectrum, the methylene protons resonated at δ 5.08 (singlet, *trans*) and 5.04 (singlet, *cis*). The methine proton was observed at 3.20 (multiplet, *cis*) and 2.50 (multiplet, *trans*). The vinylic proton for the *cis* isomer appeared at 6.50 (d, J = 6.4 Hz), while the one for the *trans* isomer was eclipsed with aromatic protons. In the ^{13}C NMR spectrum, the signals for the C=N carbon were observed at δ 157.37 (*cis* isomer) and 155.85 (*trans* isomer), each as a doublet. The OCH_2 carbon resonated at δ 75.54 (t, *cis* isomer) and 75.39 (t, *trans* isomer).



68

The reactions of cerium ester enolates **16** and **22** with imine **68** were attempted. However, neither of these enolates were found to undergo addition to *N*–benzyloxy imine **68**. Under a variety of conditions, only the starting imine **68** was recovered. These negative results could be accounted for by the low electrophilicity of *N*–benzyloxy imine due to the electron–donating effect of the OBn group. Thus, the C=N double bond of *N*–benzyloxyimine becomes more electron rich and less electrophilic than that of normal imines.

In conclusion, we have developed an efficient procedure for the stereoselective synthesis of azetidinones, making use of the cerium ester enolate–imine condensation process. Cerium ester enolates are superior nucleophiles which react with both enolizable and non–enolizable imines readily to afford β–lactams directly. This methodology is potentially useful for the synthesis of β–lactam antibiotics.

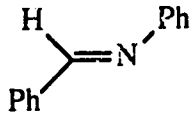
EXPERIMENTAL

General

For detailed experimental remarks, see the Experimental Sections of Chapters I and II.

All simple esters were prepared either by treatment of the parent acid with concentrated sulfuric acid in refluxing methanol or ethanol or by the reaction of an acyl chloride with methanol in the presence of pyridine.

Aniline-*N*-phenylidene (1).



Imine **1** was prepared in 84% yield (15.20 g, 0.084 mol) after recrystallization from ethanol according to the known procedure[35] involving the condensation of aniline (9.30 g, 0.10 mol) and benzaldehyde (10.60 g, 0.1 mol) in ethanol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1 H, CH=N), 7.90 (m, 2 H, ArH), 7.46 (m, 3 H, ArH), 7.40 (m, 2 H, ArH), 7.20 (m, 3 H, ArH); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 160.40 (d, CH=N), 152.15 (s, Ph), 136.28 (s, Ph), 131.40 (d, Ph), 129.18 (d, Ph), 128.84 (d, Ph), 128.80 (d, Ph), 125.96 (d, Ph), 120.90 (d, Ph); FT-IR ($CHCl_3$) 1628 (C=N), 1591, 1578 (Ph) cm^{-1}; HRMS M^+ 181.0886 (calcd for $C_{13}H_{11}N$ 181.0892).

General Procedure for the Synthesis of β–Lactams by Cerium Enolate–Imine Condensation

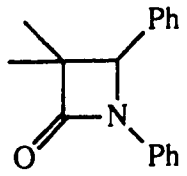
(a) Preparation of Cerium Ester Enolates

The general procedure for the preparation of cerium ester enolates as described in the Experimental Section of Chapter II was followed. Several additional esters were used as starting material.

(b) Condensation of Cerium Ester Enolate and Imines

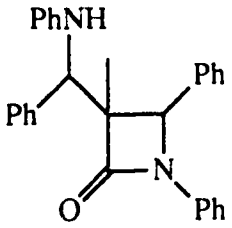
A solution (1.00 mmol) in THF (4 mL) was added dropwise with a syringe to a freshly formed cerium ester enolate suspension (2.00 mmol, 2.0 equiv. for enolizable imine **10**; 1.0 mmol, 1.0 equiv. for nonenolizable imine **1**) in THF at -78°C. The resulting mixture was stirred at -78°C for several hours under an atmosphere of dry argon. The progress of the reaction was monitored by TLC analysis on silica gel. In some cases, the mixture was gradually warmed up to 0°C or room temperature and further stirred until the completion of reaction. When the reaction was complete, saturated aqueous NH_4Cl was added to the mixture at -78°C. The resulting mixture was extracted with Et_2O–hexane (3 × 20 mL). The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave the crude β–lactam which was purified either by flash column chromatography on silica gel or by recrystallization (hexane or hexane–EtOAc).

3,3-Dimethyl-1,4-diphenyl-2-azetidinone (3).



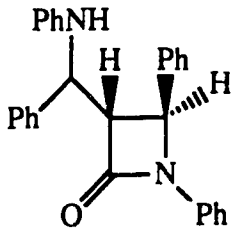
By following the standard procedure, imine **1** (580 mg, 3.20 mmol) was added to the cerium enolate **2** (3.75 mmol) in THF at -78°C and the mixture was stirred for 10 h at the same temperature. TLC indicated that the reaction proceeded smoothly at -78°C. To ensure complete reaction, the reaction mixture was warmed up to room temperature and further stirred for 10 h. After the usual-work up, β-lactam **3**[6] was isolated as a white solid in 91% yield (730 mg, 2.91 mmol): mp 145-146°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00-7.10 (m, 1 H, ArH), 7.20-7.40 (m, 9 H, ArH), 4.82 (s, 1 H, NC**H**Ph), 1.53 (s, 3 H, Me), 0.85 (s, 3 H, Me); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 171.50 (s, C=O), 137.96 (s, Ph), 135.61 (s, Ph), 129.04 (d, Ph), 128.71 (d, Ph), 128.05 (d, Ph), 126.61 (d, Ph), 123.69 (d, Ph), 117.30 (d, Ph), 66.56 (d, NCHPh), 55.45 (s, O=C**C**Me$_2$), 22.86 (q, CH_3), 17.98 (q, CH_3); FT-IR ($CHCl_3$) 1744 (C=O), 1735 (C=O), 1498 (Ph) cm^{-1}; HRMS M$^+$ 251.1306 (calcd for $C_{17}H_{17}NO$ 251.1310); Anal. Calcd for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.38; H, 6.93; N, 5.58.

3-Methyl-3-(1-phenylaminobenzyl)-1,4-diphenyl-2-azetidinone (7).



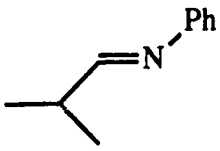
Condensation of imine **1** (470 mg, 2.60 mmol) and cerium enolate **4** (3.70 mmol) in THF at temperatures ranging from -78°C (24 h) to 0°C (5 h) afforded azetidinone **7**[36] as a yellowish solid in 55% yield (300 mg, 0.72 mmol) after flash column chromatography eluting with 5% EtOAc in hexane: mp 165–167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50–7.60 (m, 20 H, ArH), 5.30 (s, 1 H, H–4), 4.76 (br s, 2 H, N**H** and PhNHC**H**), 0.90 (s, 3 H, CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 169.55 (s, C=O), 147.52 (s, Ph), 139.16 (s, Ph), 137.33 (s, Ph), 134.56 (s, Ph), 129.10 (d, Ph), 129.07 (d, Ph), 128.70 (d, Ph), 128.13 (d, Ph), 128.09 (d, Ph), 126.84 (d, Ph), 126.63 (d, Ph), 124.14 (d, Ph), 118.51 (d, Ph), 117.47 (d, Ph), 117.32 (d, Ph), 114.69 (d, Ph), 63.92 (d, CHPh), 62.82 (d, PhNHCHPh), 62.31 (s, O=CC), 13.25 (q, CH_3); FT–IR ($CHCl_3$) 3400 (NH), 1740 (C=O), 1601 and 1501 (Ph) cm^{-1}; HRMS M^+ 418.2019 (calcd for $C_{29}H_{26}N_2O$ 418.2045).

(3*R, 4*S**)–3–(1–Phenylaminobenzyl)–1,4–diphenyl–2–azetidinone (9).**



Imine **1** (580 mg, 3.20 mmol) was treated with cerium enolate **8** (3.70 mmol) in THF for 10 h at -78°C and 5 h at 25°C. Azetidinone **9** was isolated in 32% yield (210 mg, 0.52 mmol) as a yellowish solid after flash column chromatography on silica gel (eluting with 10% EtOAc in hexane): mp 160–165°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–7.60 (m, 17 H, ArH), 6.50–6.80 (m, 3 H, ArH), 4.94 (br t, *J* = 7 Hz, 1 H, PhC**H**NHPh), 4.80 (d, *J* = 2 Hz, 1 H, O=CNC**H**Ph), 4.68 (d, *J* = 7 Hz, 1 H, PhNH), 3.60 (dd, *J* = 6.5, 2 Hz, 1 H, COCH); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 164.92 (s, C=O), 146.42 (s, Ph), 139.68 (s, Ph), 137.41 (s, Ph), 137.21 (s, Ph), 129.27 (d, Ph), 129.22 (d, Ph), 129.06 (d, Ph), 128.89 (d, Ph), 128.61 (d, Ph), 128.00 (d, Ph), 127.15 (d, Ph), 125.93 (d, Ph), 124.09 (d, Ph), 118.17 (d, Ph), 117.17 (d, Ph), 113.95 (d, Ph), 65.15 (d, OCNCHPh), 58.14 (d, PhCHNHPh), 56.99 (d, COCH); FT–IR ($CHCl_3$) 3400 (NH), 3061 (NH), 3030 (NH), 1745 (C=O), 1651 (C=O), 1600 (Ph) cm^{-1}; HRMS M^+ 404.1891 (calcd for $C_{28}H_{24}N_2O$ 404.1888).

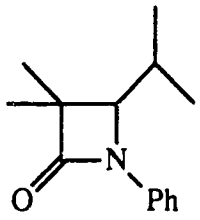
Aniline *N*–isobutylidene (10).



A solution of isobutyraldehyde (1.52 g, 0.022 mol) in Et_2O (5 mL) was added slowly to a stirred solution of aniline (1.70 g, 0.018 mol) in Et_2O (5 mL) at -10°C. After the mixture was stirred for 6 h at 0°C, the water produced by the condensation reaction was separated and the organic layer was dried over $MgSO_4$. Evaporation of the solvent *in vacuo* provided the crude imine **10** which was subjected to bulb–to–bulb distillation (40°C, 0.1 mmHg) to afford

the pure imine **10** in 86% yield (2.28 g, 0.015 mol) as a colorless oil which had an unpleasant smell: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 4.5 Hz, 1 H, CH=N), 7.30 (m, 2 H, ArH), 7.10–7.20 (m, 1 H, ArH), 7.00 (m, 2 H, ArH), 2.62 (m, 1 H, $CHMe_2$), 1.19 (d, J = 7 Hz, 6 H, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 170.62 (d, CH=N), 152.37 (s, Ph), 128.90 (d, Ph), 125.22 (d, Ph), 120.32 (d, Ph), 34.64 (d, Me_2CH), 19.06 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1667 (C=N), 1649 (C=N), 1602, 1588 (Ph) cm^{-1}; HRMS M^+ 147.1045 (calcd for $C_{10}H_{13}N$ 147.1048).

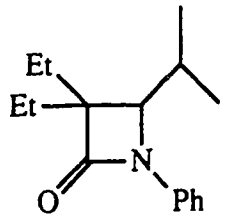
4–Isopropyl–3,3–dimethyl–1–phenyl–2–azetidinone (11).



By the standard procedure, imine **10** (400 mg, 2.72 mmol) was treated with cerium enolate **2** (5.50 mmol) in THF at -78°C for 4 h and then at room temperature for 24 h. Pure azetidinone **11** (531 mg, 90%) was obtained, after column chromatography on silica gel (5%–10% EtOAc in hexane as eluant), as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.40 (m, 4 H, ArH), 7.10 (m, 1 H, ArH), 3.60 (d, J = 9 Hz, 1 H, NCHPr–*i*), 2.10 (m, 1 H, $CHMe_2$), 1.38 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.00 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 0.96 (d, J = 6.5 Hz, 3 H, $CHCH_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.88 (s, C=O), 138.25 (s, Ph), 128.82 (d, Ph), 124.24 (d, Ph), 119.50 (d, Ph), 69.42 (d, NCHPr–*i*), 52.37 (s, O=CC), 30.29 (d, $CHMe_2$), 23.91 (q, CH_3), 21.25 (q, CH_3), 20.05 (q, CH_3), 17.27 (q, CH_3); FT–IR ($CHCl_3$) 1752 (C=O), 1599,

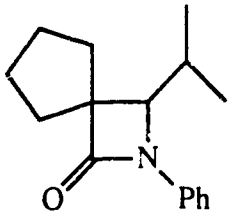
1500 (Ph) cm^{-1}; HRMS M^+ 217.1467 (calcd for $C_{14}H_{19}NO$ 217.1466); Anal. Calcd for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.21; H, 8.53; N, 6.39.

3,3-Diethyl-4-isopropyl-1-phenyl-2-azetidinone (14).



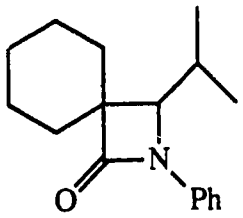
The above standard procedure was followed, using imine **10** (360 mg, 2.45 mmol) and cerium enolate **13** (5.50 mmol). The reaction mixture was stirred at -78°C for 10 h and then 5 h at 25°C under argon. Column chromatography of the crude product on silica gel, eluting with 5% EtOAc in hexane, gave pure β-lactam **14** in 94% yield (564 mg, 2.30 mmol) as a white solid: mp 67–68°C (hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 4 H, ArH), 7.10 (m, 1 H, ArH), 3.64 (d, J = 8 Hz, 1 H, NCHPr-*i*), 2.10–2.20 (m, 1 H, $CHMe_2$), 1.80–2.00 (m, 2 H, CH_2), 1.60–1.70 (m, 2 H, CH_2), 1.15 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.00 (d, J = 7 Hz, 3 H, CH_3CHCH_3), 0.96 (t, J = 7 Hz, CH_3CH_2), 0.94 (d, J = 7 Hz, 3 H, $MeCHCH_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.31 (s, C=O), 138.19 (s, Ph), 128.74 (d, Ph), 124.11 (d, Ph), 119.59 (d, Ph), 67.18 (d, NCHPr-*i*), 60.03 (s O=CC), 29.29 (d, $CHMe_2$), 25.62 (t, CH_2), 21.44 (q, CH_3), 21.16 (t, CH_2), 20.81 (q, CH_3), 9.29 (q, CH_3), 8.79 (q, CH_3); FT-IR ($CHCl_3$) 1745 (C=O), 1599, 1500 (Ph) cm^{-1}; HRMS M^+ 245.1781 (calcd for $C_{16}H_{23}NO$ 245.1779); Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.40; N, 5.70. Found: C, 78.53; H, 9.50; N, 5.75.

1–Isopropyl–3–oxo–2–phenyl–2–azaspiro[3.4]octane (17).



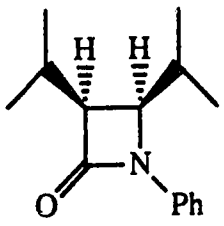
Reaction of imine **10** (310 mg, 2.10 mmol) with cerium enolate **16** (5.50 mmol) at -78°C for 6 h and 8 h at 25°C gave, after the usual work–up and flash column chromatography using 5% EtOAc in hexane as eluant, the pure β–azetidinone **17** (509 mg, 2.10 mmol, 100%) as a colorless oil which did not solidify even at -78°C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 4 H, ArH), 7.08 (m, 1 H, ArH), 3.78 (d, *J* = 7 Hz, 1 H, NCHPr–*i*), 2.00–2.20 (m, 3 H), 1.60–1.90 (m, 6 H), 1.00 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3), 0.99 (d, *J* = 7 Hz, 3 H, CH_3CHCH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 173.09 (s, C=O), 138.22 (s, Ph), 128.78 (d, Ph), 123.81 (d, Ph), 118.75 (d, Ph), 68.26 (d, OCNCH), 62.13 (s, O=CC), 35.98 (t, CH_2), 30.02 (d, $CHMe_2$), 27.78 (t, CH_2), 25.99 (t, CH_2), 25.36 (t, CH_2), 19.83 (q, CH_3), 19.39 (q, CH_3); FT–IR ($CHCl_3$) 1748 (C=O) and 1600 (Ph) cm^{-1}; HRMS M$^+$ 243.1620 (calcd for $C_{16}H_{21}NO$ 243.1623). Anal. Calcd for $C_{16}H_{21}NO$: C, 79.01; H, 8.64; N, 5.76. Found: C, 78.79; H, 8.71; N, 5.84.

1–Isopropyl–3–oxo–2–phenyl–2–azaspiro[3.5]nonane (20).



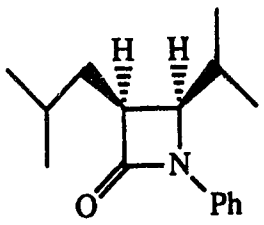
The reaction of imine **10** (300 mg, 2.04 mmol) and cerium ester enolate **19** (5.50 mmol) in THF at -78°C for 6 h and then 12 h at room temperature afforded the pure β–lactam **20** (484 mg, 1.88 mmol, 93%) as a white crystal after purification by column chromatography on silica gel using 5% EtOAc in hexane as eluant: mp 61–61.4°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 4 H, ArH), 7.10 (m, 1 H, ArH), 3.48 (d, J = 8 Hz, 1 H, NCH), 1.50–2.20 (m, 11 H), 1.03 (d, J = 7 Hz, 3 H, $MeCHCH_3$), 0.93 (d, J = 7 Hz, 3 H, $CHCH_3Me$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.54 (s, C=O), 138.49 (s, Ph), 128.71 (d, Ph), 123.88 (d, Ph), 119.10 (d, Ph), 68.88 (d, NCH), 56.79 (s, O=CC), 34.92 (t, CH_2), 28.91 (d, $CHMe_2$), 28.19 (t, CH_2), 25.89 (t, CH_2), 23.35 (t, 2 × CH_2); 20.89 (q, CH_3), 20.79 (q, CH_3); FT–IR ($CHCl_3$) 1741 (C=O), 1599 and 1500 (Ph) cm^{-1}; HRMS M^+ 257.1778 (calcd for $C_{17}H_{23}NO$ 257.1779); Anal. Calcd for $C_{17}H_{23}NO$: C, 79.32; H, 8.95; N, 5.44. Found: C, 79.43; H, 9.21; N, 5.40.

cis–3,4–Diisopropyl–1–phenyl–2–azetidinone (23).



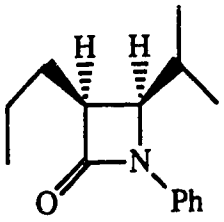
The standard procedure was followed for the preparation of β–lactam **23**, starting with imine **10** (180 mg, 1.22 mmol) and cerium ester enolate **22** (2.70 mmol). After the reaction mixture was stirred for 3 h at -78°C, TLC analysis showed the complete disappearance of the starting imine **10**. The reaction mixture was then worked up at -78°C and the crude product was purified either by column chromatography using 5% EtOAc in hexane as eluant or by recrystallization from hexane to give pure azetidinone **23** in 98% yield (276 mg, 1.20 mmol) as a white crystal: mp 91–92°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.40 (m, 4 H, ArH), 7.00–7.10 (m, 1 H, ArH), 4.12 (dd, *J* = 6, 4.2 Hz, 1 H, PhNC**H**Pr–*i*), 3.10 (dd, *J* = 9.4, 6 Hz, 1 H, O=CC**H**Pr–*i*), 2.10–2.30 (m, 2 H, 2 × C**H**Me$_2$), 1.26 (d, *J* = 6.5 Hz, 3 H, CHC**H**$_3$Me), 1.16 (d, *J* = 7 Hz, 3 H, CHMeC**H**$_3$), 1.02 (d, *J* = 6.5 Hz, 3 H, CHC**H**$_3$Me), 0.95 (d, *J* = 6.5 Hz, 3 H, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 168.28 (s, C=O), 138.51 (s, Ph), 128.88 (d, Ph), 123.94 (d, Ph), 118.80 (d, Ph), 60.59 (d, NCH), 59.18 (d, O=CCH), 28.31 (d, CHMe$_2$), 25.25 (d, CHMe$_2$), 23.43 (q, CH_3), 22.58 (q, CH_3), 20.96 (q, CH_3), 19.26 (q, CH_3); FT–IR ($CHCl_3$) 1725 (C=O), 1686 (C=O), 1596 (Ph) cm^{-1}; HRMS M$^+$ 231.1622 (calcd for $C_{15}H_{21}NO$ 231.1623); Anal. Calcd for $C_{15}H_{21}NO$: C, 77.93; H, 9.16; N, 6.06. Found: C, 77.95; H, 8.96; N, 6.08.

***cis*–3–Isobutyl–4–isopropyl–1–phenyl–2–azetidinone (26).**



Reaction of imine **10** (300 mg, 2.04 mmol) with cerium enolate **25** (5.50 mmol) in THF at -78°C for 2 h gave the desired azetidinone **26** in 94% yield (470 mg, 1.92 mmol) as a colorless oil after column chromatography on silica gel using 10% EtOAc in hexane as eluant. The β–lactam **26** which did not solidify showed the following physical properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.40 (m, 4 H, ArH), 7.02–7.12 (m, 1 H, ArH), 4.04 (dd, *J* = 6.5, 6 Hz, 1 H, NC**H**Pr–*i*), 3.40 (ddd, *J* = 10, 5.5, 5.5 Hz, 1 H, O=CCH), 2.15 (m, 1 H), 1.92–2.00 (m, 1 H), 1.80 (ddd, *J* = 13.5, 10, 5.5 Hz, 1 H, *i*–PrC**H**HCH), 1.45 (ddd, *J* = 13.5, 8.5, 5 Hz, 1 H, *i*–PrCH**H**CH), 1.04 (d, *J* = 7 Hz, 3 H, CHC**H**$_3$Me), 1.00 (d, *J* = 7 Hz, 3 H, CHMeC**H**$_3$), 0.98 (d, *J* = 7 Hz, 3 H, CHC**H**$_3$Me), 0.96 (d, *J* = 7 Hz, 3 H, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 169.44 (s, C=O), 138.31 (s, Ph), 128.84 (d, Ph), 123.95 (d, Ph), 118.78(d, Ph), 60.49 (d, NCH), 50.13 (d, O=CCH), 34.02 (t, CH_2), 29.17 (d, $CHMe_2$), 26.89 (d, $CHMe_2$), 23.43 (q, CH_3), 22.03 (q, CH_3), 20.53 (q, CH_3), 20.13 (q, CH_3); FT–IR ($CHCl_3$) 1748 (C=O), 1600, 1500 (Ph) cm^{-1}; HRMS M$^+$ 245.1778 (calcd for $C_{16}H_{23}NO$ 245.1779); Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.38; N, 5.71. Found: C, 78.32; H, 9.26; N, 5.63.

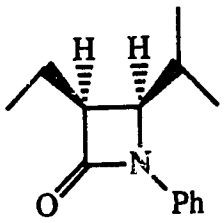
cis–4–Isopropyl–1–phenyl–3–propyl–2–azetidinone (29).



By the standard procedure, imine **10** (300 mg, 2.04 mmol) was treated with cerium ester enolate **28** (5.40 mmol) in THF at -78°C for 3 h. TLC showed the

complete consumption of the imine **10** after this period. After the usual work–up, the crude azetidinone **29** was purified by flash column chromatography on silica gel (elution with 7% EtOAc in hexane) to furnish the β–lactam **29** in 92% yield (436 mg, 1.89 mmol) as a colorless oil. The azetidinone **29** did not solidify even at -78°C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 4 H, ArH), 7.05–7.12 (m, 1 H, ArH), 4.01 (dd, *J* = 7, 6 Hz, 1 H, NCHPr–*i*), 3.30 (ddd, *J* = 10, 6, 6 Hz, 1 H, O=CCH), 2.16 (m, 1 H, $CHMe_2$), 1.40–1.90 (m, 4 H, CH_2CH_2), 1.04 (d, *J* = 7 Hz, 3 H, $CHCH_3Me$), 0.99 (t, *J* = 7 Hz, 3 H, CH_3CH_2), 0.97 (d, *J* = 7 Hz, 3 H, $CHMeCH_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 169.46 (s, C=O), 138.27 (s, Ph), 128.84 (d, Ph), 123.98 (d, Ph), 118.82 (d, Ph), 60.50 (d, NCH), 51.91 (d, O=CCH), 29.22 (d, $CHMe_2$), 27.55 (t, CH_2), 21.81 (t, CH_2), 20.36 (q, 2 × CH_3), 14.24 (q, CH_3); FT–IR ($CHCl_3$) 1747 (C=O), 1599 (Ph) cm^{-1}; HRMS M^+ 231.1623 (calcd for $C_{15}H_{21}NO$ 231.1623); Anal. Calcd for $C_{15}H_{21}NO$: C, 77.58; H, 9.05; N, 6.03. Found: C, 77.67; H, 9.17; N, 6.01.

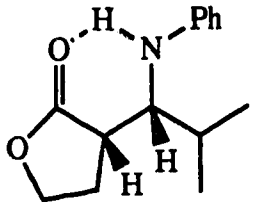
***cis*–3–Ethyl–4–isopropyl–1–phenyl–2–azetidinone (32).**



According to the standard procedure, imine **10** (300 mg, 2.04 mmol) was reacted with cerium ester enolate **31** (5.40 mmol) at -78°C for 6 h under an atmosphere of argon. TLC analysis indicated the complete disappearance of the starting imine **10**. The crude product was chromatographed on silica gel (10%

EtOAc in hexane as eluant) to give azetidinone **32** (422 mg, 1.95 mmol, 95%) as a white solid: mp 54–55°C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.40 (m, 4 H, ArH), 7.05–7.10 (m, 1 H, ArH), 4.02 (dd, *J* = 7, 5.9 Hz, 1 H, NCH), 3.24 (ddd, *J* = 10, 5.9, 5.9 Hz, 1 H, O=CCH), 2.15 (m, 1 H, C**H**Me$_2$), 1.82–2.00 (m, 1 H, C**H**H), 1.64–1.80 (m, 1 H, CH**H**), 1.20 (t, *J* = 7 Hz, 3 H, C**H**$_3$CH$_2$), 1.04 (d, *J* = 7 Hz, CHC**H**$_3$Me), 0.98 (d, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 169.44 (s, C=O), 138.25 (s, Ph), 128.85 (d, Ph), 123.99 (d, Ph), 118.84 (d, Ph), 60.58 (d, NCH), 53.70 (d, O=CCH), 29.21 (d, $CHMe_2$), 20.39 (q, CH_3), 20.32 (q, CH_3), 18.79 (t, CH_2), 13.13 (q, CH_3); FT–IR ($CHCl_3$) 1747 (C=O), 1599 and 1499 (Ph) cm^{-1}; HRMS M$^+$ 217.1464 (calcd for $C_{14}H_{19}NO$ 217.1467); Anal. Calcd for $C_{14}H_{19}NO$: C, 77.36; H, 8.76; N, 6.45. Found: C, 76.99; H, 8.72; N, 6.34.

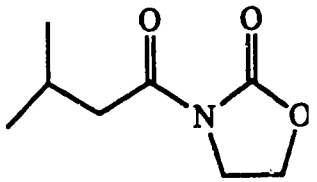
(2*S)–2–[(1*R**)–2–Methyl–1–phenylaminopropyl]–5–oxacyclo pentanone (35).**



According to the standard procedure, imine **10** (300 mg, 2.04 mmol) was treated with cerium ester enolate **34** (5.40 mmol) at -78°C for 8 h. Then the reaction mixture was gradually warmed up to room temperature and stirred for 8 h under argon. Usual work–up of the reaction mixture afforded an oily residue which was purified by flash column chromatography on silica gel (eluting with 25% EtOAc in hexane), furnishing the amino γ-lactone **35** (269

mg, 56%) as a white solid: mp 105–106°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.20 (m, 2 H, ArH), 6.68–6.76 (m, 3 H, ArH), 4.30 (ddd, *J* = 8, 8, 4 Hz, 1 H, OCHH), 4.20 (ddd, *J* = 8, 8, 7 Hz, 1 H, OCHH), 3.80 (m, 1 H, NHCH), 3.45 (br d, *J* = 8.5 Hz, 1 H, NH), 2.85 (dt, *J* = 3.5, 9.5 Hz, 1 H, O=CCH), 2.20–2.30 (m, 2 H, OCH_2CH_2), 1.86–1.90 (m, 1 H, $CHMe_2$), 0.94 (d, *J* = 6.5 Hz, 3 H, $MeCHCH_3$), 0.90 (d, *J* = 6.5 Hz, 3 H, CH_3CHMe); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 178.76 (s, C=O), 148.36 (s, Ph), 129.40 (d, Ph), 118.07 (d, Ph), 113.87 (d, Ph), 66.71 (t, OCH_2), 59.18 (d, HNCH), 42.45 (d, O=CCH), 33.33 (d, $CHMe_2$), 24.02 (t, OCH_2CH_2), 20.37 (q, CH_3), 18.87 (q, CH_3); FT-IR ($CHCl_3$) 3350 (NH), 1759 (γ-lactone C=O), 1601 and 1511 (Ph) cm^{-1}; HRMS M^+ 233.1415 (calcd for $C_{14}H_{19}NO_2$ 233.1416); Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00. Found: C, 72.09; H, 8.15; N, 5.99.

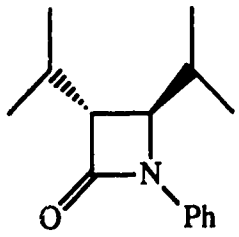
3-(3-Methyl-1-oxobutyl)-2-oxazolidinone (39).



To a solution of 2-oxazolidone (3.00 g, 34.45 mmol) in THF (80 mL), was added *n*-BuLi (2.40 M in hexane, 15 mL, 36.17 mmol) dropwise at -78°C under an atmosphere of argon. After the mixture was stirred for 20 min, isovaleryl chloride (4.58 g, 37.98 mmol) in THF (10 mL) was added in one portion to the lithium salt of 2-oxazolidone at -78°C. The resulting solution was stirred for 30 min at -78°C, then warmed up to 0°C and stirred for 15 min. After the reaction mixture was quenched with saturated NH_4Cl at -78°C, the

mixture was extracted with $CHCl_3$ (3 × 20 mL) and the organic extracts were washed with water and brine and dried over $MgSO_4$. Concentration gave an oil residue which was purified either by column chromatography on silica gel (20% EtOAc in hexane as eluant) or by bulb–to–bulb distillation (80–90°C, 0.1 mmHg) to afford the desired **39** in 90% yield (5.30 g, 30.99 mmol) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, J = 8 Hz, 2 H, CH_2), 4.02 (t, J = 8 Hz, 2 H, CH_2), 2.81 (d, J = 7 Hz, 2 H, $CH_2C{=}O$), 2.19 (m, 1 H, $CHMe_2$), 0.99 (d, J = 7 Hz, 6 H, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 172.87 (s, C=O), 153.55 (s, C=O), 61.95 (t, OCH_2), 43.58 (t, NCH_2), 42.55 (t, $CH_2C{=}O$), 25.03 (d, $CHMe_2$), 22.50 (q, 2 × CH_3); FT–IR ($CHCl_3$) 1778 (C=O), 1698 (C=O) cm^{-1}; HRMS M^+ 171.0895 (calcd for $C_8H_{13}NO_3$ 171.0895); Anal. Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.19. Found: C, 55.98; H, 7.62; N, 8.14.

Attempted Reaction of Cerium Enolate of Amide 39 with Imine 10 to Prepare *trans*–β–Lactam 41.

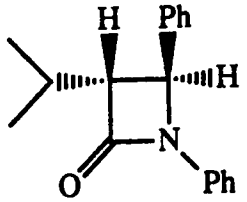


According to the standard procedure for the preparation of cerium enolate, 2–oxazolidinone **39** (470 mg, 2.75 mmol) was deprotonated with LDA (1.1 equiv.) in THF (15 mL) at -78°C and the resulting colorless solution of lithium enolate was added to a suspension of cerium chloride (2.80 mmol) in THF at

-78°C. The resulting mixture was stirred for 2 h at -78°C under an atmosphere of argon. To the cerium enolate of 2–oxazolidinone **39** thus formed was added dropwise a solution of imine **10** (150 mg, 1.02 mmol) in THF (2 mL). The reaction mixture was stirred at -78°C for 10 h. The progress of the reaction was monitored by analytical TLC. TLC showed that no reaction took place at -78°C. Thus, the reaction temperature was increased to 0°C. After 24 h, TLC indicated no product formation. The reaction mixture was warmed up to room temperature. The TLC analysis did not reveal any product after the mixture was stirred for 24 h. After the usual work–up, the crude product was subjected to ^{1}H NMR analysis which indicated the absence of the desired β–lactam.

Attempted reaction of cerium enolate and lithium enolate of 2–azetidinone **39** with nonenolizable imine **1** also failed. No addition reaction was observed.

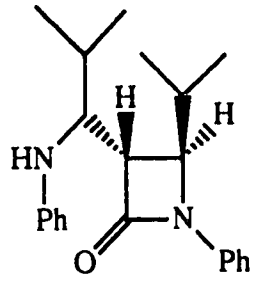
Attempted Reaction of Boron Enolate of Amide 39 with Imine 1 to Prepare the Corresponding *trans*–β–Lactam 42.



To a solution of (*n*–Bu)$_2$BOTf (1.0 M in CH_2Cl_2, 3.1 mL, 3.10 mmol) and EtN(Pr–*i*)$_2$ (401 mg, 3.10 mmol) in anhydrous ether (10 mL) at -78°C, was added a solution of 2–oxazolidinone **39** (480 mg, 2.80 mmol) in ether (4 mL) dropwise. The reaction mixture was stirred at -78°C for 30 min and then 30 min at -10°C. The appearance of a white solid precipitate indicated the

formation of the boron enolate. To this boron enolate solution at -78°C, imine **1** (480 mg, 2.65 mmol) in Et_2O (5 mL) was added. The reaction mixture was stirred at -78°C for 2 h and then 24 h at room temperature. After the usual work–up of the reaction mixture, the crude product was examined by ^1H NMR and TLC. However, only starting imine **1** and amide **39** were detected.

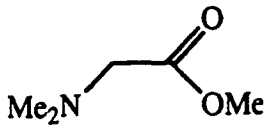
3,4-*trans*-4-Isopropyl-3-(2-methyl-1-phenylaminopropyl)-1-phenyl-2-azetidinone (47).



According to the standard procedure, cerium enolate **8** (5.40 mmol) was reacted with imine **10** (340 mg, 2.31 mmol) in THF for 2 h at -78°C and 2 h at 0°C. The crude product was purified by the column chromatography on silica gel, using 5% EtOAc in hexane as eluant, to afford azetidinone **47** (118 mg, 0.35 mmol, 31%) which was recrystallized from EtOAc–hexane as a colorless crystal: mp 152°C (hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–7.40 (m, 7 H, ArH), 6.10–6.20 (m, 3 H, ArH), 3.94 (dd, *J* = 4, 2 Hz, 1 H, NCH), 3.75 (m, 1 H, PhNHC**H**), 3.50 (br d, *J* = 9.5 Hz, 1 H, PhN**H**), 3.16 (dd, *J* = 10, 2 Hz, 1 H, O=CCH), 2.20–2.40 (m, 2 H, 2 × C**H**Me_2), 1.00 (d, *J* = 7 Hz, 3 H, CHCH_3Me), 0.99 (d, *J* = 7 Hz, 3 H, CHMeCH_3), 0.96 (d, *J* = 7 Hz, 3 H, CHCH_3Me), 0.84 (d, *J* = 7 Hz, 3 H, CHMeCH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 165.80 (s, C=O), 148.33 (s, Ph), 137.73 (s, Ph), 129.45 (d, Ph),

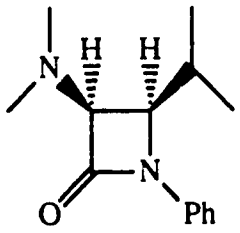
129.14 (d, Ph), 123.93 (d, Ph), 117.49 (d, Ph), 117.19 (d, Ph), 112.79 (d, Ph), 60.79 (d, PhNCH), 57.88 (d, O=CCH), 53.49 (d, PhNHCH), 31.41 (d, $CHMe_2$), 27.50 (d, $CHMe_2$), 20.69 (q, CH_3), 19.01 (q, CH_3), 16.30 (q, CH_3), 15.26 (q, CH_3); FT–IR ($CHCl_3$) 3360 (NH), 1732 (C=O), 1600 (Ph), 1525 (Ph) cm^{-1}; HRMS M^+ 336.2203 (calcd for $C_{22}H_{28}N_2O$ 336.2201); Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.52; H, 8.33; N, 8.33. Found: C, 78.20; H, 8.33; N, 8.34.

Methyl (*N*,*N*–dimethylamino)acetate (48).



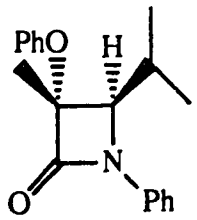
To a solution of dimethylamine (11.55 g, 0.26 mol) in dry benzene (20 mL) was added $BrCH_2CO_2Me$ (19.61 g, 0.13 mol) dropwise at 0°C. The white precipitate appeared immediately. The reaction mixture was stirred overnight at 25°C and then refluxed for 30 min. The mixture was acidified with 1N HCl and benzene layer was separated. The aqueous layer was washed with Et_2O, made basic with ice–cold 1N NaOH and extracted with Et_2O (3 × 20 mL). The organic extracts were washed with water and brine and dried over $MgSO_4$. The crude product was distilled (60°C, 60 mmHg) to give the α–amino ester **48** (24.50 g, 0.21 mol, 80%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 3.20 (s, 2 H, Me_2NCH_2), 2.40 (s, 6 H, 2 × CH_3); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 170.22 (s, C=O), 59.58 (t, CH_2), 50.71 (q, OCH_3), 44.52 (q, $N(CH_3)_2$); FT–IR ($CHCl_3$) 1756 and 1740 (C=O) cm^{-1}; HRMS M^+ 117.0791 (calcd for $C_5H_{11}NO_2$ 117.0789).

cis-4-Isopropyl-3-(_N_,_N_-dimethylamino)-1-phenyl-2-azetidinone (50).

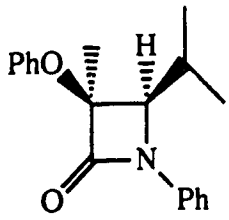


Following the standard procedure, imine **10** (310 mg, 2.11 mmol) was treated with cerium ester enolate **49** (5.20 mmol) derived from α-amino ester **48** (608 mg, 5.20 mmol) (both lithium and cerium enolate were jelly-like, not very soluble in THF, and hard to stir) for 6 h at -78°C. TLC showed no addition reaction occurred. The reaction mixture was warmed up to room temperature and stirred overnight. TLC analysis indicated only one product was produced. After the usual work-up, the oily residue was chromatographed on silica gel, eluting with 10% EtOAc in hexane, to furnish azetidinone **50** (305 mg, 1.31 mmol, 62%) as a white solid: mp 74°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.40 (m, 4 H, ArH), 7.10 (m, 1 H, ArH), 4.00 (dd, J = 5.5, 5.5 Hz, 1 H, PhNC**H**), 3.84 (d, J = 5.5 Hz, 1 H, Me_2NC**H**), 2.50 (s, 6 H, $(CH_3)_2N$), 2.20 (m, 1 H, **CH**Me_2), 1.11 (d, J = 6.5 Hz, 3 H, CHC**H**$_3$Me), 1.00 (d, J = 6.5 Hz, 3 H, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 166.16 (s, C=O), 138.36 (s, Ph), 128.90 (d, Ph), 124.16 (d, Ph), 118.53 (d, Ph), 73.38 (d, Me_2NCH), 63.06 (d, PhNCH), 44.84 (q, $(CH_3)_2N$), 28.88 (d, **CH**Me_2), 21.04 (q, CH_3), 19.55 (q, CH_3); FT-IR ($CHCl_3$) 1745 (C=O), 1649 (C=O), 1599 (Ph), 1499 (Ph) cm^{-1}; HRMS M^+ 232.1573 (calcd for $C_{14}H_{20}N_2O$ 232.1576); Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.07. Found: C, 72.22; H, 8.76; N, 12.08.

(3*R, 4*R**)-(54) and (3*S**, 4*R**)-(55)-4-Isopropyl-3-methyl-3-phenoxy-1-phenyl-2-azetidinone.**



54



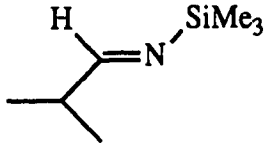
55

By following the standard procedure, imine **10** (180 mg, 1.22 mmol) was reacted with cerium enolate **53** (2.70 mmol) in THF at -78°C for 10 h. TLC showed the appearance of products but imine **10** was still present. Thus, the reaction mixture was warmed up to room temperature and stirred for 5 h. The mixture was worked up as usual to leave an oily residue which was subjected to flash column chromatography on silica gel (5% EtOAc in hexane as eluant) to afford two fractions. The minor diastereoisomer **55** (first fraction, less polar, 45 mg, 0.15 mmol, 13%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–7.50 (m, 10 H, ArH), 3.94 (d, J = 7 Hz, 1 H, PhNC**H**), 2.50 (m, 1 H, C**H**Me$_2$), 1.62 (s, 3 H, CH$_3$), 1.18 (d, J = 7 Hz, 3 H, CHC**H**$_3$Me), 1.10 (d, J = 7 Hz, 3 H, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 166.79 (s, C=O), 154.85 (s, PhO), 137.69 (s, Ph), 129.52 (d, Ph), 129.29 (d, Ph), 129.03 (d, Ph), 122.72 (d, Ph), 120.05 (d, Ph), 118.78 (d, Ph), 87.06 (s, O=CCOPh), 70.10 (d, PhNCH), 29.06 (d, CHMe$_2$), 19.67 (q, CH$_3$), 19.54 (q, CH$_3$), 19.07 (q, CH$_3$); FT-IR ($CHCl_3$) 1751 (C=O), 1598 (Ph), 1494 (Ph) cm^{-1}; HRMS M$^+$ 295.1576 (calcd for $C_{19}H_{21}NO_2$ 295.1572).

^{1}H NMR analysis of the second fraction (373 mg) indicated that it was a mixture of **54** and ester **52** (**54**:**52** = 4:1). Since **52** and **54** have the same R_f value on TLC, they were inseparable by column chromatography. Accordingly, the second fraction was subjected to bulb–to–bulb distillation (30°C, 0.1 mmHg) for one week to remove ester **52**. The major diastereoisomer **54** (300 mg, 1.02 mmol, 83%) was obtained as a white solid: mp 84–85°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–7.40 (m, 10 H, ArH), 4.14 (d, J = 7.5 Hz, 1 H, PhNC**H**), 2.20 (m, 1 H, C**H**Me$_2$), 1.70 (s, 3 H, CH_3), 1.10 (d, J = 7 Hz, 3 H, CHC**H**$_3$Me), 0.95 (d, J = 7 Hz, 3 H, CHMeC**H**$_3$); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 167.43 (s, C=O), 154.65 (s, PhO), 137.04 (s, Ph), 129.43 (d, Ph), 128.95 (d, Ph), 125.16 (d, Ph), 123.40 (d, Ph), 120.90 (d, Ph), 120.18 (d, Ph), 89.85 (s, O=C**C**OPh), 68.14 (d, PhN**C**H), 29.11 (q, CH_3), 20.21 (q, CH_3), 15.56 (q, CH_3); FT–IR ($CHCl_3$) 1756, 1750 (C=O), 1598 (Ph), 1468 (Ph) cm^{-1}; HRMS M^+ 295.1574 (calcd for $C_{19}H_{21}NO_2$ 295.1572); Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.26; H, 7.18; N, 4.52.

3,3–Diethyl–4–isopropyl–2–azetidinone (67).

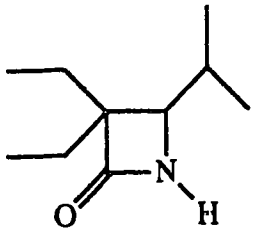
(a) Preparation of *N*–Silyl Imine **66.**



To a solution of hexamethyldisilazane (436 mg, 2.61 mmol) in anhydrous tetrahydrofuran (5 mL) at -78°C was added *n*–butyllithium in hexane (2.50 M,

1.0 mL, 2.50 mmol) dropwise. The resulting solution was stirred for 20 min at 0°C and 20 min at 25°C. It was then cooled to -35°C. A solution of isobutyraldehyde (180 mg, 2.50 mmol) in THF (2 mL) was added dropwise and the resulting solution was stirred for 30 min at -35°C under an atmosphere of argon. The resulting cold solution (-35°C) of *N*–trimethylsilyl imine **66** was used directly for the following condensation reaction with cerium enolate **13**.

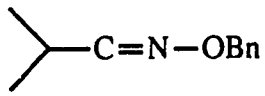
(b) Synthesis of Azetidinone **67**.



According to the standard procedure, cerium enolate **13** (5.40 mmol) was prepared by the metal exchange reaction of its lithium enolate with $CeCl_3$ suspension in THF at -78°C. The solution of *N*–silyl imine **66** in THF (see above) was added *via* cannula. The reaction mixture was stirred at -78°C for 5 h. TLC showed that β–lactam was not formed after this period of reaction. As a result, the reaction mixture was gradually warmed up to 25°C and stirred for 15 h. TLC analysis indicated the formation of a product. The reaction mixture was first diluted with Et_2O (20 mL) and then treated with 1N HCl to bring it to pH = 7. Azetidinone **67** was obtained (313 mg, 1.85 mmol, 74%) as a colorless crystal after column chromatography on silica gel (25% EtOAc in hexane as eluting solvent): mp 67°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (br s, 1 H, NH), 2.93 (d, J = 10 Hz, 1 H, NHCH), 1.80 (m, 3 H), 1.62 (m, 2 H), 1.08 (t, J = 5

Hz, CH_3CH_2), 0.94 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 0.93 (d, J = 6.5 Hz, 3 H, $MeCHCH_3$), 0.89 (d, J = 6.5 Hz, 3 H, CH_3CHMe); ^{13}C APT NMR (75 MHz, $CDCl_3$) δ 174.68 (s, C=O), 65.14 (d, NHCH), 61.01 (s, $HNCOCEt_2$), 28.34 (d, $CHMe_2$), 24.79 (t, CH_2), 21.23 (t, CH_2), 20.21 (q, CH_3), 19.58 (q, CH_3), 8.98 (q, CH_3), 8.75 (q, CH_3); FT–IR ($CHCl_3$) 3208 (NH), 1760 (C=O), 1709 (C=O), 1465 (N–H) cm^{-1}; HRMS $(M–CONH)^+$ 126.1411 (calcd for C_9H_{18} 126.1409), Low resolution MS (EI method) M^+ 169; Anal. Calcd for $C_{10}H_{19}NO$: C, 71.01; H, 11.24; N, 8.28. Found: C, 71.11; H, 11.51; N, 8.17.

_O_–Benzylhydroxyamine _N_–isobutylidene (68).



A solution of _O_–benzylhydroxyamine hydrochloride (1.10 g, 6.31 mmol) and isobutyraldehyde (0.50 g, 7.14 mmol) in pyridine (5 mL) and ethanol (10 mL) was heated at reflux for 24 h. After the reaction mixture was cooled to room temperature and the solvents were removed *in vacuo*, an oily residue was obtained. Water (10 mL) was added and the resulting mixture was extracted with $CHCl_3$ and organic extracts were washed with water and brine and then dried over $MgSO_4$. After removal of the solvent, the residue was subjected to bulb–to–bulb distillation (75°C, 0.1 mmHg) to give oxime derivative **68** in 96% yield (1.07 g, 6.05 mmol) as a mixture of *trans* and *cis* isomers (*trans*:*cis* = 70:30): ^1H NMR (300 MHz, $CDCl_3$) *trans* isomer δ 7.25–7.40 (m, 6 H, ArH and CH=N), 5.04 (s, 2 H, OCH_2), 2.50 (m, 1 H, Me_2CH), 1.08 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$); *cis* isomer δ 7.25–7.40 (m, 5 H, ArH), 6.50 (d, J = 6.4 Hz, 1 H, CH=N), 5.08 (s, 2 H, OCH_2), 3.20 (m, 1 H, Me_2CH), 1.04 (d, J = 7 Hz, 6 H,

$CH(CH_3)_2$); ^{13}C APT NMR (75 MHz, $CDCl_3$) *trans* isomer δ 155.85 (d, CH=N), 137.69 (s, Ph), 128.18 (d, Ph), 128.13 (d, Ph), 75.39 (t, OCH_2), 29.19 (d, $CHMe_2$), 19.95 (q, $2 \times CH_3$); *cis* isomer δ 157.37 (d, CH=N), 137.00 (s, Ph), 127.69 (d, Ph), 127.60 (d, Ph), 75.54 (t, OCH_2), 25.03 (d, $CHMe_2$), 19.62 (q, $2 \times CH_3$); FT–IR ($CHCl_3$) 1454, 1367 cm^{-1}; HRMS M^+ 177.1154 (calcd for $C_{11}H_{15}NO$ 177.1154); Anal. Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47; N, 7.91. Found: C, 74.70; H, 8.48; N, 7.91.

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