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# Synthetic studies on silyl cuprates, and synthesis of A58365B, an inhibitor of angiotensin-converting enzyme

by

Yuanxi Zhou 

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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Yuanxi Zhou

June 6, 1997.

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Synthetic studies on silyl cuprates and synthesis of A58365B, an inhibitor of angiotensin-converting enzyme** submitted by Yuanxi Zhou in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Dr. J. W. Lown

Dr. G. Kotovych

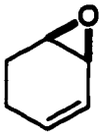
Dr. M. Pickard

Dr. G. Poulton

(External Examiner)

## Abstract

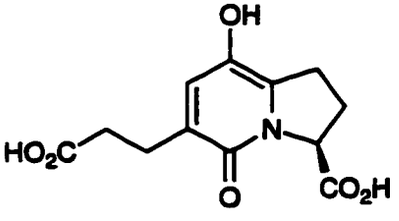
This thesis describes two projects. In the first, the response of vinyl epoxides **56** and **87** to dimethylphenylsilyl cuprates was examined. The results show that the course of the reactions is sensitive to the stoichiometry of the reagent.



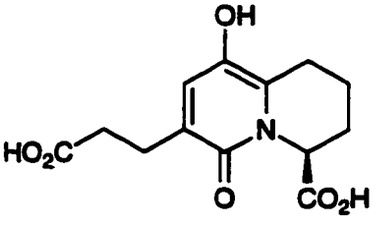
**56**

**87**

The second section of the thesis describes the total synthesis of A58365B – an inhibitor of angiotensin-converting enzyme. This section also reports the preparation of optically active material of high, but, as yet, undetermined, optical purity.

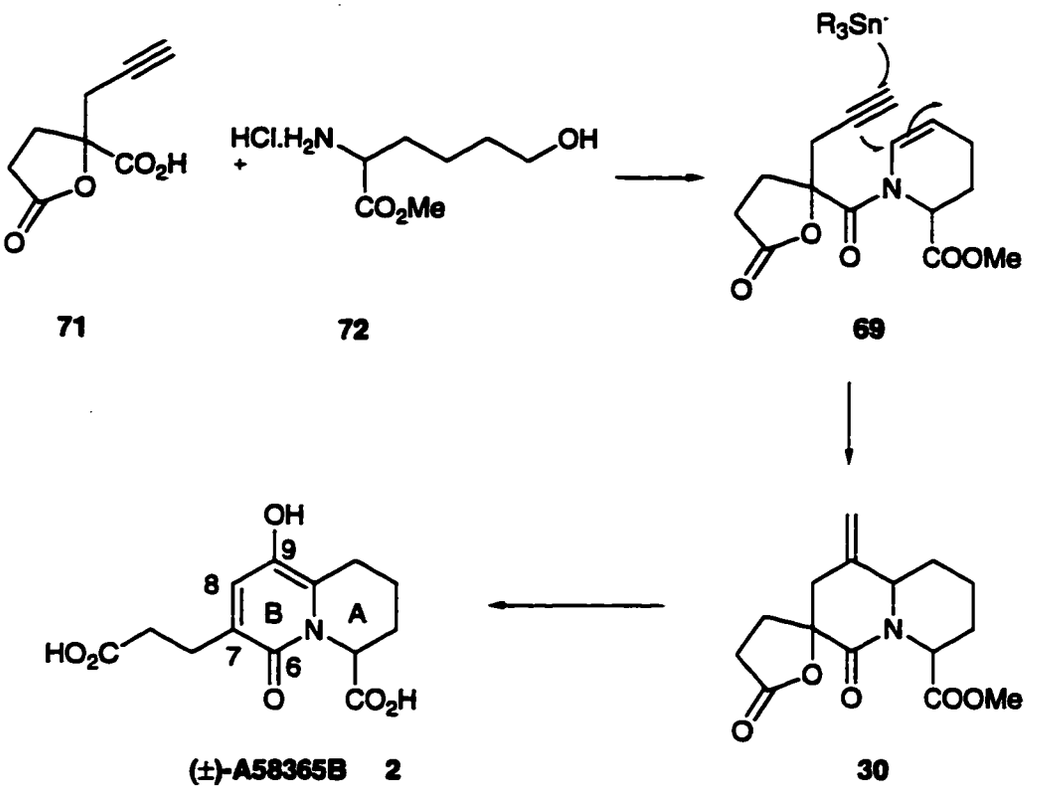



**A58365A 1**




**A58365B 2**

A58365B **2**, and the related pyridone **1**, are water-soluble metabolic products of *Streptomyces chromofuscus* NRRL 19098. Both substances inhibit angiotensin-converting enzyme.




The racemic form of A58365B was synthesized by a key process based on enyne radical cyclization. In this approach, the C(7)–C(8) unsaturation is introduced early – but in the disguised form of a spirolactone. Compound **71** represents all the carbons that make up the C(6)–C(9) segment of the natural product, including the propionic side chain. The ring B portion of **2** was constructed from ε-hydroxy-norleucine methyl ester (**72**). Compounds **71** and **72** were coupled, and subjected to further elaboration into **69**. Enyne radical cyclization, followed by functional group manipulation, led to racemic A58365B. Optically active material was also obtained following an identical route, but using (L)-ε-hydroxynorleucine as the starting material.

**ACKNOWLEDGMENTS**

I would like to express my gratitude to my supervisor, dear Professor D.L.J. Clive, for his advice, encouragement and support during my whole Ph.D. program, and for his assistance in the preparation of this thesis.

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I also extend my appreciation to my colleagues in my research group for those discussions of research and life.

Most importantly, I want to thank my husband, J. Sun, and my daughter, H. Sun, for their constant support and understanding.

## TABLE OF CONTENTS

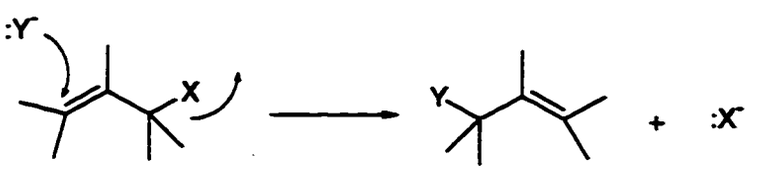
## List of Abbreviations

| | |
|---|---|
| AIBN | 2,2'-azobisisobutyronitrile |
| BOC | *tert*-butoxycarbonyl |
| DCC | *N,N'*-dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DMAP | 4-(dimethylamino)pyridine |
| DME | 1,2-dimethoxyethane |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| EDCI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide |
| HOBT | 1-hydroxybenzotriazole hydrate |
| LDA | lithium diisopropylamide |
| LTMP | lithium 2,2,6,6-tetramethylpiperidide |
| *m*-CPBA | *m*-chloroperoxybenzoic acid |
| NMM | *N*-methylmorpholine |
| PCC | pyridinium chlorochromate |
| TBAF | tetrabutylammonium fluoride |
| Tf | trifluoromethanesulfonyl (triflyl) |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |

# (I) Introduction

## $S_N2'$ Addition of Organocopper Reagents to Vinyloxiranes

Allylic systems, in addition to undergoing ordinary substitutions without rearrangement, can also react with rearrangement of the double bond, as indicated in **Scheme 1**. This transformation is called an $S_N2'$ reaction.




1 2

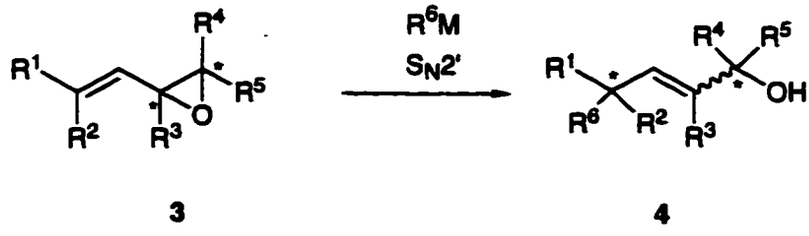
**Scheme 1**


Syn Anti

**Scheme 2**

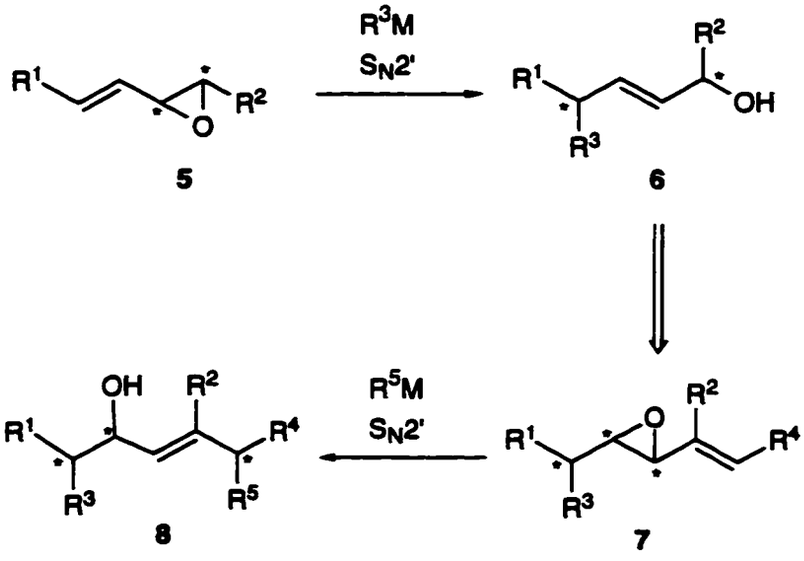
The $S_N2'$ mechanism, as shown above, involves the movement of three pairs of electrons, but there is no evidence that requires that bond making and breaking be concerted. The stereochemistry of the $S_N2'$ reaction has been investigated and it is found that both *syn*[1,2] and *anti*[3,4]

substitution can take place, depending on the nature of X and Y, though the *syn* pathway predominates in most cases (**Scheme 2**).




3 4

**Scheme 3**



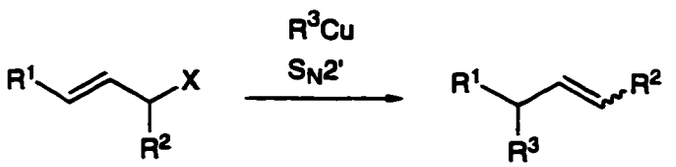

5 6 8 7

**scheme 4**

Vinyloxiranes constitute a special subset of allylic electrophiles. The $S_N2'$ addition of organocopper reagents to vinyloxiranes represents a potentially versatile route to a variety of allylic alcohols which are very important synthetic intermediates (**Scheme 3**). Allylic alcohols in turn, are readily and stereoselectively transformed into

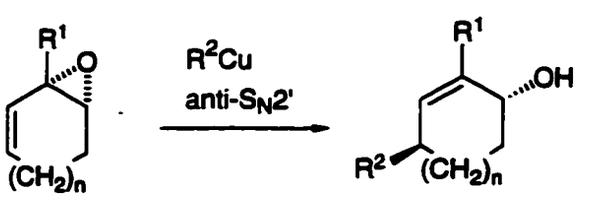
vinyloxiranes,[5] thus allowing for iterative stereoselective chain elongation (**Scheme 4**). First observed in 1970 by Anderson and Johnson[6,7] with butadiene epoxide and isoprene monoepoxide, this reaction was subsequently explored by others, using cyclic vinyloxiranes with endocyclic or exocyclic double bonds.

*Acyclic vinyloxiranes*




**9** **10**

**Scheme 5**

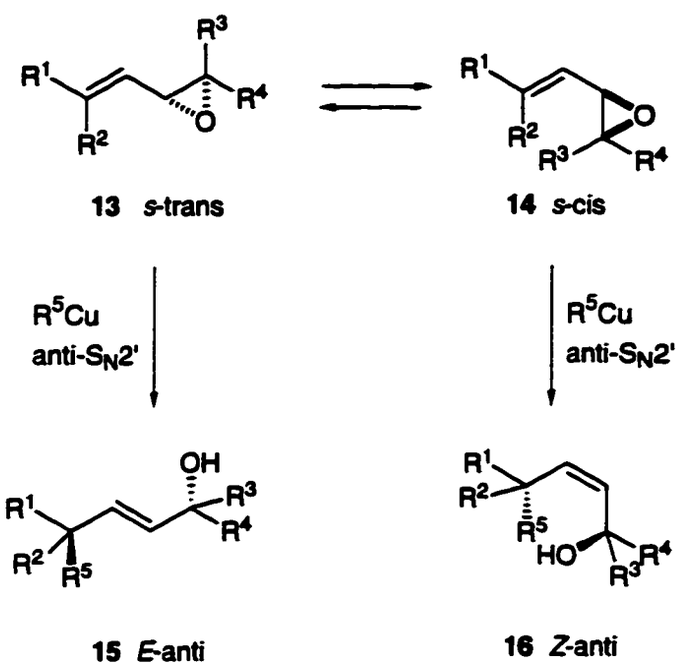



**11** **12**

**scheme 6**

In general, $S_N2'$ displacements on allylic alcohol derivatives (**Scheme 5**) and cyclic vinyloxiranes (**Scheme 6**) by organocopper reagents have been found to proceed with inversion (*anti* pathway).[8,9,10] Acyclic vinyloxiranes would be expected to follow an analogous course. However, unlike

their cyclic counterparts, the acyclic system can react via either *s*-cis or *s*-trans conformers and thus yield mixtures of *E* and *Z* $S_N2'$ products[8] (**Scheme 7**).

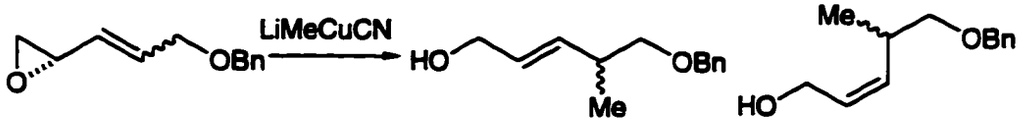



**Scheme 7**

Additions of various methyl copper reagents to the optically pure acyclic vinyloxirane were performed by Marshall and Trometer[11] in order to evaluate *E*/*Z* and *syn*/*anti* preferences.

The unsubstituted vinyloxirane **17** (*E*) and **18** (*Z*) gave a mixture of $S_N2$ and $S_N2'$ products with the four reagents examined, $Me_2CuLi$, MeCuCNLi, $Me_2CuMgBr$ and $MeLiCuI.BF_3$. A high $S_N2':S_N2$ product ratio was obtained with MeCuCNLi, and *Z*-vinyloxirane **18** gave a better $S_N2':S_N2$ ratio than the *E*

isomer **17** (**Scheme 8**). The higher preference for the *E*-$S_N2'$ product indicated the *s-trans* transition state conformations of **17** (*E*) and **18** (*Z*) were stereoelectronically favored (**Scheme 8**).




**17** (*E*)
**18** (*Z*)

**19** (*E*-$S_N2'$)

**20** (*Z*-$S_N2'$)


**21** (*E*-$S_N2$)
**22** (*Z*-$S_N2$)

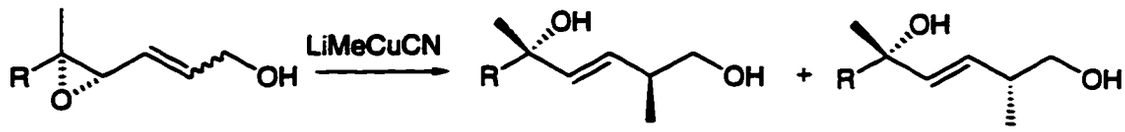
| | | $S_N2'$ | | $S_N2$ | | |
|---|---|---|---|---|---|---|
| substrate | yield | **19** (*E*) | **20** (*Z*) | **21** (*E*) | **22** (*Z*) | $S_N2'/S_N2$ |
| **17** (*E*) | 87% | 70 | 7 | 12 | 0 | 6.4 |
| **18** (*Z*) | 83% | 81 | 0 | 3 | 6 | 9 |

**Scheme 8**

They also examined other substrates in which stereochemical preferences might be more readily discerned.[11] Compounds **23** (*E*) and **24** (*Z*) seemed well suited on several counts. In the first place, the oxirane methyl substituent should increase the energy of *s*-cis conformers thereby diminishing the amounts of *Z*-$S_N2'$ product. Secondly, the presence of additional substituents on the oxirane ring would be expected to disfavor $S_N2$ product formation. Finally, *anti*

and *syn* $S_N2'$ displacements would lead to diastereoisomers, not enantiomers, whose analysis would not depend upon assumptions regarding optical purity.

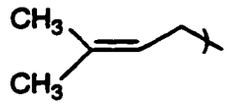
Addition of MeCuCNLi to the *E*-vinyloxirane **23** afforded an 88:12 mixture of the two *E*-$S_N2'$ products **25** (*anti*-addition) and **26** (*syn*-addition). The *Z*-vinyloxirane **24**, on the other hand, yield a 1:99 mixture of isomer **25** (*syn*-addition) and **26** (*anti*-addition) under the same conditions. In neither case was an $S_N2$ product detected (**Scheme 9**).




**23** (*E*)
**24** (*Z*)

**25** (*anti-E*)

**26** (*syn-E*)

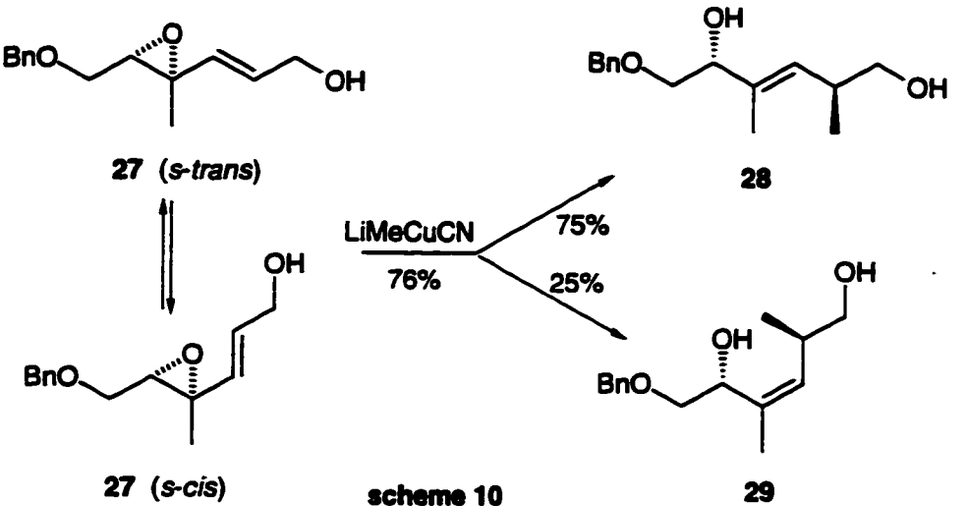
R = 


| substrate | yield | $S_N2'$ products: **25** (*anti-E*) | $S_N2'$ products: **26** (*syn-E*) | mode of addition: *anti*/*syn* |
|---|---|---|---|---|
| **23** (E) | 84% | 88 | 12 | 7.3 |
| **24** (Z) | 88% | 1 | 99 | 99 |

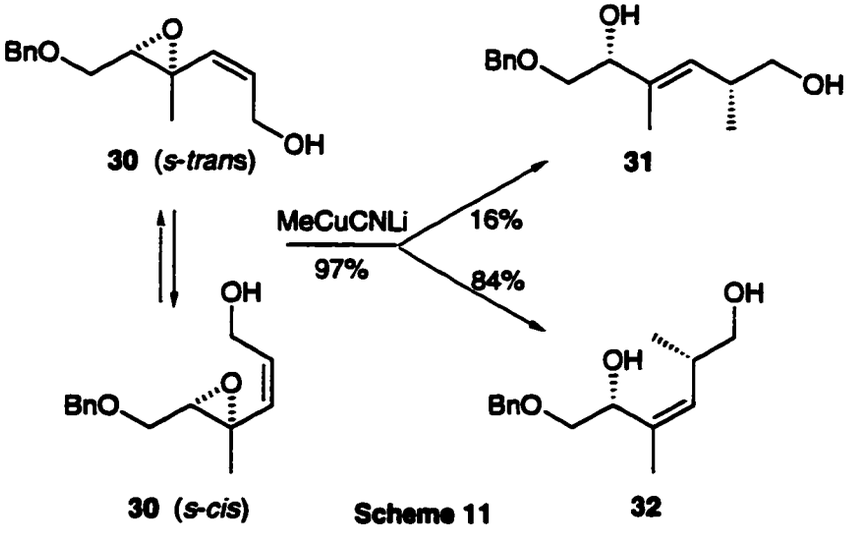
**Scheme 9**

The effect of substituents and geometry on stereoselectivity was further explored with the nonracemic vinyloxiranes **27**, **30**, **33** and **34**.[12] *Anti*-addition of MeCuCNLi to the *E*-vinyloxirane **27** afforded only two products, the *anti-E* **28** and *anti-Z* **29** as a 75:25 mixture (**Scheme 10**).

*Anti*-addition *Z*-vinyloxirane **30** also yielded two products, the *syn-E* **31** and *syn-Z* **32** in an isomer ratio of 16:84 (**Scheme 11**).



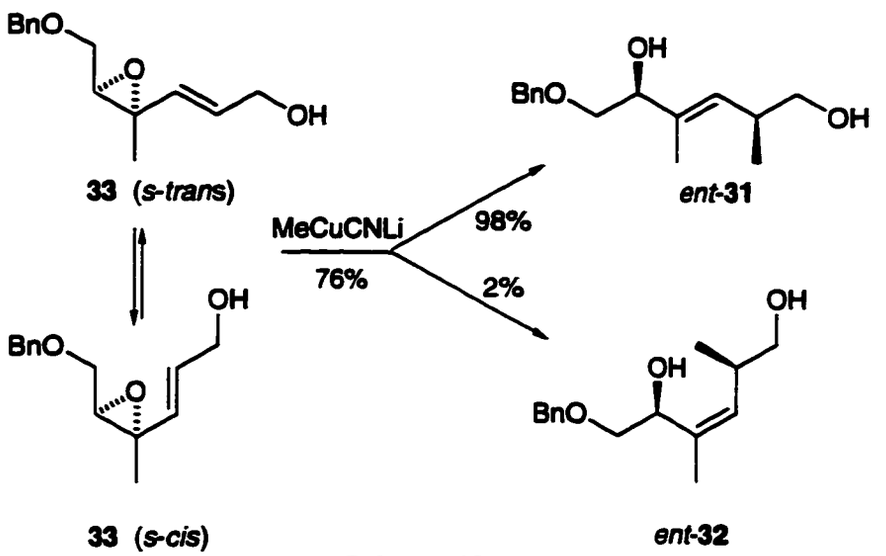

scheme 10



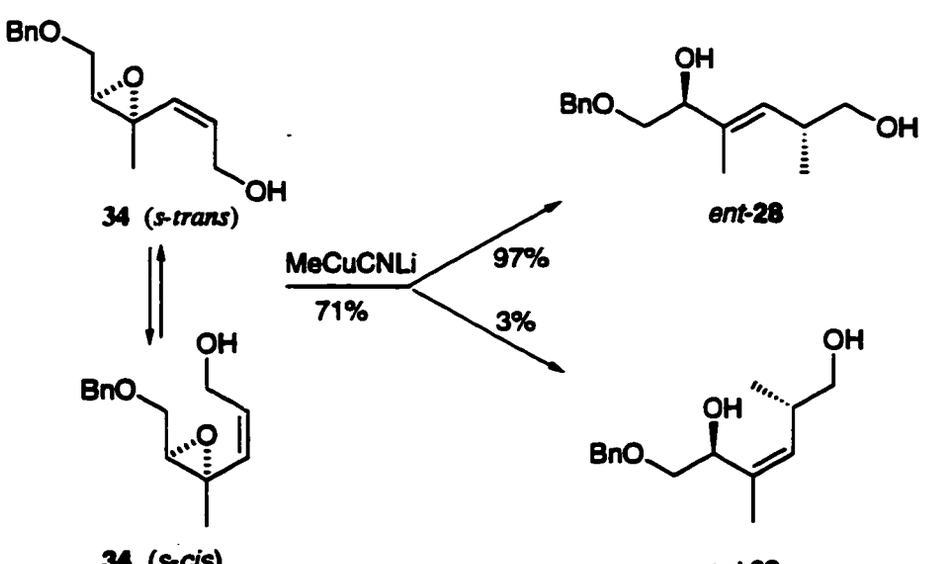

Scheme 11

Another two vinyloxiranes, **33** and **34**, were examined next. *Anti*-addition of MeCuCNLi to the *E* isomer **33** yielded *syn-E ent*-**31** and *syn-Z ent*-**32** in a 49:1 ratio (**Scheme 12**).

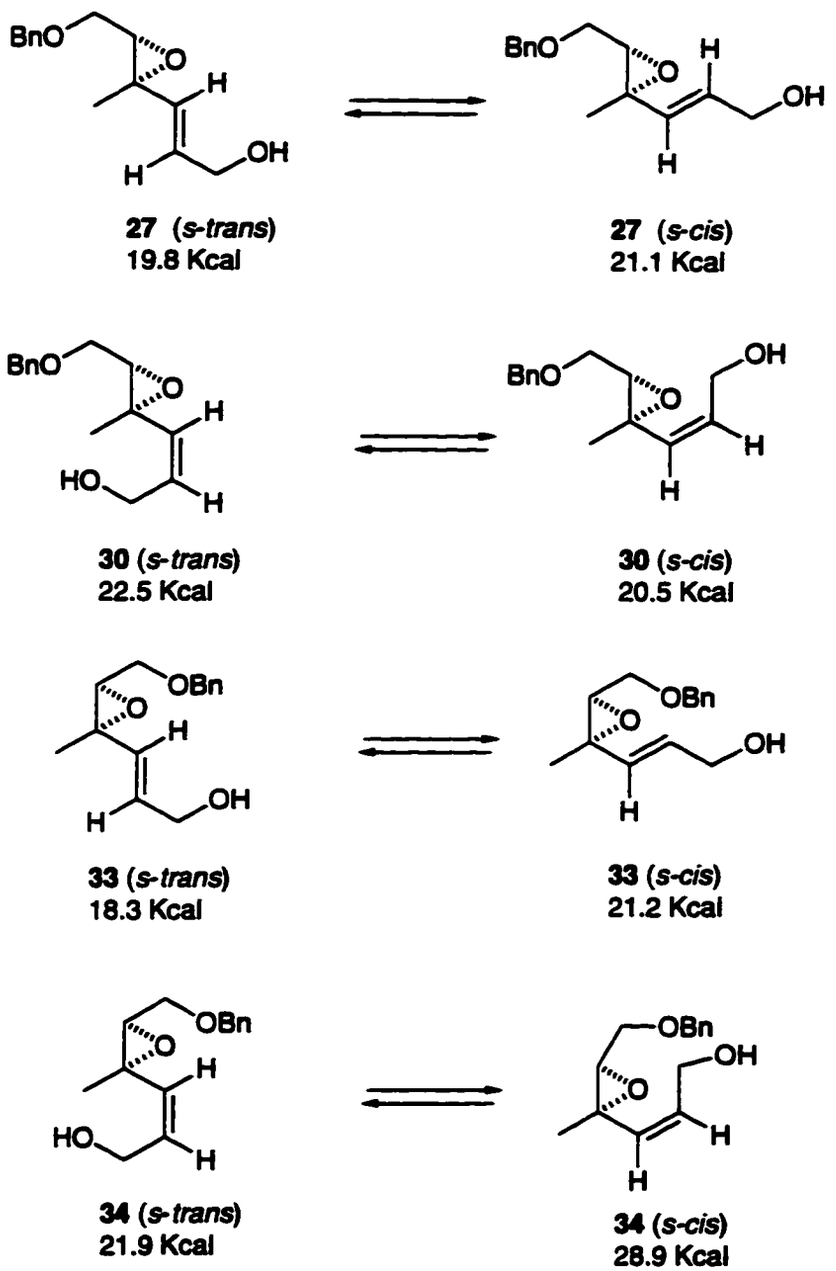
*Anti*-addition *Z*-vinyloxirane **34** gave mainly *anti-E ent*-**28** (**Scheme 13**).




**Scheme 12**




**Scheme 13**




**Scheme 14**

The experimental facts reveals two interesting trends: (1) Acyclic vinyloxiranes **27**, **30**, **33** and **34** show a high *anti* preference in $S_N2'$ addition of methylcuprate. (2) The *E/Z* ratio is significantly influenced by the geometry of the vinyloxirane substrate.

The ratios reflect transition state energies related to the *s-trans* and *s-cis* conformers of the respective vinyloxiranes. Molecular modeling calculations on the *s-cis* and *s-trans* conformers were carried out[12] and the results are shown in **Scheme 14**.

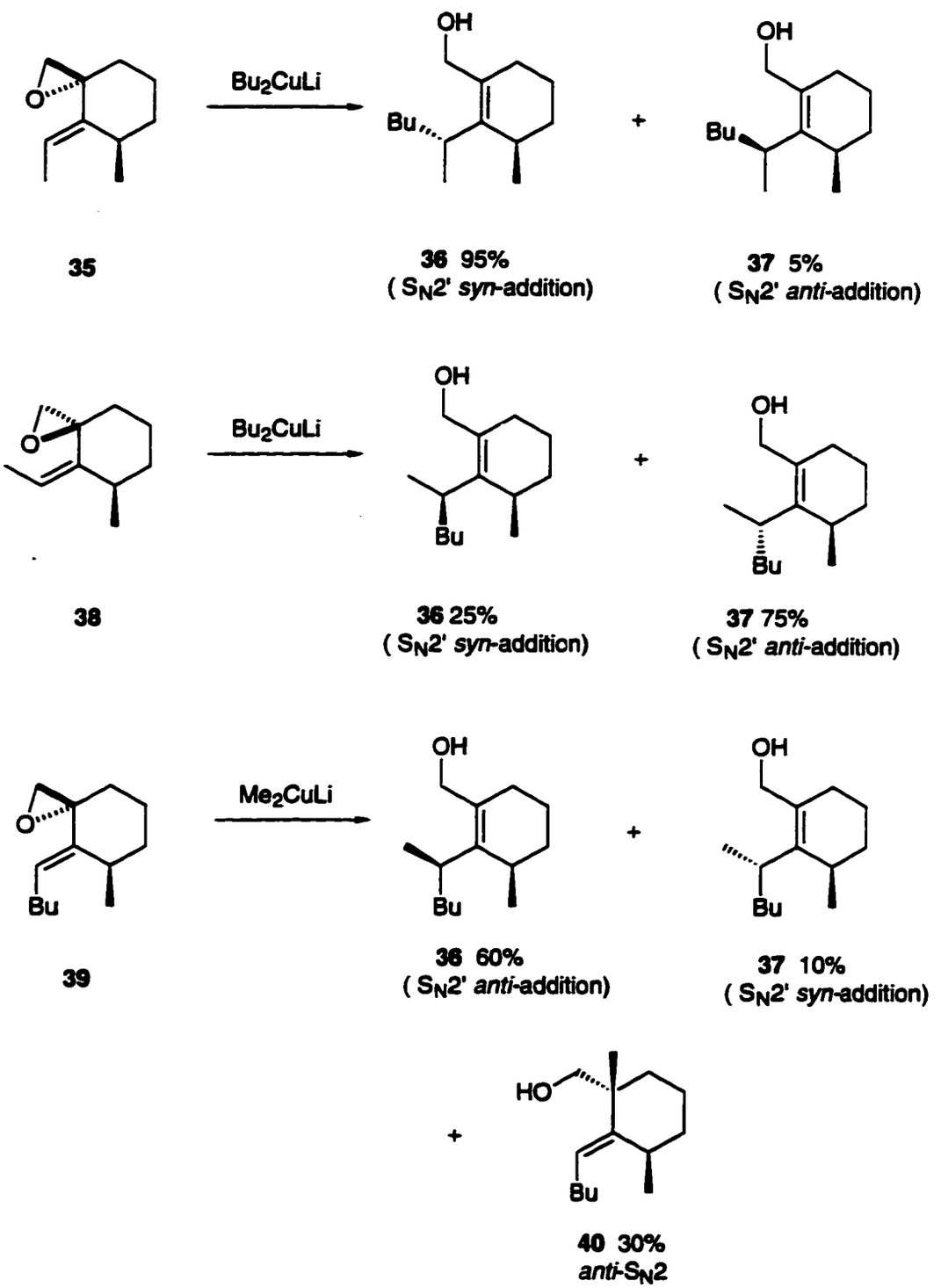
Two significant conclusions can be drawn from **Scheme 14**. (1) Compound **27** shows the smallest energy difference between the *s-trans* and *s-cis* conformers. Therefore $S_N2'$ addition to **27** has the lowest *E/Z* selectivity. (2) Compounds **27**, **33** and **34** were calculated to favor the *s-trans*, whereas **30** prefers the *s-cis* conformation. $S_N2'$ addition to **30** therefore gives more of the *Z* product than similar addition to **27**, **33** and **34**.

*Alkylidene Exocyclic Epoxides*

Ziegler and Cady were the first to employ exocyclic epoxides for the introduction of stereocenters in a side chain by $S_N2'$ alkylation.[13]

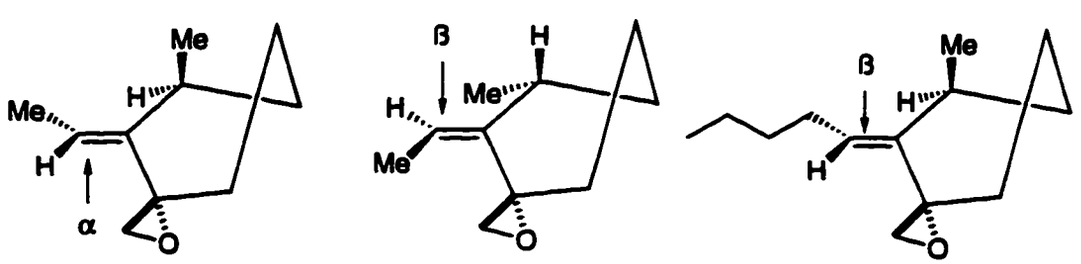
Treatment of oxirane **35** with $Bu_2CuLi$ at -25 °C gave rise to **36** ($S_N2'$ *syn*-addition) and **37** ($S_N2'$ *anti*-addition) in a ratio of 95:5. Exposure of *Z*-oxirane **38** to $Bu_2CuLi$ yielded both **36** ($S_N2'$ *syn*-addition) and **37** ($S_N2'$ *anti*-addition) in a ratio of 25:75. Treatment of **39** with $Me_2CuLi$ gave the products derived from both modes of allylic addition ($S_N2'$ and $S_N2$) to the vinyloxirane. Most (70%) of the reaction mixture consisted of isomers **36** ($S_N2'$ *anti*-addition) and **37**

($S_N2'$ *syn*-addition) in an 85:15 ratio, and the remaining 30% consisted of the single compound **40** (*anti*-$S_N2$) (**Scheme 15**).




**Scheme 15**

It can be argued that **35** and **38** have different conformational preferences, and that vinyloxirane **35** would exist in a twist conformation in transition state **40** where the axial C-O bond maintains overlap, and A-strain could be avoided. The preferred mode of $Bu_2CuLi$ attack would occur from the α face of the double bond, *syn* to the oxygen. Oxirane **38**, on the other hand, would preferentially react through conformation **41**. Although A-strain must develop to some extent between the oxirane methane and ethylidene groups, this difficulty must be accommodated in order to attain overlap. Therefore, the approach of the cuprate is favored on the β face in an *anti*-mode and distal to the ring methyl group. The results obtained from **39** might be attributed to the transition state **42** which leads to the major regioisomer **36** via an *anti* approach to the vinyl oxirane system and from the β face, in spite of the axial methyl group (**Scheme 16**).

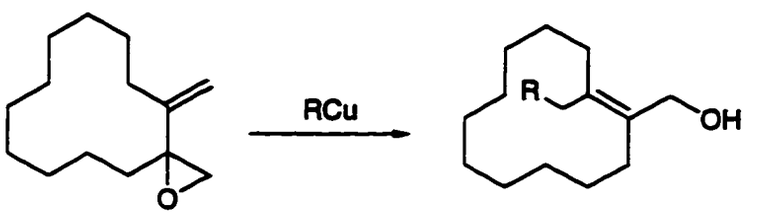



**40** **41** **42**

**Scheme 16**

Cuprate addition to the methylenecyclododecylidene

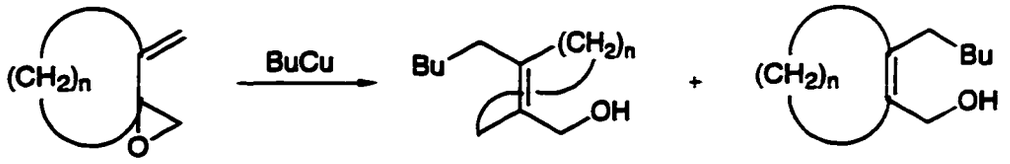
epoxide **43** was studied by Marshall and Flynn,[14a] and it was found that epoxide **43** reacted cleanly with organocuprate via $S_N2'$ substitution to give the *trans* $S_N2'$ product **44** (**Scheme 17**).




**43** **44**

**scheme 17**

In several cases, in which the nature of R in RCu was varied, the $S_N2'$ *trans* product predominated over the *cis* by 95:5. Presumably, the predominance of *trans* products reflects certain conformational preferences of the cyclododecylidene epoxide **43** in the transition state.[15] This type of stereocontrol is of special interest in connection with macrocyclic natural product synthesis. In order to clarify the stereochemical results, the addition of butyl cuprates to the medium and large ring cycloalkylidene epoxides **46a-46f** was also studied,[16] and the results are summarized in **Scheme 18**. In all cases, the *trans* $S_N2'$ product **47** was formed as the major product. The addition thus appears to be relatively insensitive to the nature of the cuprate species.



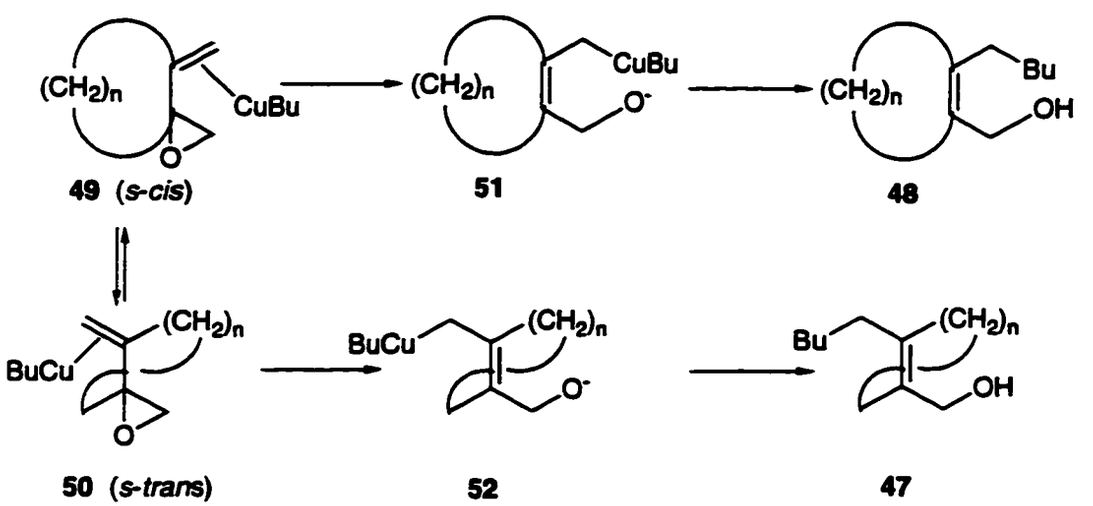

**46a-46f** **47a-47f** **48a-48f**

| n | epoxide | cuprates | yield | 47 | 48 |
|---|---|---|---|---|---|
| 8 | **46a** | BuMgBr/CuI | 87% | 85 | 15 |
| 10 | **46b** | BuMgBr/CuI | 76% | 98 | 2 |
| 11 | **46c** | BuMgBr/CuI | 52% | 95 | 5 |
| 12 | **46d** | BuMgBr/CuI | 82% | 90 | 10 |
| 13 | **46e** | BuMgBr/CuI | 71% | 93 | 7 |
| 14 | **46f** | BuMgBr/CuI | 87% | 94 | 6 |
| 10 | **46b** | LiBuCuCN | 61% | 95 | 5 |
| 10 | **46b** | $LiBu_2Cu$ | 77% | 98 | 2 |

**Scheme 18**

It is known that the addition of organocuprates to an allylic system involves initial π-complexation of the cuprate on the less hindered face of the double bond followed by $S_N2'$ oxidative addition, leading to a σ-copper complex, which undergoes reductive elimination to produce the product with retention of stereochemistry.[17] In the present case, $S_N2'$ oxidative addition of the initial π-complex can occur via transition states **49** (*s-cis*) or **50** (*s-trans*) to give the *cis* or *trans* α-allyl intermediates **51** or **52**, respectively, and this pathway would lead to products **48** and **47**. The

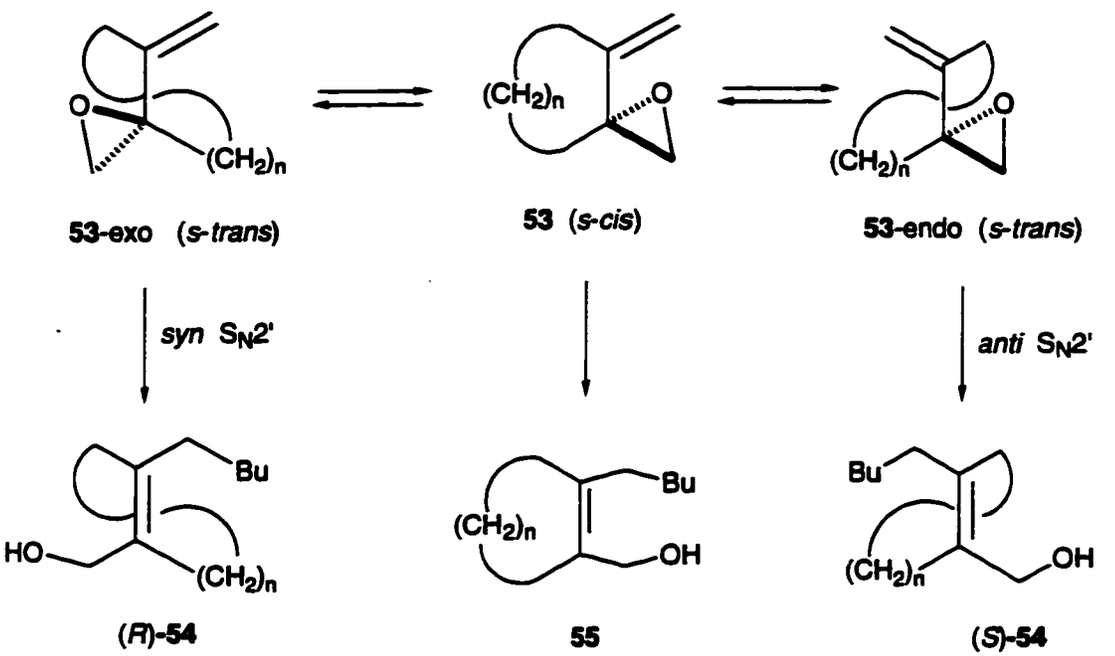
calculations using Still's RINGMAKER/BAKMO[16] program indicate that the *s-trans* conformation is favored over the *s-cis* conformation by 2-3 kcal/mole.[16] Accordingly, the preference for *trans* products in $S_N2'$ additions of organocuprate to epoxides **46a-46f** could come from a favored transition state involving the π-complex **50** of the lower energy *s-trans* conformation (**Scheme 19**).




**Scheme 19**

*Syn-anti* preferences of these additions were determined through studies on the (*R*)-cycloalkylidene epoxides **53a** and **53b** (see Scheme 21).[18] These cycloalkenes are chiral and, depending upon the *syn* or *anti* preference of the addition, an *R* or *S* enantiomer would be produced. In these cases, *syn* $S_N2'$ addition to the (*R*)-epoxides **53** would afford the allylic alcohols (*R*)-**54** (see **Scheme 20**), whereas *anti* addition would give (*S*)-**54**. The foregoing analysis is based on the assumption that the bridging methylene chain effectively

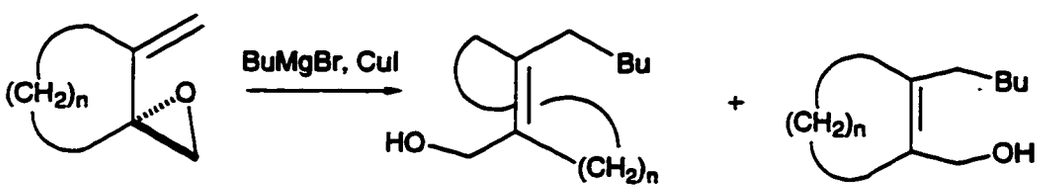
blocks attack on the double bond from within the ring cavity. Thus, the *exo* conformer must undergo *syn* $S_N2'$ addition and the *endo* conformer can give only the *anti* $S_N2'$ adduct. These two reaction pathways yield enantiomeric products (*R*)-**54** and (*S*)-**54** (**Scheme 20**). It should be noted that the two *s-trans* conformers **53**-*exo* and **53**-*endo* in **Scheme 20** are calculated to be nearly equal in energy and lower than the *s-cis*[18]




**Scheme 20**

In fact, treatment of the 12-membered cycloalkylidene epoxide **53a** with *n*-butylmagnesium bromide-CuI afforded a 99:1 mixture of *trans* and *cis* allylic alcohols **54a** and **55a**; compound **54a** was determined to have the *R* configuration. Therefore, the foregoing addition must proceed via the *syn* $S_N2'$ pathway from the *s-trans* exo conformer of **53a**, and the allylic alcohol (*R*)-**54a** is formed with high stereoselectivity

(**Scheme 21**). The 14-membered cycloalkylidene epoxide **53b** behaved analogously. Treatment with the butylcopper reagent gave a 94:6 mixture of allylic alcohols **54b** and **55b**. The sign of rotation of **54b** is suggestive of the *R* configuration, as would be expected from *syn* $S_N2'$ addition to the *s-trans* exo conformer of epoxide **53b** (**Scheme 21**).




**53a**
**53b**

**(*R*)-54a**
**(*R*)-54b**

**55a**
**55b**

| epoxides | n | yield | ee% | 54:55 |
|---|---|---|---|---|
| **53a** | 10 | 68 | 92 (*R*) | 99:1 |
| **53b** | 12 | 59 | 82 (*R*) | 94:6 |

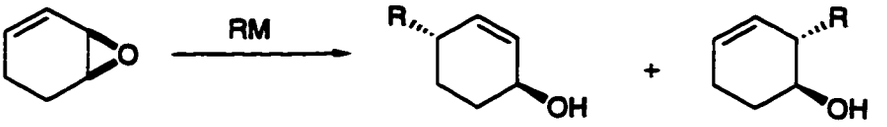
**Scheme 21**

The preferred *syn* $S_N2'$ addition to epoxides **53** is thought to reflect differences in the ability of the epoxide oxygen to coordinate with the metal cation in the exo and endo *s-trans* conformers (**Scheme 20**). This coordination would be hampered by the bridging methylene chain in the endo conformer, thereby decreasing its reactivity toward $S_N2'$ attack. The exo oxygen on the other hand, is readily accessible to the metal ion.

*Cyclic 1,3-Diene Monoepoxides*

Initial stereochemical studies on the $S_N2'$ addition of cuprates to cyclic vinyloxiranes employed the monoepoxide of 1,3-cyclohexadiene (**56**) as the substrate.[19a] Use of a rigid structure, such as **56**, is potentially more informative from a mechanistic standpoint.

The results of the reaction of **56** with Gilman organocuprate compounds are summarized in **Scheme 22**. These results show that the conjugate and direct addition reactions are competitive processes, and a strong preference for *anti* addition is observed in both $S_N2$ and $S_N2'$ reactions.



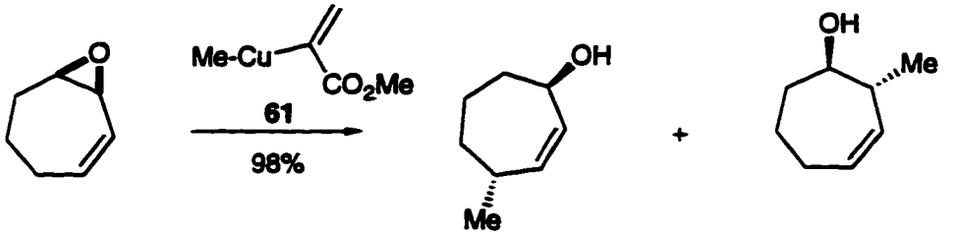

**56** **57** **58**

| RM | Yield | 57 | 58 |
|---|---|---|---|
| $Me_2CuLi$ | 91% | 54 | 46 |
| $Ph_2CuLi$ | 87% | 31 | 69 |
| $(t\text{-}Bu)_2CuLi$ | 72% | 65 | 35 |

**Scheme 22**

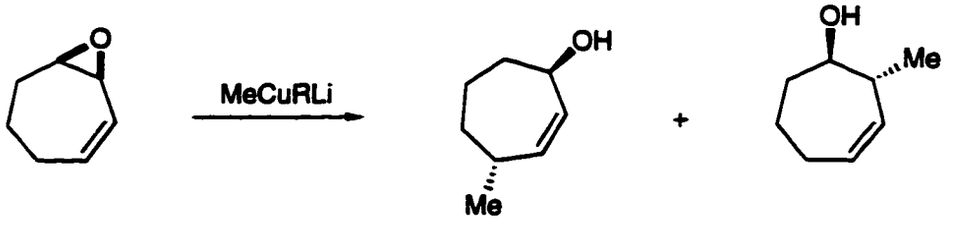
*Anti* addition has been also observed in the case of 1,3-cycloheptadiene monoepoxide (**59**),[19b] a high yield of methyl transfer products being obtained, and the ratio of **61** (*anti* $S_N2'$ product) and **62** (*anti* $S_N2$ product) was found to be 97:3

(**Scheme 23**).

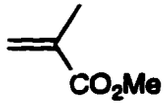



**59** **61** (97%) **62** (3%)

**Scheme 23**




**59** **61** **62**

| R | yield | 61 | 62 |
|---|---|---|---|
| Me | 91% | 70 | 30 |
| *n*-Bu—≡— | 95% | 85 | 15 |
| CN | 95% | 90 | 10 |
|  | 98% | 97 | 3 |



**Scheme 24**

From this result, it was felt that the strongly electron-withdrawing acrylate ligand might be responsible for the highly specific *anti* 1,4-addition. In order to confirm this point, several mixed cuprates, containing a methyl group

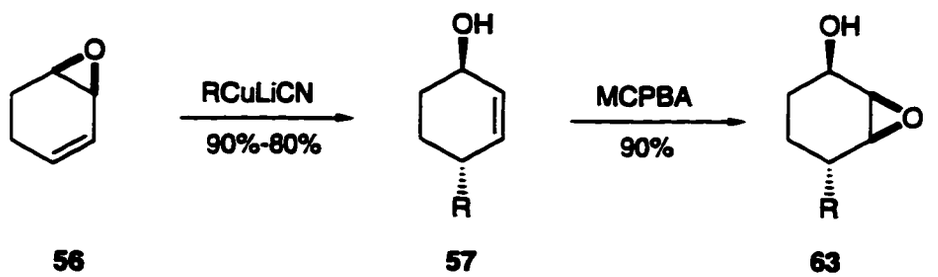
and an electron-withdrawing ligand, were examined, and the results are listed in **Scheme 24**. In fact, there is a progression of increasing regiospecificity from the homocuprate (R = Me) to the acrylate mixed cuprate. From a practical standpoint, the cyano methylcuprate is the most convenient to prepare, but the acrylate ligand exerts the greatest influence on the regiospecificity, followed closely by the cyano group.

A significant extension of this methodology followed the discovery that enol derivatives of cyclic α,β-epoxyketones underwent highly stereoselective *anti* $S_N2'$ addition by cyano cuprate reagents.

Alam and Martin reported the facile introduction of three stereogenic centers and the overall functionalization of five carbon atoms of a six-carbon unit.[20] This methodology is based on the stereospecific functionalization of the readily available 1,3-cyclohexadiene monoepoxide (**56**) and the subsequent oxidative cleavage of the final cyclohexene derivative. This approach relies on repetitive stereocontrolled 1,4-openings of an epoxide, as described below.

Mixed cyanocuprates add stereospecifically (100% *anti* addition) and highly stereoselectively (the isomer ratio of 1,4-addition > 95%) to epoxide **56** to give the allylic alcohol

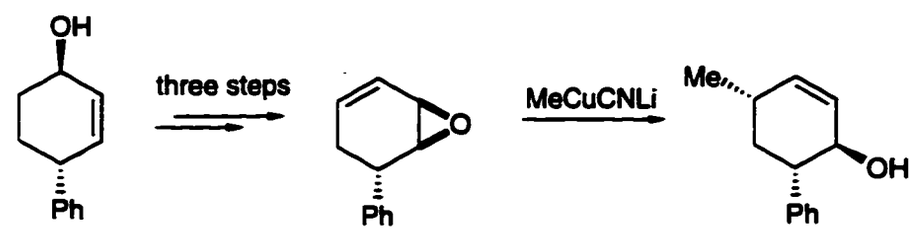
**57**, which can be transformed into the new epoxide **63** stereospecifically by MCPBA (**Scheme 25**).




**56** **57** **63**

a, R = Me, b, R = Ph

**Scheme 25**

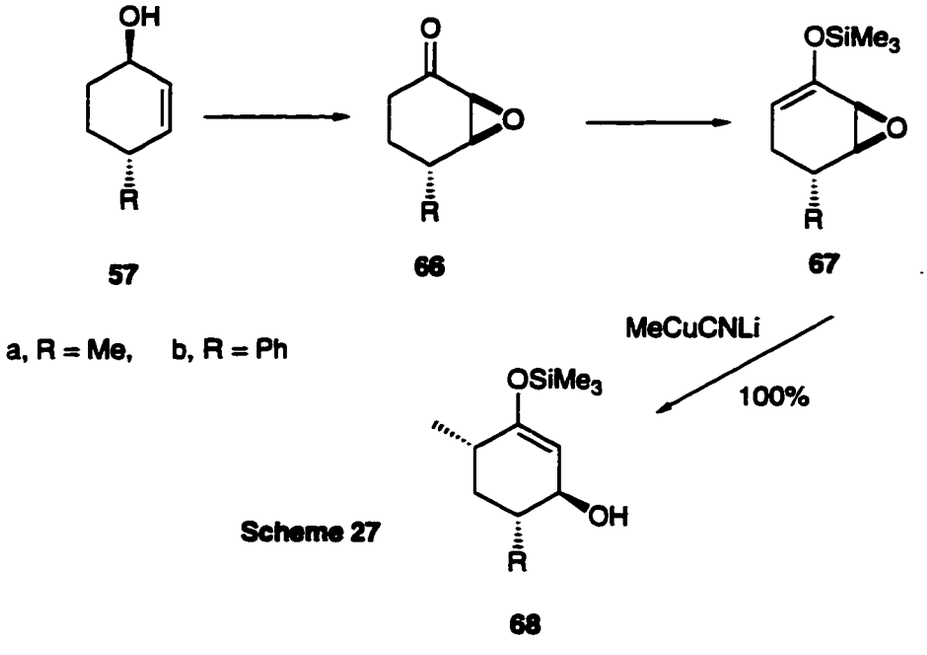



**57b** **64** **65**

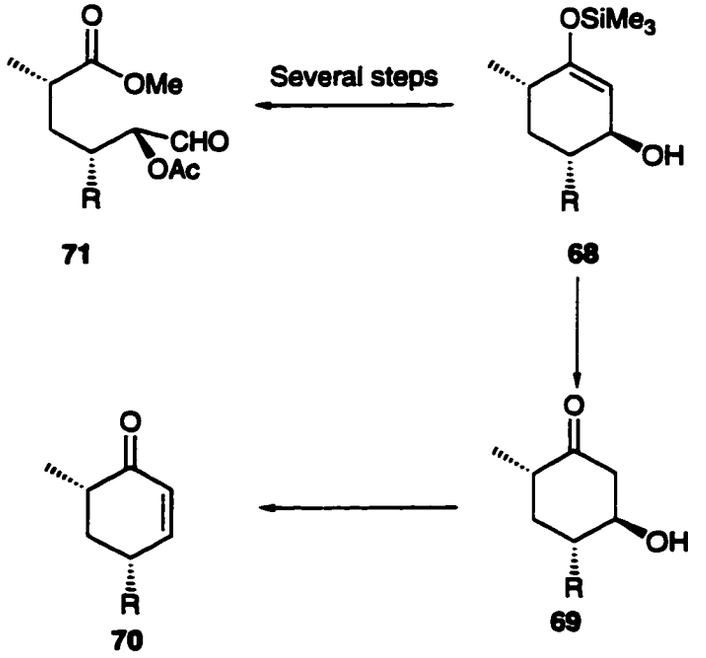
**Scheme 26**

In order to repeat the 1,4-addition to an epoxy alkene system, **57b** was converted into epoxide **64** in a three-step procedure. When **64** was treated with lithium methyl cyanocuprate, cyclohexene **65** was produced stereospecifically (**Scheme 26**). An alternative strategy for the introduction of a second carbon substituent via an epoxy alkene is shown in **Scheme 27**. In this approach, **57** was oxidized first, and then the resulting product was silylated to silyl enol ether **67**, which underwent the 1,4-addition reaction with MeCuCNLi

to produce **68** in essentially quantitative yield. As shown in **Scheme 28**, compound **68** can be either desilylated to the aldol **69** or oxidized to **71** by ozonolysis.




Scheme 27

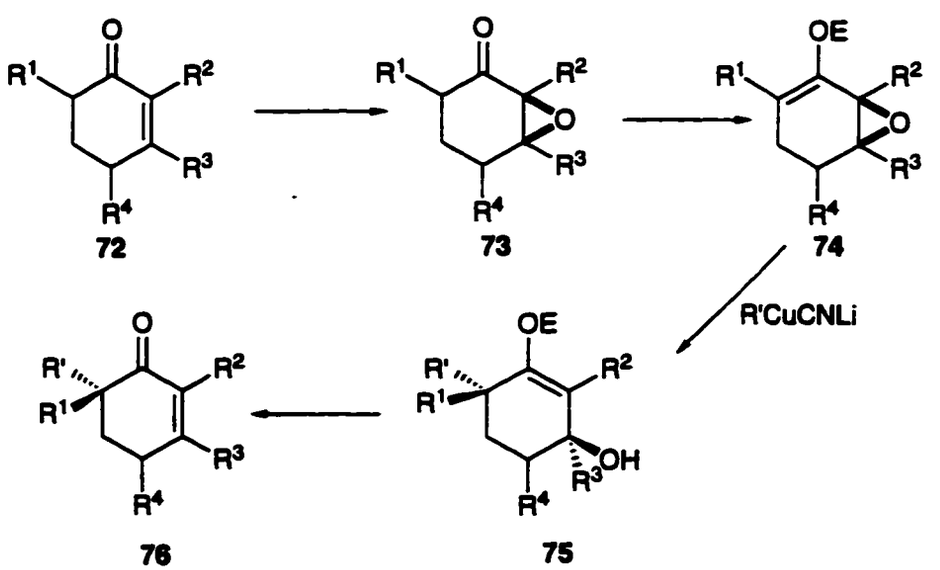



Scheme 28

The α-substitution of ketones and other carbonyl

compounds is most directly accomplished by alkylation of enolates with an electrophile. This general approach fails with highly substituted and non aliphatic electrophiles. Also, α'-alkylation of α,β-unsaturated ketones can be complicated by the existence of multiple sites for deprotonation.

Marino, Jaén and Floyd reported a new strategy for α'-substitution of α,β-epoxyketones.[19] This approach is based on the stereospecific 1,4-addition of organocuprates to enol silyl ethers of α,β-epoxyketones or the enol esters, and represents an umpolung of reactivity for the carbon atom α to the ketone functionality (**Scheme 29**).




**Scheme 29**


77 78

| $R^4$ | $R^3$ | $R^2$ | $R^1$ | R' | 78 |
|---|---|---|---|---|---|
| H | H | H | H | *t*-Bu | 100% |
| H | Me | H | H | Me | 95% |
| H | Me | H | H | *n*-Bu | 80% |
| α-Me | Me | H | H | Me | 80% |
| α-Me | Me | H | H | *n*-Bu | 94% |
| β-Me | Me | H | H | *n*-Bu | 70% |
| H | H | Me | H | *n*-Bu | 100% |
| H | H | Me | H | *t*-Bu | 100% |
| H | H | H | H | Ph | 72% |
| H | Me | H | H | $CH_2$=CH | 80% |

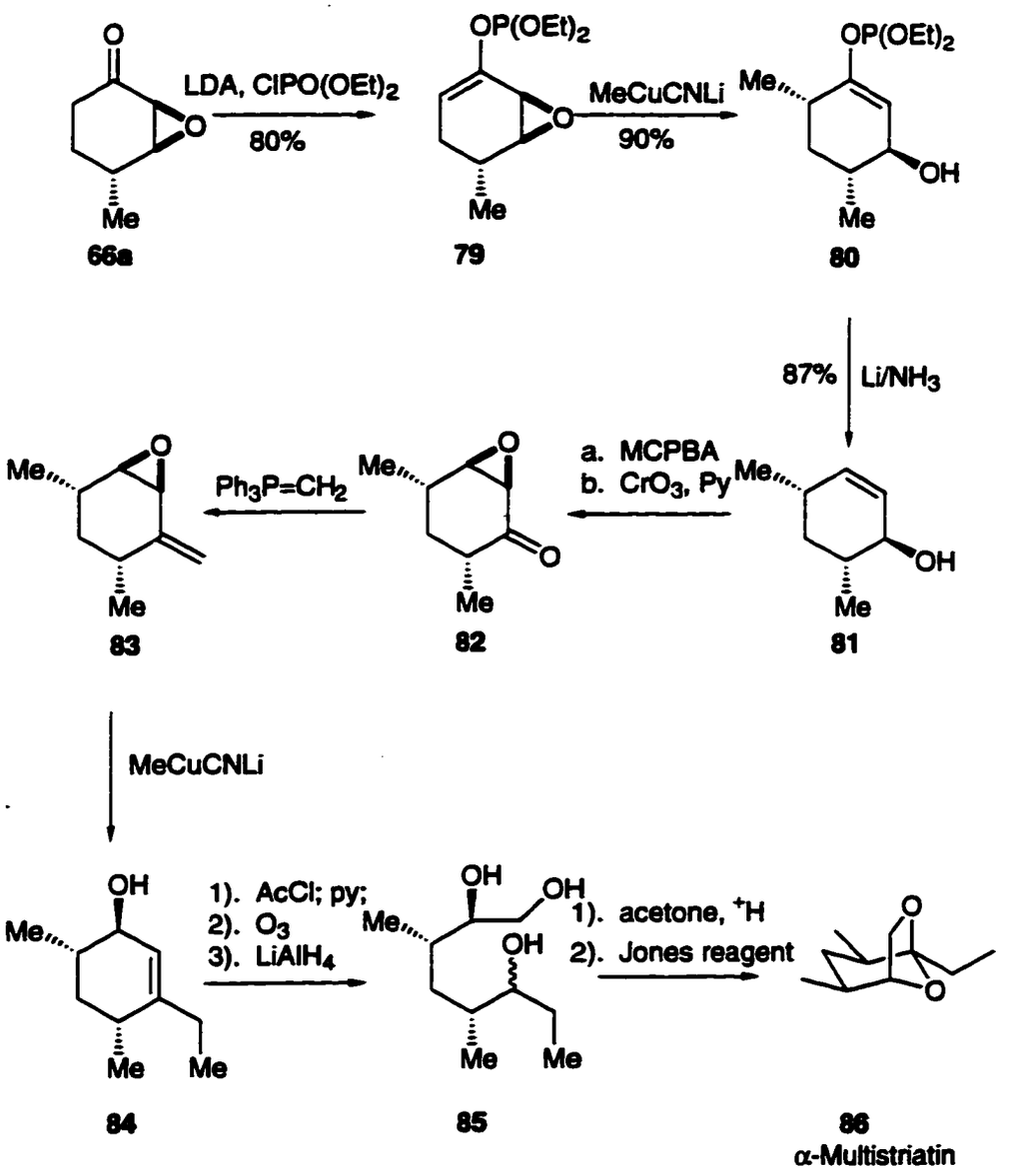
**Scheme 30**

Since the organocopper reagents are not subject to the steric requirements of the electrophile or the reactivity profiles of the nucleophile, they provide a unique route for the introduction of vinyl, aryl, and highly substituted alkyl groups α to the ketone group. The organocopper method also allows stereochemical control of the newly introduced α'-substituent.

This reaction was found to be applicable to a variety of substituted epoxycyclohexenyl silyl ethers[21] (**Scheme 30**). In all of the cases in **Scheme 30**, *anti*-$S_N2'$ products **78** were obtained.

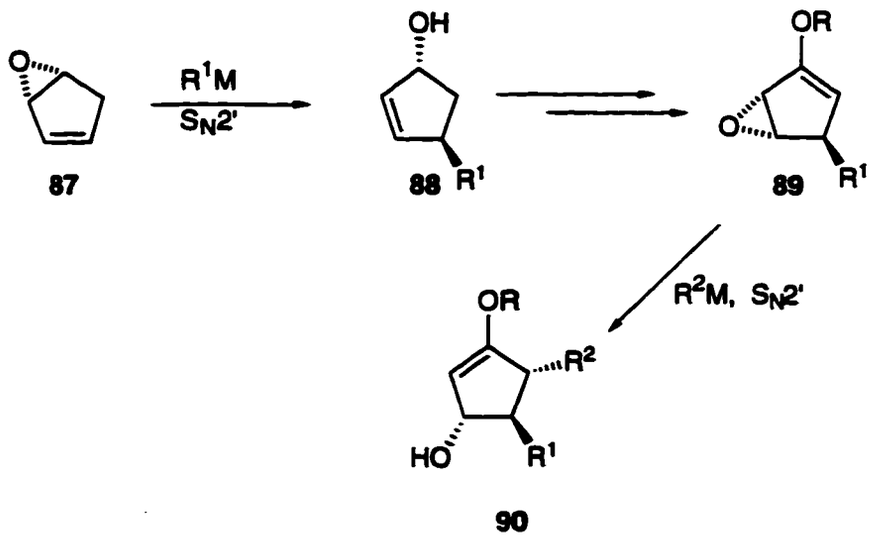
Marino applied the enol phosphate methodology to a synthesis of α-multistriatin (**86**), an aggregation pheromone of the European elm bark beetle.[21]

This synthesis is noteworthy for its use of sequential regio- and stereoselective $S_N2'$ addition for elaboration of the carbon framework. Epoxyketone **66a**, available from 1,3-cyclohexadiene monoepoxide (**56**), as outlined in **Scheme 25** and **Scheme 26** (followed by oxidation), was converted into the enol phosphate **79**. Addition of MeCuCNLi gave the *anti* $S_N2'$ product **80**. Hydrogenolysis of the phosphonate with $Li/NH_3$ yielded the allylic alcohol **81**, which underwent sequential hydroxyl-directed epoxidation and oxidation to the epoxyketone **82**. This was converted into the alkylidene epoxide **83** through Wittig methylenation. Compound **83**, when treated with MeCuCNLi, gave the $S_N2'$ product **84** exclusively. Acetylation, followed by ozonolysis and reduction, afforded triol **85**, from which natural product (±)-α-multistriatin (**86**) could be elaborated (**Scheme 31**).

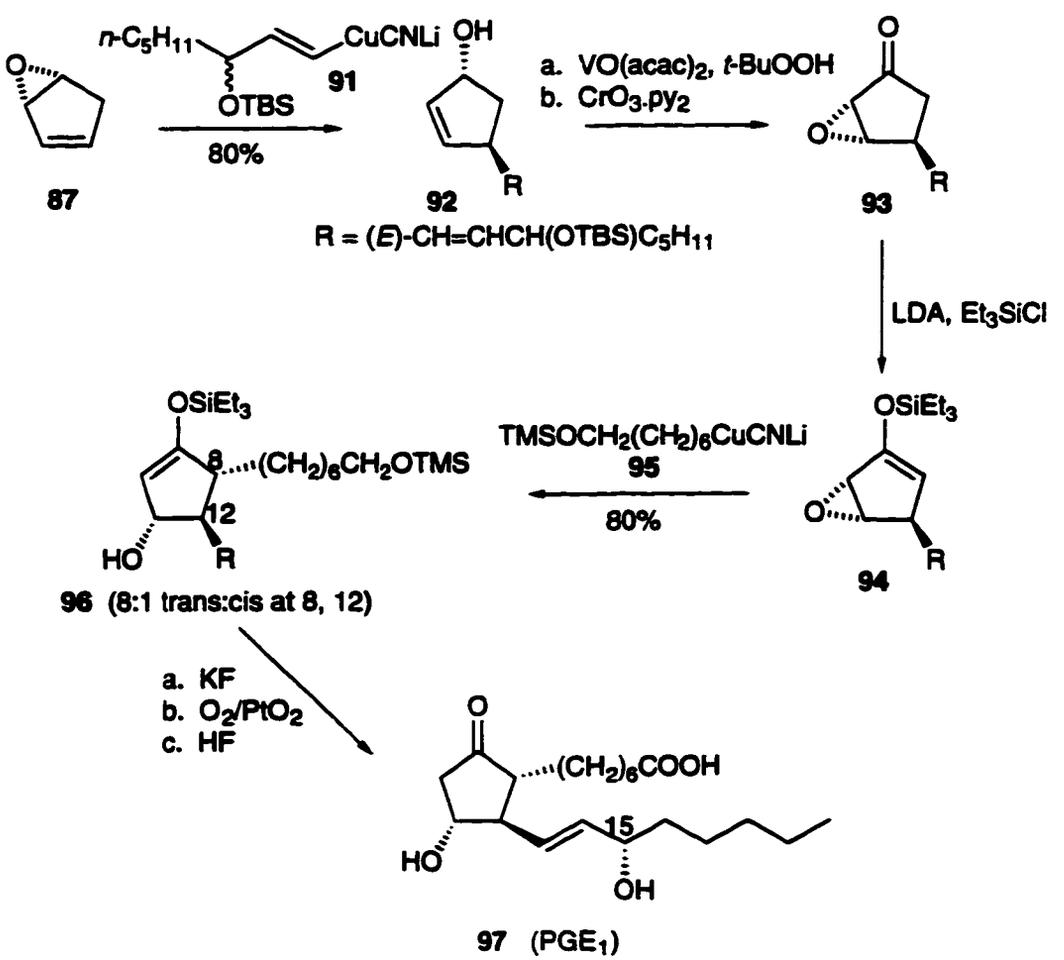



**Scheme 31**

The use of 1,3-cyclopentadiene monoepoxide would afford a 2,3-dialkylated cyclopentanone. A potential application is described in **Scheme 32**. However, it should be noted that the stereochemistry of the second $S_N2'$ addition would have to be *syn*, in contrast to all known examples in cyclohexene systems. In the event, *syn* addition was found to occur.




**Scheme 32**




**Scheme 33**

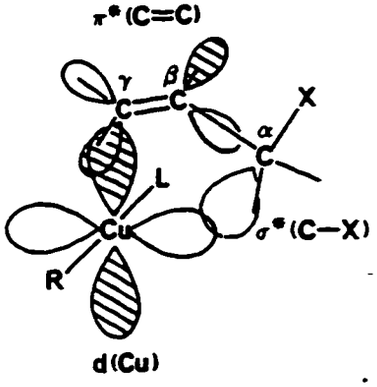
This methodology has been successfully used in the total synthesis of prostaglandins by Marino and Pradilla.[22] As shown in **Scheme 33**, epoxide **87** was treated with organocuprate **91**, and compound **92** was obtained in 80% yield. Several transformations led to the epoxy enol silyl ether **94**, which afforded an 8:1 mixture of $S_N2'$ adducts in 80% yield, upon treatment with the cyanocuprate **95**. Separation of the C-15 diastereoisomers, followed by sequential deprotection and oxidation, led to racemic $PGE_1$ (**97**) (**Scheme 33**).

*Mechanistic Considerations*

Cuprate reagents show remarkable *anti*-selectivity in $S_N2'$ reactions for a wide variety of systems, the only cases of clear *syn* predominance that do not involve chelation of the cuprate to the leaving group can be attributed to overriding steric constraints. The strong *anti* selectivity and the high rates of reaction of organocopper reagents as compared to other carbon nucleophiles imply that some special structural feature of the cuprate may play a pivotal role in $S_N2'$ displacement.

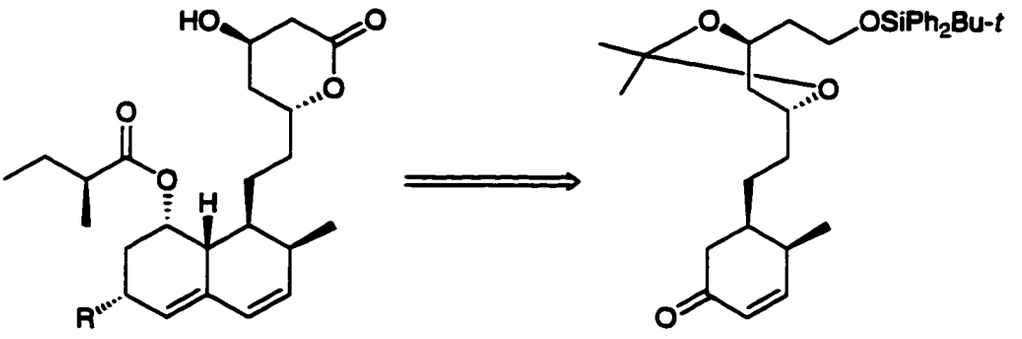
Corey and Boaz suggest that this preference derives from orbital symmetry.[23] Accordingly, nucleophilic displacements by $d^{10}$ copper most likely will involve an electron pair in a sterically accessible high energy d orbital. The electron density in this orbital will have the usual binodal symmetry and, moreover, it will be exceedingly diffuse due to

electron-electron repulsion in $d^{10}$ systems, and this characteristic leads to bidentate overlap in allylic systems so that the transition state for $S_N2'$ attack has some $S_N2$ character. The binding in this transition state can be described as resulting from the simultaneous interaction of a copper d orbital with the LUMO ($\pi^*$) at the $\gamma$ carbon and, to a considerably smaller extent, with the antibonding orbital ($\sigma^*$) at the backside of the $\alpha$ carbon. Such binding is pictured in **Scheme 34**. If the phasing of the $\pi^*$ (C=C) and $\sigma^*$ (C-X) orbitals is appropriate for an $S_N2'$ transition state, the symmetry of the d(Cu) orbital allows binding between d(Cu), $\pi^*$ (C=C) and $\sigma^*$ (C-X) orbitals, as shown in **Scheme 34**. Thus, these cuprate displacements possess $S_N2'$ and $S_N2$ character, with the latter stereoelectronically controlling the *anti* stereochemistry.




**Scheme 34**

## (II) Results and discussion



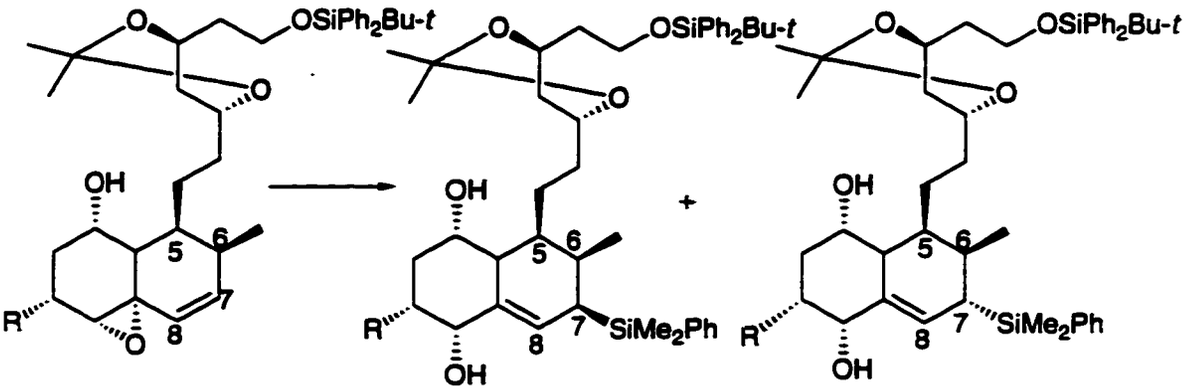

**98a** R = Me
**98b** R = H

**99**

**Scheme 35**

During studies on the degradation of mevinolin (**98a**) and compactin (**98b**) to the enone **99**[24,25] (**Scheme 35**), the response of vinyl epoxide **100a** to $(PhMe_2Si)_2CuLi$[26,27,28] (prepared from CuI and $PhMe_2SiLi$[29]) was examined, and two isomeric products **101a** and **102a** were obtained. The ratio of these isomers was variable and the major product from one experiment could be the minor product in next run. For this reason, $PhMe_2SiLi$[29] was tried. Although the desired allylic silane **101a** was produced,[24,30] the yields were erratic (40-91%) and also depended inversely on the scale of the reaction. When the compactin series (**100b**)[25] was examined later, a complex mixture was obtained with the lithium reagent; therefore, it was decided to try silyl cuprates, but made this time from CuCN.[29] Such reagents[31] gave reproducible results and afforded the isomeric silanes **101b** and **102b**. The ratio of the isomers, which was established without

separation, by $^1$H NMR measurements, depended on the stoichiometry of the cuprate mixture (**Scheme 36**).




**100a** R = Me
**100b** R = H

**101a** R = Me
**101b** R = H

**102a** R = Me
**102b** R = H

| epoxide | $PhMe_2SiLi$ : Cu | yield% | 101 : 102 |
|---|---|---|---|
| **100b** | 1 : 1 | 93 | 1 : 6 |
| **100b** | 2 : 1 | 95 | 11 : 1 |
| **100b** | 3 : 1 | 97 | 15 : 1 |
| **100a** | 1 : 1 | 98 | 1 : 8 |
| **100a** | 2 : 1 | 97 | 7 : 1 |
| **100a** | 3 : 1 | 96 | 7 : 1 |

**Scheme 36**

The stereochemistry of **101b** and **102b** was established by $^1$H NMR measurements, the characteristic features being that $J_{7,8}$ = 0 Hz and $J_{6,7}$ = 3.4 Hz for **101b**, while $J_{7,8}$ = 5.5 Hz and $J_{6,7}$ = 0 Hz for **102b**. Examination of Dreiding models shows that the *J*-values are entirely consistent with the dihedral angles measured on the models.

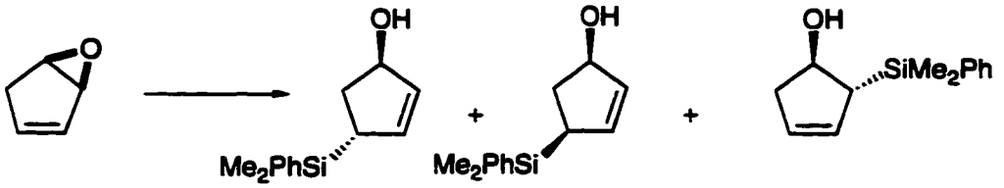
It is not clear why the different reagent mixtures produce stereoisomeric products. Reaction of carbon organocuprates with vinyl epoxides generally[32,33] proceeds by an *anti*-$S_N2'$ pathway,[32] as discussed above, but the mechanism is clearly complicated.[23,32,33] In the present case, additional considerations are that the effective reagent in each of the $PhMe_2SiLi$/CuCN equilibrium mixtures[29b] has different steric requirements and offers different opportunities for prior complexation with the epoxide oxygen.

The mevinolin series was reexamined next, but using the CuCN-derived reagents, and entirely comparable results were found (**Scheme 36**). Again, the multiplicity of the vinyl signal in the $^1H$ NMR spectra was characteristic, being a singlet for **101a** and a doublet ($J$ = 4.5 Hz) for **102a**.

These unexpected results mean that the stereochemistry of the products can be controlled by using different relative amounts of $PhMe_2SiLi$ and CuCN. In order to find if this method is general, we studied two other examples.

We have treated vinyl epoxide **87** with the three silyl cuprates (**Scheme 37**), and once more the outcome was found to be sensitive to reagent composition. However, the results are now complicated by direct epoxide opening, which was not observed in the mevinolin (**100a**) or compactin (**100b**) series.

Addition of pure $PhMe_2SiLi$ to compound **87** gave only *anti*-$S_N2$ product **105** in 27% yield. A 1:1 mixture of $PhMe_2SiLi$ and CuCN yielded both *anti* and *syn* $S_N2'$ products **103** and **104** (total yield 72%) in the isomeric ratio of 5.6:1. But the *syn*-$S_N2'$ product **104** was not observed at all in the 2:1 and 3:1 mixtures; in both these cases, a mixture of *anti*-$S_N2'$ product **103** and *anti*-$S_N2$ product **105** was obtained (79% yield for the 1:2 case and 70% for the 1:3 mixture) (**Scheme 37**).



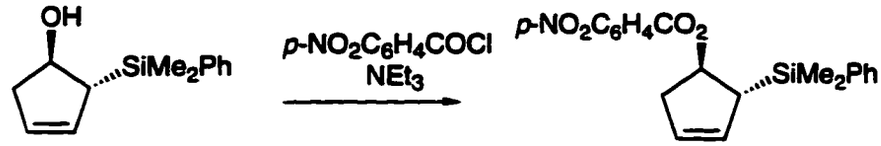

87 103 104 105

| reagents | 103 | 104 | 105 | total yield% |
|---|---|---|---|---|
| $PhMe_2SiLi$ | x | x | 27% | 27% |
| 1:1/$PhMe_2SiLi$:CuCN | 5.6 | 1 | x | 72% |
| 2:1/$PhMe_2SiLi$:CuCN | 1.17 | x | 1 | 79% |
| 3:1/$PhMe_2SiLi$:CuCN | 1 | x | 1.5 | 70% |

**Scheme 37**

We were unable to purify the *anti*-$S_N2$ product **105**, and so its *p*-nitrobenzoyl ester **106** was prepared (**Scheme 38**) in order to get good spectral data. The structure and stereochemistry of the product from **87** were readily apparent from the $^{13}C$ and $^{1}H$ NMR spectra, taken together with

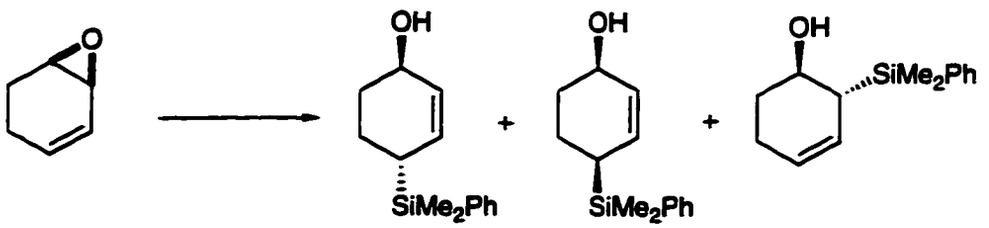
mechanistic considerations. We assume that direct epoxide opening of **87** with $PhMe_2SiLi$ occurs by the normal *trans* pathway. Assignment of *cis* and *trans* stereochemistry to the $S_N2'$ products **103** and **104** was guided by the characteristic chemical shift difference[9a] between the two methylene protons, the *cis* isomer having the larger difference (0.57 ppm for *cis*-product **104** and 0.26 for *trans*-product **103** isomer).




**105** **106**

**Scheme 38**

1,3-Cyclohexadiene monoepoxide (**56**) was also examined by using three different stoichiometries of the cuprate mixture, and the results are shown in **Scheme 39**. Addition of pure $PhMe_2SiLi$ to epoxide **56** produced only the *anti*-$S_N2$ product **109**. In the case of the 1:1 ratio ($PhMe_2SiLi$/CuCN), only the *anti*-$S_N2'$ product **107** was obtained in 70% yield. The corresponding 2:1 and 3:1 cuprate reagents yielded a mixture of *anti*-$S_N2'$ compound **107** (major product) and *anti*-$S_N2$ compound **109** in a yield of 94% for 2:1 reagent combination, and in 90% yield for the for 3:1 combination. In this example, the *syn*-$S_N2'$ product **108** was not observed at all. Evidently, direct epoxide opening, in the case of simple six-membered rings, is easier than the *syn*-$S_N2'$ pathway.




**56** **107** **108** **109**

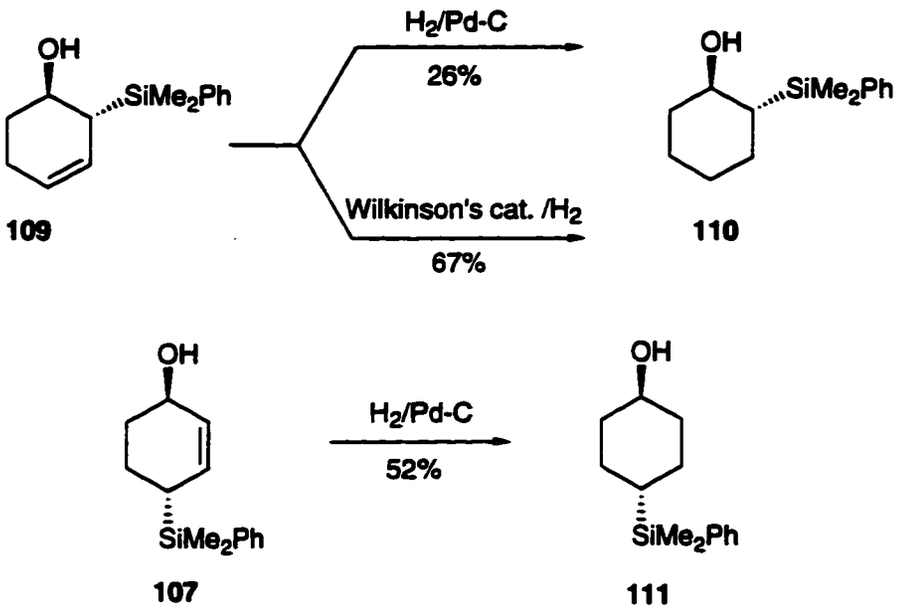
| reagents | 107 | 108 | 109 | total yield% |
|---|---|---|---|---|
| $PhMe_2SiLi$ | x | x | 40% | 40% |
| 1:1/$PhMe_2SiLi$:CuCN | 70% | x | x | 70% |
| 2:1/$PhMe_2SiLi$:CuCN | 4.9 | x | 1 | 94% |
| 3:1/$PhMe_2SiLi$:CuCN | 1.5 | x | 1 | 90% |

**Scheme 39**

The stereochemistry of **107** and **109** could be assigned only after hydrogenation to the corresponding cyclohexanols **110** and **111** (**Scheme 40**).

Pure ($^1$H NMR, 200 MHz) *trans*-4-(dimethylphenylsilyl)-cyclohexanol (**111**) has: $^{13}$C NMR (75.5 MHz, $C_6D_6$): δ -5.02 (**C**$H_3$Si), 24.67 (**C**HSi), 26.23 (**C**$H_2$), 37.53 (**C**$H_2$), 70.70 (**C**HOH), 128.00 (aryl **C**H), 129.11 (aryl **C**H), 134.14 (aryl **C**H), 138.24 (aryl **C**Si). $^1$H NMR ($C_6D_6$): δ C**H**OH 3.2 (tt, $J$ = 10.75, 3.8 Hz). For comparison purposes we note that *cis* and *trans* 4-*t*-butylcyclohexanol have δ C**H**OH at 3.75 and 3.24, respectively in $C_6D_6$. *Trans*-2-(Dimethylphenylsilyl)cyclo-hexanol (**110**) has: $^{13}$C NMR (75.5 MHz, $C_6D_6$) δ -3.24 (**C**$H_3$Si), -2.78 (**C**$H_3$Si), 25.41 (**C**$H_2$), 27.04 (C$H_2$, two overlapping

signals), 34.80 (**C**HSi), 38.34 (**C**$H_2$), 72.86 (**C**HOH), 127.93 (aryl **C**H), 128.99 (aryl **C**H), 134.52 (aryl **C**H), 139.93 (aryl **C**Si). Four $CH_2$ signals in the $^{13}C$ NMR spectrum of the saturated alcohol **110** indicated that the product **109** is generated though the *anti*-$S_N2$ pathway from **57**.




**Scheme 40**

In summary, our results show that the course of reactions of dimethylphenylsilyl cuprates with vinyl epoxides is sensitive to the stoichiometry of the reagent and, in favorable cases, significant stereochemical control is possible in preparatively useful $S_N2'$ experiments.

## (III) General experimental procedures

Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst and then through a similar column

of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30 °C, using a rotary evaporator.

Melting points were determined on a Kofler block melting point apparatus.

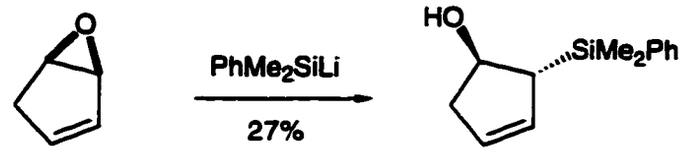
Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl, dry PhH was distilled from Na, and dry $CH_2Cl_2$ was distilled from $CaH_2$.

The symbols s', d', t', and q' used for $^{13}C$ NMR spectra indicate 0, 1, 2, or 3 attached protons.

**Reaction of 1,3-cyclopentadiene monoepoxide (87) with**

**$PhMe_2SiLi$. (No CuCN).**

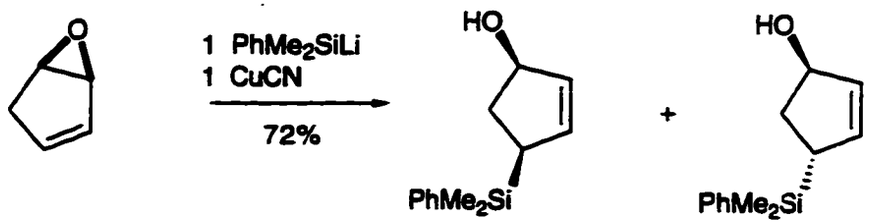



**87** **105**

1,3-Cyclopentadiene monoepoxide (**87**) (79 mg, 0.97 mmol) in THF (1.5 mL plus 2 x 1 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of $PhMe_2SiLi$[29] (0.33 M in THF, 3.0 mL, 0.99 mmol). Stirring was continued for 3 h, saturated aqueous $NaHCO_3$ (1 mL) was added, the cold-bath was removed, and the mixture allowed to attain room temperature (*ca.* 20 min). The mixture was diluted with EtOAc (20 mL), washed with saturated aqueous $NaHCO_3$ (2 x 15 mL), water (1 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:9 EtOAc-hexane and then 2:8 EtOAc-hexane, gave **105** (53 mg, 27%) (see **105** data after).

We did not detect (TLC) the 1,4-*cis* or *trans* isomers in the reaction mixture.

**Reaction of 1,3-cyclopentadiene monoepoxide (87) with $PhMe_2SiLi$ and CuCN (1:1 molar ratio of $PhMe_2SiLi$ and CuCN).**

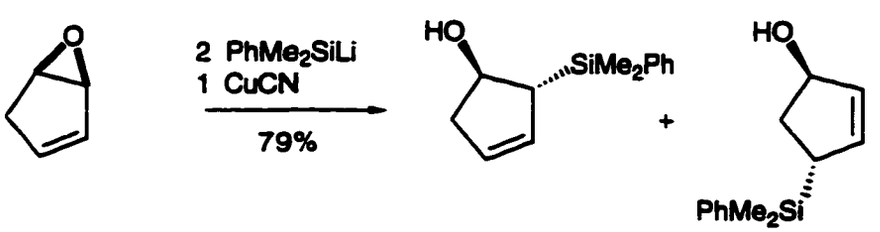



**87** **104** **103**

Copper(I) cyanide (Aldrich, 105 mg, 1.18 mmol) was suspended in THF (1.5 mL) at -23 °C. $PhMe_2SiLi$ (0.3 M in THF, 4 mL, 1.19 mmol) was added dropwise with stirring and, after 30 min, the mixture was cooled to -78 °C. After 10 min cyclopentene oxide (**87**) (104 mg, 0.99 mmol) in THF (0.5 mL plus 2 x 0.5 mL as a rinse) was added dropwise (over 2 min). Stirring was continued for *ca.* 3 h and then saturated aqueous $NaHCO_3$ was added (2 mL). The cold-bath was removed and the mixture was allowed to attain room temperature. The mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 15 mL), water (1 x 20 mL) and brine (1 x 20 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of residue over silica gel (5 x 25 cm), using first 1:9 EtOAc-hexane and then 2:8 EtOAc-hexane, gave two the isomers (186 mg, 72%) **104** (less polar) and **103** (more polar) in a 15:85 ratio, respectively, as judged by $^1H$ NMR (300 MHz). Pure ($^1H$ NMR, 300 MHz) compound **104** had: FTIR ($CHCl_3$, cast) 3300 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 0.15 (s, 6 H), 0.6-0.8 (br s, 1 H), 1.5-1.6 (m, 1 H), 1.85-1.95 (m, 1 H), 2.05-2.1 (m, 1 H), 4.65-4.75 (br s, 1 H), 5.55-5.65 (m, 1 H), 5.65-5.75 (m, 1 H), 7.15-7.30 (m, 3 H),

7.35-7.45 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $C_6D_6$) δ -4.68, -4.39, 34.26, 35.18, 77.66, 129.50, 131.75, 133.44, 134.37, 135.92, 137.68; exact mass *m/z* calcd for $C_{13}H_{18}OSi$ 218.1127, found 218.1106. Pure ($^1H$ NMR, 300 MHz) compound **103** had: FTIR ($CHCl_3$, cast) 3320 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.1 (s, 6 H), 1.7-1.9 (m, 1 H), 2.0-2.15 (m, 2 H), 2.15-2.3 (m, 1 H), 4.64-4.7 (br s, 1 H), 5.6-5.65 (m, 1 H), 5.7-5.75 (m, 1 H), 7.2-7.3 (m, 3 H), 7.35-7.45 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $C_6D_6$) δ -4.82, -4.67, 33.29, 36.13, 77.66, 129.99, 131.93, 134.09, 135.54, 137.96 (two overlapping signals); exact mass *m/z* calcd for $C_{13}H_{16}Si$ 200.1021, found 200.1023.

**Reaction of 1,3-cyclopentadiene monoepoxide (87) and $PhMe_2SiLi$ and CuCN (2:1 molar ratio of $PhMe_2SiLi$ and CuCN).**

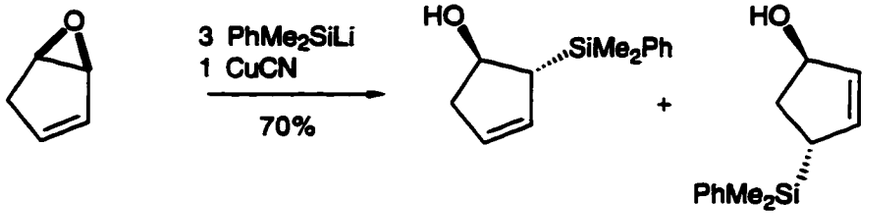



**87** **105** **103**

The procedure for the 1:1 ratio of reagents was followed, using copper(I) cyanide (126 mg, 1.41 mmol) in THF (1.5 mL), $PhMe_2SiLi$ (0.33 M in THF, 8.5 mL, 2.81 mmol), and 1,3-cyclopentadiene monoepoxide (**87**) (78 mol% in $CH_2Cl_2$, 143 mg, 1.36 mmol) in THF (0.5 mL plus 2 x 1.5 mL as a rinse). A mixture (238 mg, 79%) of **105** and **103** in a ratio of 46:54,

respectively, was obtained. Pure ($^1$H NMR, 300 MHz) compound **105** (the less polar isomer) had: FTIR ($CHCl_3$, cast) 3320 $cm^{-1}$; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 0.1 (s, 6 H), 2.1-2.15 (br s, 1 H), 2.15.2.25 (m, 3 H), 4.2-4.3 (br s, 1 H), 5.4-5.6 (m, 1 H), 5.6-5.7 (m, 1 H), 7.2-7.3 (m, 3 H), 7.4-7.5 (m, 2 H); $^{13}$C NMR (75.5 MHz, $C_6D_6$) $\delta$ -4.47, 43.87, 46.67, 73.48, 125.10, 128.05, 129.51, 130.20, 135.91, 137.89. See above for characterization data for **103**.

**Reaction of 1,3-cyclopentadiene monoepoxide (87) with $PhMe_2SiLi$ and CuCN (3:1 molar ratio of $PhMe_2SiLi$ and CuCN).**

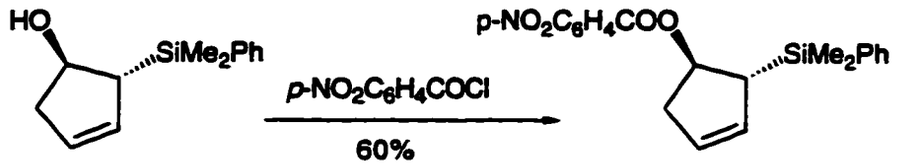



**87** **105** **103**

The procedure for the 1:1 ratio of reagents was followed, using copper(I) cyanide (97 mg, 1.08 mmol) in THF 1.5 mL, $PhMe_2SiLi$ (0.33 M in THF, 9.8 mL, 3.23 mmol) and cyclopentadiene oxide (**87**) (78 mol% in $CH_2Cl_2$, 83 mg, 1.01 mmol) (1 mL plus 2 x 1 mL as rinse). A mixture (202 mg, 70%) of **105** (less polar) and **103** (more polar) in a ratio of 60:40, respectively, was obtained.

**Characterization of 1,2-addition product from 1,3-**

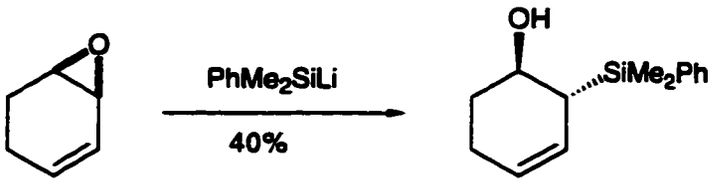
**cyclopentadiene monoepoxide (87).**




**105** **106**

Compound **105** (132 mg, 0.61 mmol) in $CH_2Cl_2$ (1 mL plus 2 x 1 mL as rinses) and then dry $Et_3N$ (0.2 mL, 1.4 mmol) were added dropwise to a stirred and cooled (ice-bath) suspension of *p*-nitrobenzoyl chloride (241 mg, 1.30 mmol) in $CH_2Cl_2$ (2 mL). The ice-bath was left in place, but not recharged, and stirring was continued for 10 h. The mixture was then evaporated, and flash chromatography of the residue over silica gel (5 x 25 cm), using 1:9 EtOH-hexane and then 2:8 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **106** (133 mg, 60%): FTIR ($CH_2Cl_2$ cast) 1720 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.4 (s, 6 H), 2.4-2.5 (m, 3 H), 5.55 (d, $J$ = 5 Hz, 1 H), 5.75-5.80 (m, 1 H), 5.75-5.86 (m, 1 H), 7.3-7.4 (m, 3 H), 7.5-7.6 (m, 2 H), 8.1-8.2 (m, 2 H), 8.2-8.3 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ -4.72, -4.08, 40.44, 43.57, 78.87, 123.44, 124.91, 127.84, 129.44, 130.44, 130.68, 133.82, 136.23, 136.65; mass (CI) *m/z* calcd for $C_{20}H_{25}N_2O_4Si$ 367, found 385 (M + $NH_4$).

**Reaction of 1,3-cyclohexadiene monoepoxide (56) with $PhMe_2SiLi$. (No CuCN).**

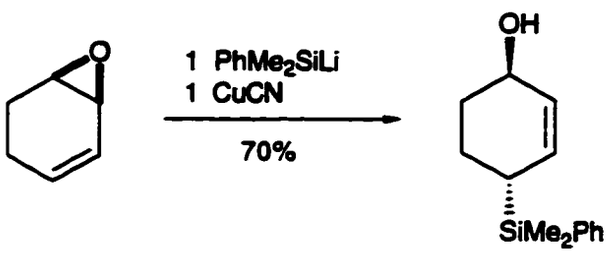



**56** **109**

1,3-Cyclohexadiene monoepoxide (**56**) (122 mg, 1.27 mmol) in THF (0.5 mL plus 2 x 0.5 mL as rinse) was added dropwise to a stirred and cooled (-78 °C) solution of $PhMe_2SiLi$ (0.36 M in THF, 4.0 mL, 1.44 mmol). Stirring was continued for 3 h. A mixture (1 mL) of 1:9 saturated aqueous $NH_4Cl$ and concentrated aqueous ammonia solution was added, the cold-bath was removed, and the mixture allowed to attain room temperature (*ca.* 20 min). The mixture was diluted with EtOAc (20 mL) and washed with a mixture (2 x 15 mL) of 1:9 saturated aqueous $NH_4Cl$ and concentrated aqueous ammonia solution, and brine (1 x 20 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using first 1:9 EtOAc-hexane and then 2:8 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **109** (93 mg, 40%): FTIR ($CHCl_3$, cast) 3330 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 0.35 (s, 6 H), 0.95-1.10 (br s, 1 H), 1.45-1.55 (m, 2 H), 1.75-1.85 (m, 2 H), 1.95-2.10 (m, 1 H), 3.75-3.85 (q, $J$ = 6 Hz, 1 H), 5.50-5.60 (m, 2 H), 7.2-7.25 (m, 3 H), 7.40-7.51 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $C_6D_6$) $\delta$ -4.10 (q'), -3.62 (q'), 22.44 (t'), 30.68 (t'), 36.42 (d'), 67.60 (d'), 125.00 (d'), 125.68 (d'), 128.11 (d'), 129.36 (d'), 134.28 (d'), 137.98 (s'); exact mass *m/z* calcd for $C_{14}H_{20}OSi$

232.1377, found 232.1283.

**Reaction of 1,3-cyclohexadiene monoepoxide (56) with $PhMe_2SiLi$ and CuCN (1:1 molar ratio of $PhMe_2SiLi$ and CuCN).**

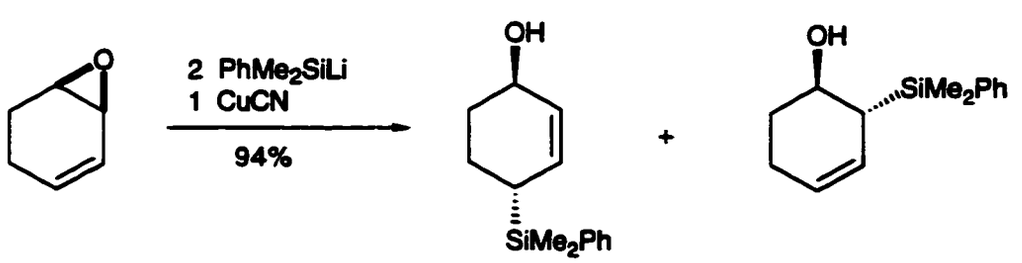



**56** **107**

Copper(I) cyanide (145 mg, 1.62 mmol) was suspended in THF (1.5 mL) at -30 °C. $PhMe_2SiLi$ (0.30 M in THF, 5.2 mL, 1.56 mmol) was added dropwise with stirring and, after 30 min, the mixture was cooled to -78 °C. After 10 min, cyclohexene oxide (**56**) (118 mg, 1.22 mmol) in THF (0.5 mL plus 2 x 0.5 mL as a rinse) was added dropwise (over 20 min). Stirring was continued for *ca.* 3 h, and then a mixture of 1:9 saturated aqueous $NH_4Cl$ and concentrated aqueous ammonia solution (1 mL) was added. The cold-bath was removed and the mixture was allowed to attain room temperature. The mixture was diluted with EtOAc (20 mL) and washed with a mixture of 1:9 saturated aqueous $NH_4Cl$ and concentrated aqueous ammonia solution (2 x 15 mL), water (1 x 20 mL) and brine (1 x 20 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of residue over silica gel (2.5 x 25

cm), using first 1:9 EtOAc-hexane and then 2:8 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) **107** (196 mg, 70%): FTIR ($CHCl_3$, cast) 3400 $cm^{-1}$; $^1$H NMR (300 MHz, $C_6D_6$) δ 0.15 (s, 6 H), 1.30-1.45 (m, 1 H), 1.45-1.55 (m, 1 H), 1.55-1.75 (m, 2 H), 1.70-1.90 (m, 1 H), 2.9-3.05 (br s, 1 H), 4.0-4.15 (br s, 1 H), 5.6-5.7 (m, 1 H), 5.75-5.85 (m, 1 H), 7.18-7.25 (m, 3 H), 7.35-7.45 (m, 2 H); $^{13}$C (75.5 MHz, $C_6D_6$) δ -4.79 (q'), -4.71 (q'), 20.95 (t'), 26.12 (d'), 32.4 (t'), 65.98 (d'), 128.06 (d'), 129.32 (d'), 129.62 (d'), 130.46 (d'), 134.17 (d'), 137.79 (s'); exact mass *m/z* calcd for $C_{14}H_{20}OSi$ 232.1377, found 232.1282.

**Reaction of 1,3-cyclohexadiene monoepoxide (56) with $PhMe_2SiLi$ and CuCN (2:1 molar ratio of $PhMe_2SiLi$ and CuCN).**

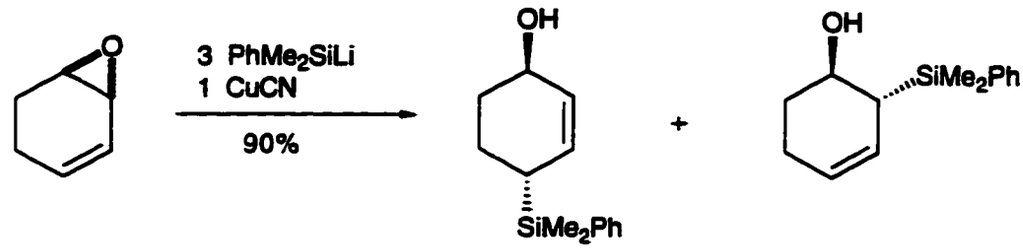



**56** **107** **109**

The procedure for the 1:1 ratio of reagents with 1,3-cyclohexadiene monoepoxide (**56**) was followed, using copper(I) cyanide (119 mg, 1.33 mmol) in THF (1.5 mL), $PhMe_2SiLi$ (0.32 M in THF, 8.2 mL, 2.62 mmol), and cyclohexene oxide (98 mg, 1.02 mmol) in THF (0.5 mL plus 2 x 0.5 mL as a rinse). A mixture (220 mg, 94%) of **109** (less polar) and **107** (more

polar) was obtained, in a ratio of 17:83, respectively.

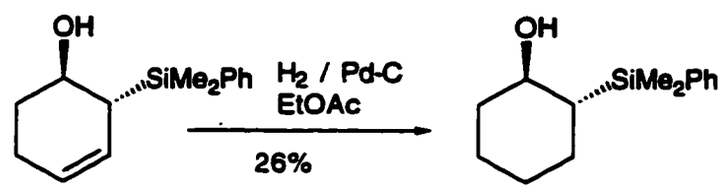
**Reaction of 1,3-cyclohexadiene monoepoxide (56) with $PhMe_2SiLi$ and CuCN (3:1 molar ratio of $PhMe_2SiLi$ and CuCN).**




**56** **107** **109**

The procedure for the 1:1 ratio of reagents with 1,3-cyclohexadiene monoepoxide (**56**) was followed, using copper(I) cyanide (101 mg, 1.13 mmol), $PhMe_2SiLi$ (0.32 in THF, 10.5 mL, 3.36 mmol) and 1,3-cyclohexadiene monoepoxide (**56**) (98 mg, 1.02 mmol) in THF (0.5 mL plus 2 x 0.5 mL as rinse). A mixture (212 mg, 90%) of **109** (less polar) and **107** (more polar) was obtained in a ratio of 40:60, respectively.

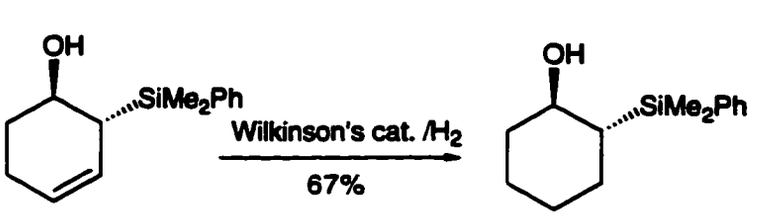
**Hydrogenation of 1,2-addition product 109 from 1,3-cyclohexadiene monoepoxide (56).**




**109** **110**

Pd/C (10%w/w, 50 mg) was added to a solution of **109** (150 mg, 0.64 mmol) in EtOAc (2 mL) and the mixture was stirred vigorously under hydrogen (balloon). After 2 h the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 1:4 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) **110** (39 mg, 26%): FTIR ($CHCl_3$, cast) 3400 $cm^{-1}$; $^1$H NMR (300 MHz, $C_6D_6$) δ 0.4 (two singlets, 6 H), 0.60-0.70 (m, 1 H), 0.8-1.1 (m, 5 H), 1.35-1.45 (m, 1 H), 1.50-1.60 (m, 2 H), 1.65-1.75 (m, 1 H), 3.10-3.25 (m, 1 H), 7.15-7.35 (m, 3 H), 7.55-7.65 (m, 2 H); $^{13}$C NMR (75.5 MHz, $C_6D_6$) δ -3.24 (q'), -2.78 (q'), 25.41 (t'), 27.04 (t', two overlapping signals), 34.80 (d'), 38.34 (t'), 72.86 (d'), 127.93 (d'), 128.99 (d'), 134.52 (d'), 139.93 (s'); exact mass *m/z* calcd for $C_{14}H_{20}Si$ (M - $H_2O$) 216.1334, found 216.1344; mass (CI) *m/z* calcd for 234, found 252 ($C_{14}H_{22}OSi$ + $NH_4$).

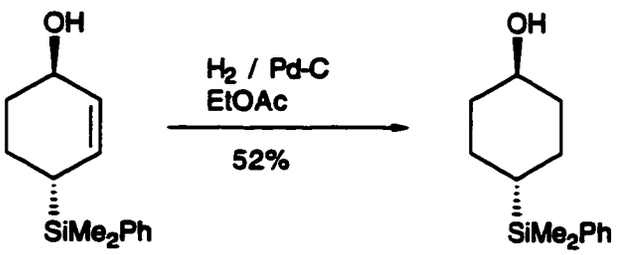
**Hydrogenation of 1,2-addition product 109 from 1,3-cyclohexadiene monoepoxide (56). Use of Wilkinson's catalyst.**




**109** **110**

A solution of **109** (150 mg, 0.64 mmol) in dry PhH (1 mL plus 1 mL as a rinse) was injected into a stirred solution of Wilkinson's catalyst (184 mg, 0.20 mmol) that had been presaturated with hydrogen (40 psi) for 1 h. The mixture was stirred at room temperature for 12 h under hydrogen (40 psi), the solvent was evaporated and the mixture was filtered through a small pad of Florisil (1 x 5 cm), using 10% EtOAc-hexane. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 25 cm), using 20% EtOAc-hexane, gave **110** (101 mg, 67%).

**Hydrogenation of *trans* 1,4-addition product 107 from 1,3-cyclohexadiene monoepoxide (56).**




**107** **111**

Pd/C (10% w/w, 30 mg) was added to a solution of **107** (85 mg, 0.36 mmol) in EtOAc (2 mL) and the mixture was stirred vigorously under hydrogen (balloon) for 10 h. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 20% EtOAc-hexane gave pure ($^1$H NMR, 300 MHz) **111** (46 mg, 52%): FTIR ($CHCl_3$ cast) 3400 $cm^{-1}$; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 0.1 (s, 6 H), 0.4-

0.5 (m, 1 H), 0.9-1.1 (m, 4 H), 1.1-1.2 (br s, 1 H), 1.55-1.65 (d, $J$ = 12, 1 H), 1.95-2.05 (br, 1 H), 3.2 (tt, $J$ = 10.75, 3.8 Hz, 1 H), 7.15-7.25 (m, 3 H), 7.35-7.45 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $C_6D_6$) $\delta$ -5.02 (q'), 24.67 (d'), 26.22 (t'), 37.53 (t'), 70.70 (d'), 128.00 (d'), 129.11 (d'), 134.14 (d'), 138.28 (s'); exact mass *m/z* calcd for $C_{14}H_{22}OSi$ 234.1488, found 234.1432.

**References and Notes**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(c) We made $PhMe_2SiLi$ according to the experimental procedure of Sharma and Oehlschlager.

30. In principle, either stereochemistry at C(6) would have been suitable for us.

31. We used CuCN from Fluka and purified it using the method of Marshall, J. A.; Trometer, J. D. *Tetrahedron* **1989**, *45*, 391.

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# (I) Introduction

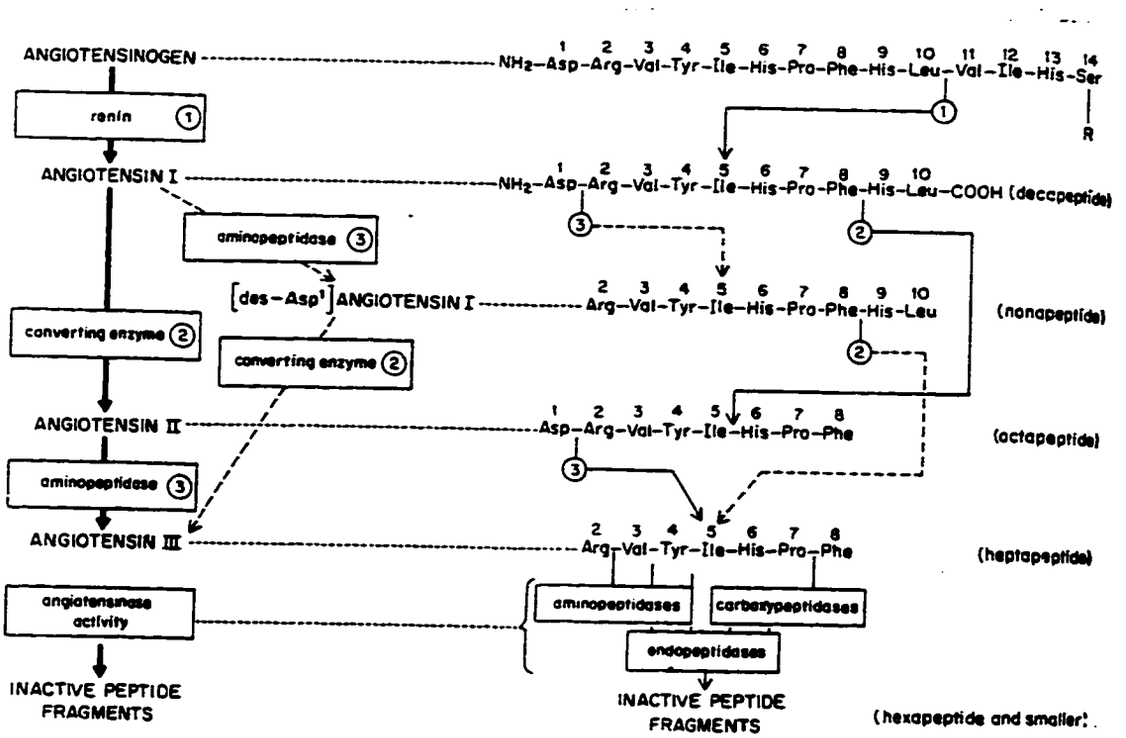
## Angiotensin[1]

The crude saline extracts of kidney contain a pressor principle called renin. It produces persistent hypertension (elevated blood pressure) in humans and animals by constricting the renal arteries. Renin is an enzyme that acts on a plasma protein substrate (called angiotensinogen) to catalyze the formation of the actual pressor material, a peptide called angiotensin.

In the 1950's, Skeggs and Peart determined the amino acid composition and sequence of angiotensin. Two forms were recognized. The first is a decapeptide (angiotensin I) and the second an octapeptide (angiotensin II). The latter is formed from angiotensin I by enzymatic cleavage by another enzyme, termed angiotensin-converting enzyme. The octapeptide, angiotensin II, was shown to be the more active species, and its synthesis in 1957 by Schwyzer and by Bumps[2] made the material available for intensive study.

The synthesis and degradation of the angiotensins are complex processes that are outlined in **figure 1**. Briefly, the process is initiated when the enzyme renin acts on angiotensinogen (the renin substrate) to release the decapeptide angiotensin I. This decapeptide has limited pharmacological activity, but it is cleaved by angiotensin-converting enzyme (ACE) to yield the highly active

octapeptide angiotensin II. This, in turn, undergoes hydrolysis by an aminopeptidase to yield the heptapeptide angiotensin III, which is also pharmacologically active. Further cleavage yields peptides with little activity. In an alternative (minor) path, angiotensin-converting enzyme and aminopeptidase act in the opposite sequence such that the decapeptide, angiotensin I, is hydrolyzed first to [des-asp$^{I}$] angiotensin I which, like the parent compound, has limited pharmacological activity. The [des-asp$^{I}$] angiotensin I is then cleaved by angiotensin-converting enzyme to form the active angiotensin III.[2,3]



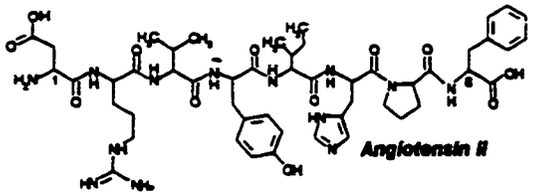

*Formation and destruction of angiotensins.*

**figure 1**

There are many fatal diseases which are related to excessive amounts of angiotensin II in blood. The compound causes vasoconstriction and often has an indirect effect on the heart, such that cardiac output is lowered. Angiotensin is the most potent pressor agent known; on a molar basis, it is about 40 times more powerful than norepinephrine. It also causes kidney disease due to its indirect effects on renal tubular function, mediated by aldosterone. Angiotensin also influences urine formation through hemodynamic and intrarenal actions that interact in a complex way.

The pharmacological properties so far described are those of angiotensin II. Angiotensin I has less than 1% of the intrinsic activity of angiotensin II. However, angiotensin III retains most of the activity of angiotensin II, although in most instances it is somewhat weaker.

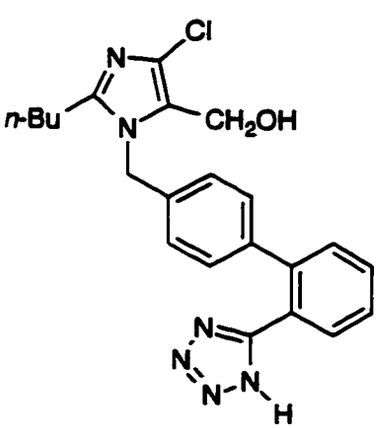
**Angiotensin II Antagonists and inhibitors of ACE**



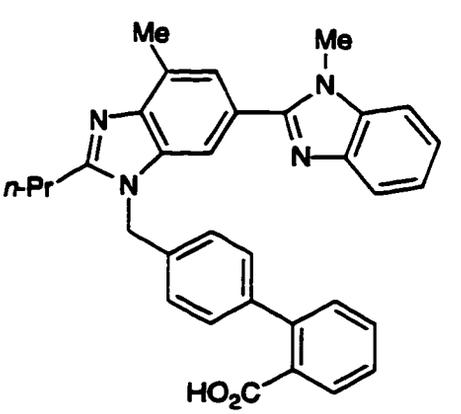

The renin-angiotensin system plays an important role in the control of renal function and blood pressure and in the pathogenesis of some forms of hypertension. Consequently,

much work has been focused on developing agents that block the renin-angiotensin system so as to maintain blood pressure in the proper range.

In the 1970's, two distinct classes of effective inhibitors of the renin-angiotensin system were identified: angiotensin II antagonists, which block receptors for the peptide, and converting enzyme inhibitors, which slow the rate of formation of angiotensin II from its inactive precursor.




Losartan, DUP 753

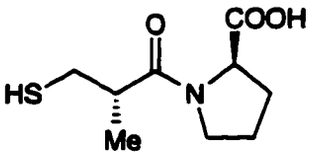



Telmisartan, BIBR 277

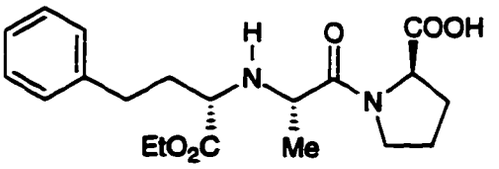
The useful antagonists of angiotensin II are slightly modified congeners in which agonist activity is profoundly attenuated by replacement of phenylalanine in position 8 with some other amino acid. The substances [$Sar^{I}$, $Val^{5}$, $Ala^{8}$] angiotensin (1-8) octapeptide, known as the Saralasin series, were introduced by Pals in 1971. Although angiotensin II analogues are highly specific antagonists, they also retain

some agonist activity, which complicates interpretation of some of their effects.[4] However, direct blockade of the angiotensin II receptor ($AT_1$ receptor) has recently become feasible by the development of a series of orally active nonpeptide antagonists for the $AT_1$ receptor. DUP 753 (Losartan, NK954) and BIBR 277 (phase III, Boehringer Ingelheim), shown above, have been found to be very powerful $AT_1$ antagonists.[5,6,7] These nonpeptide antagonists are highly selective for the $AT_1$ receptor and, in contrast to the peptide-based antagonists of angiotensin analogues, they do not show any partial agonism.

Angiotensin-converting enzyme (ACE) inhibitors are also commonly used for inhibiting the renin-angiotensin system (RAS).[1] The essential effect of these agents on the RAS is to inhibit conversion of the relatively inactive angiotensin I into the active angiotensin II (or the conversion of [des-$Asp^I$] angiotensin I to angiotensin III). In this way they attenuate or abolish responses to angiotensin I. The converting enzyme inhibitors are highly specific drugs. They do not interact directly with other components of the renin-angiotensin system, including the receptor for the peptide. Also, research has revealed that ACE inhibitors cause a greater fall in blood pressure than does angiotensin II antagonism.




Captopril (Squibb)

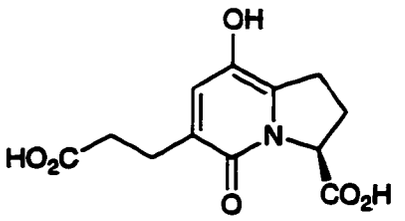



Enalapril (Merck)

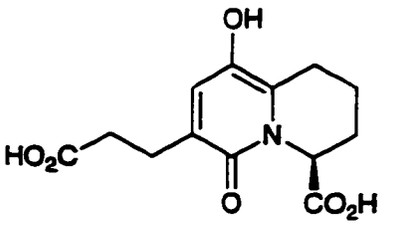
Captopril,[8] the first orally active ACE inhibitor, has been marketed for the treatment of severe or drug-resistant hypertension since the 1980's. Unfortunately, it may cause some potentially hazardous side effects, perhaps related to its sulfhydryl moiety.[9] Enalapril, a nonsulfhydryl-containing ACE inhibitor, is also used for treatment of diseases caused by angiotensin. Enalapril is a prodrug that is not itself highly active; it must be hydrolyzed to its active parent dicarboxylic acid, enalaprilate. Enalapril has been found to be more potent than Captopril and to inhibit ACE for longer periods.[8,9,10]

**A58365A and A58365B, Inhibitors of ACE**

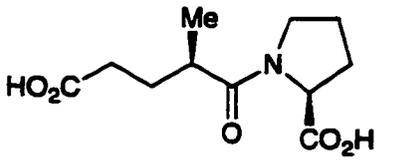
Culture A58365, NRRL 15098, identified as a new strain of *Streptomyces chromofuscus*, was isolated from a soil sample collected in Brazil. It was found to produce two novel angiotensin-converting enzyme inhibitors, A58365A and A58365B. They are homologous nitrogen-containing bicyclic structures of molecular formulae $C_{12}H_{13}NO_6$ for A58365A and $C_{13}H_{15}NO_6$ for A58365B.[11,12]




A58365A 1




A58365B 2




3

The structure elucidation of the two new ACE inhibitors has been described in detail.[13] A58365A was determined to be 3-carboxy-1,2,3,5-tetrahydro-8-hydroxy-5-oxo-6-indolizine-propanoic acid (**1**); A58365B was the homologous 4-carboxy-1,3,4,6-tetrahydro-9-hydroxy-6-oxo-2*H*-quinolizine-7-propanoic acid (**2**). A58365A is, in fact, a naturally occurring conformationally restricted analog of α-methylglutaryl-L-proline (**3**), which was a part of the structure activity relationship studies leading to captopril.

Nakatsukasa and his assistants proposed a biosynthetic pathway for A58365 by *Streptomyces chromofuscus* NRRL 15098.[14] Fermentation studies afforded an increase in the amount of the ACE inhibitor from less than 1 μg/mL to 20 μg/mL. Proline was the obligatory supplement for ACE inhibitor

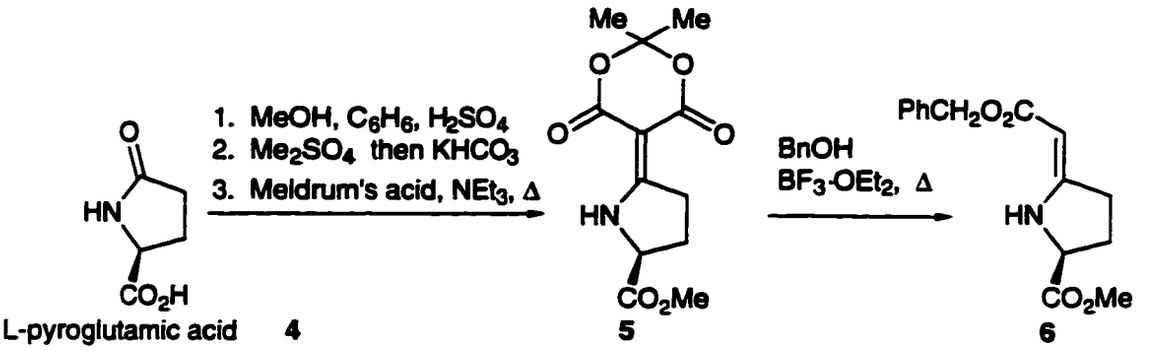
biosynthesis. Without proline, less than 1 μg/mL of both A58365A and A58365B was synthesized. D-proline or L-hydroxyproline could be substituted in place of L-proline, but were not superior to L-proline. Greater amounts of A58365A were synthesized when L-tyrosine was added to the medium. However, this regulation was evident only in combination with proline but not with tyrosine alone. The addition of lysine to the proline-supplemented medium resulted in regulating the fermentation to produce greater amounts of A58365B. Like the regulation of A58365A by proline and tyrosine, stimulation of the synthesis of A58365B was evident with proline and lysine but not lysine alone, suggesting that A58365B synthesis is closely linked to that of A58365A. The studies also show that A58365A is synthesized before A58365B.

**Total Synthesis A58365A by Danishefsky and Fang**[15]

Enantiomerically homogeneous A58365A in the natural *S*-configuration was synthesized for the first time by Danishefsky and Fang in 1989. The synthesis was done in 11 steps, but the authors pointed out that there were clearly some significant yield problems in this first generation synthesis.

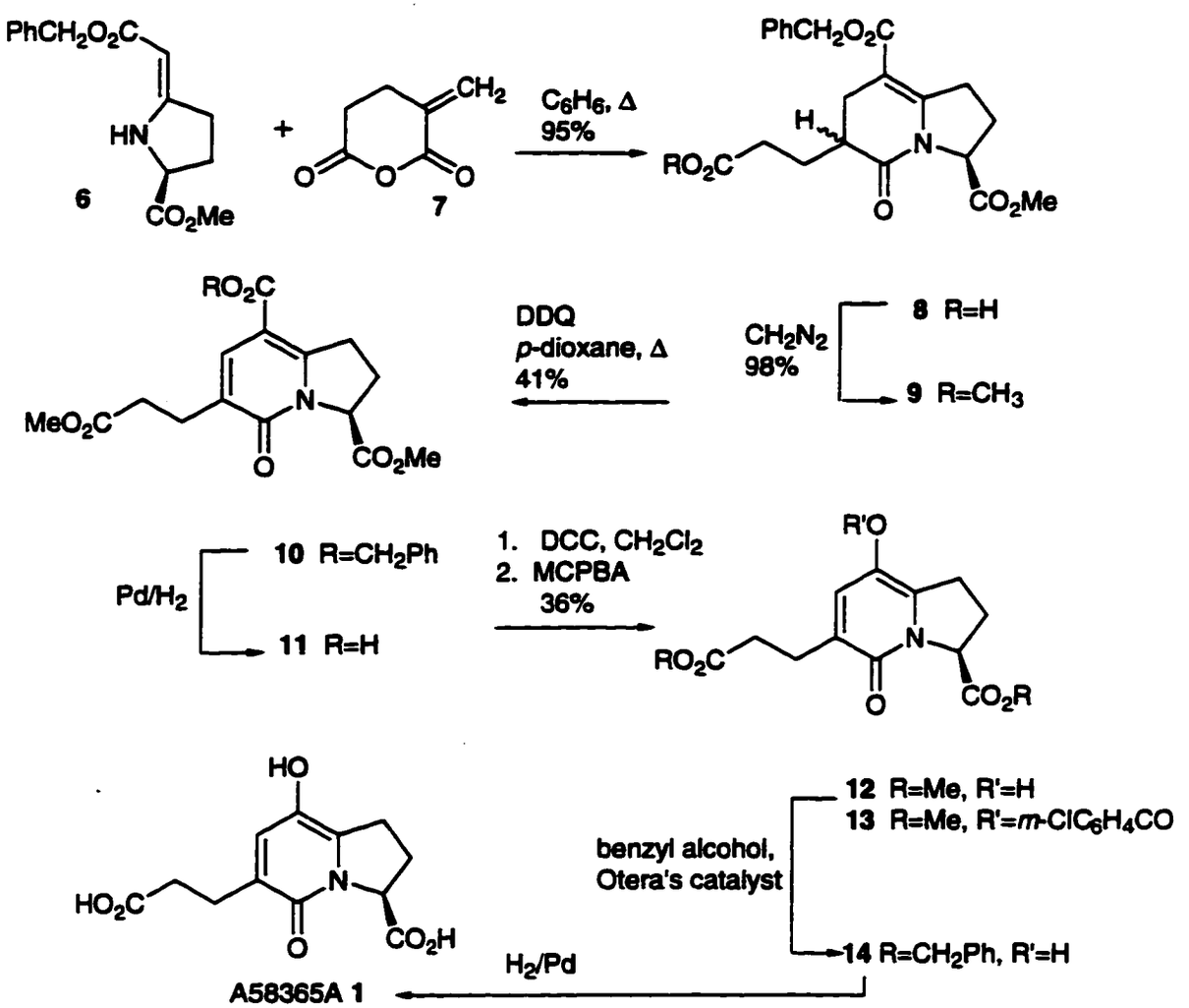
Their synthesis was accomplished by starting with L-pyroglutamate. The four-step conversion of commercially available L-pyroglutamic acid (**Scheme 1**) led to vinylogous

urethane **6**, which was the key intermediate. The annulation of **6** with α-methyleneglutaric anhydride (**7**) formed the hexahydroindolizidine **8**. Esterification, followed by DDQ




**Scheme 1**

oxidization, then gave pyridone **10**. Monocarboxylic acid **11** was obtained after debenzylation of compound **10**. Carboxy-inversion of **11** was done by successive treatment with DCC and MCPBA, to produce A58365A-dimethyl ester (**12**) and A58365A-dimethyl ester *meta*-chlorobenzoate (**13**). Compounds **12** and **13** were converted into dibenzyl ester **14** by using Otera's catalyst, the esterification being done to facilitate purification. Catalytic hydrogenation (Pd/C) of pure **14** then afforded the pure natural product A58365A **1** (**Scheme 2**).



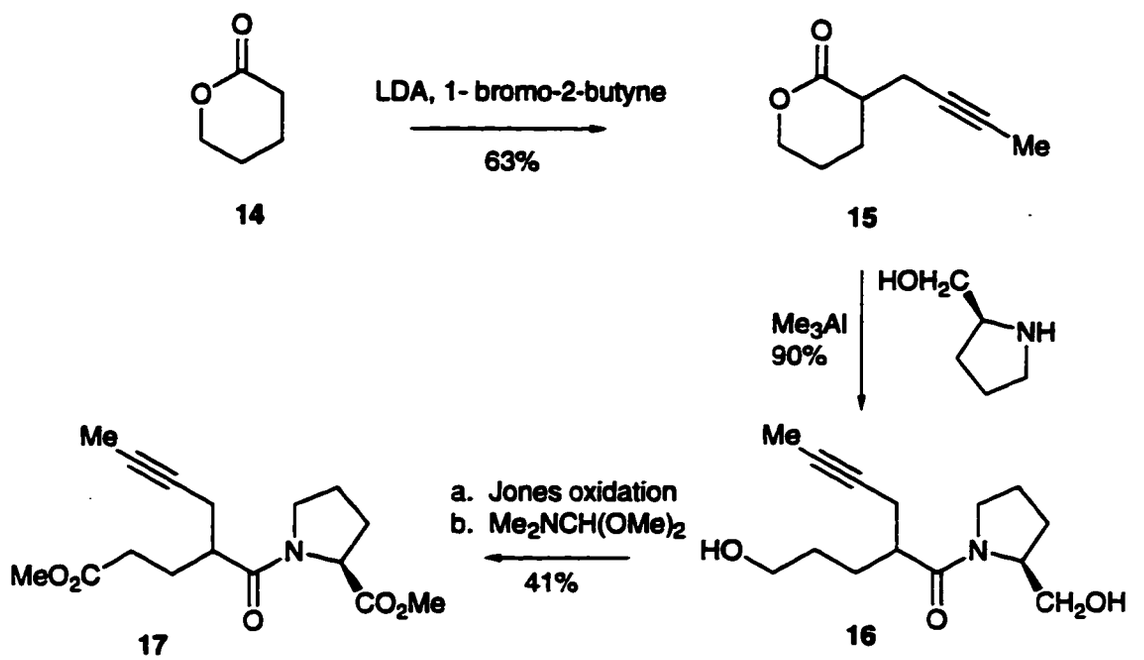

**Scheme 2**

## Total Synthesis of (-)-A58365A and (±)-A58365B by Moeller and Wong[16]

An anodic amide oxidation has been used to synthesize (-)-A58365A and (±)-A58365B by Moeller and Wong.[16] Both syntheses take advantage of the ability of electrochemical methods to selectively oxidize an amide in the presence of a disubstituted acetylene nucleophile (see below).

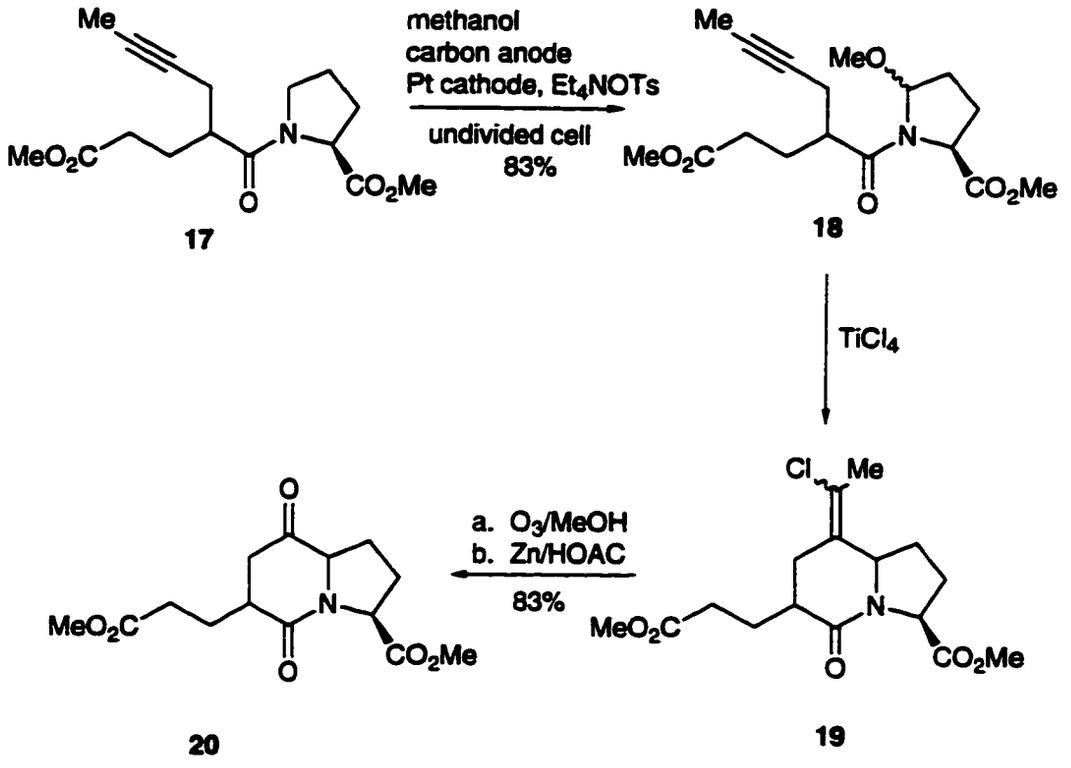
**(-)-A58365A**

In the synthesis of (-)-A58365A, the key intermediate **17** for electrolysis was synthesized in 4 steps from *S*-(+)-2-pyrrolidinemethanol (**Scheme 3**).



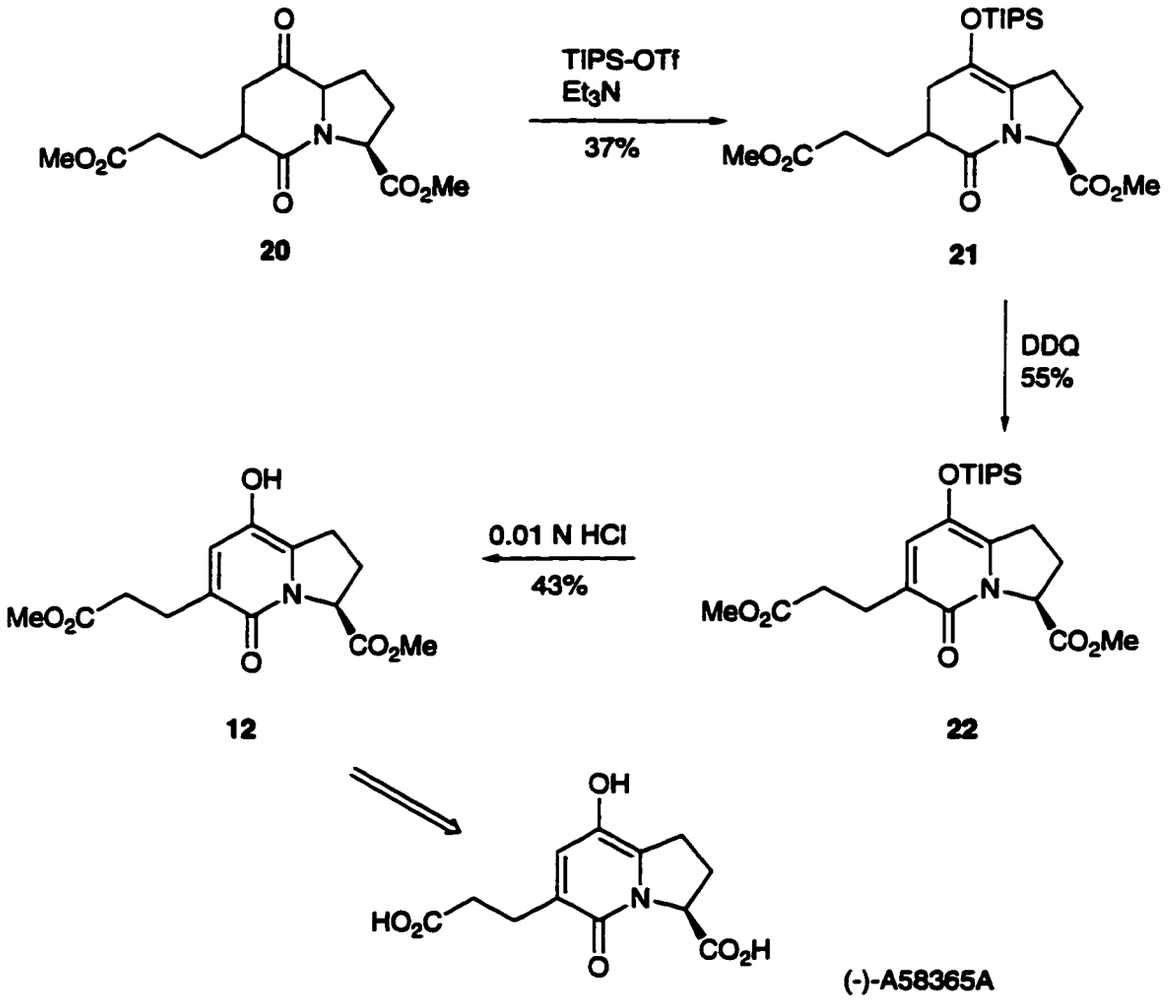

**Scheme 3**

The oxidation of key intermediate **17** proceeded (**Scheme 4**) in an undivided cell (81.5 mA, 5.2 F/mol) to afford the methoxylated amide **18**, which was treated with $TiCl_4$ to give the bicyclic vinyl chloride **19**. Crude **19** was immediately ozonolyzed, followed by workup with Zn/AcOH, and keto-amide **20** was obtained in this two step process.




**Scheme 4**

The keto-amide **20** was treated with triisopropylsilyl triflate and triethylamine to afford enol ether **21** (**Scheme 5**). Treatment of **21** with DDQ led to the six-membered ring aromatic compound **22**, which was then stirred with a solution of 0.01 N HCl in order to cleave the silyl ether protecting group and converge on the synthesis of Danishefsky and Fang. The optical purity of the final product, A58365A, was *ca.* 90% (**Scheme 5**).



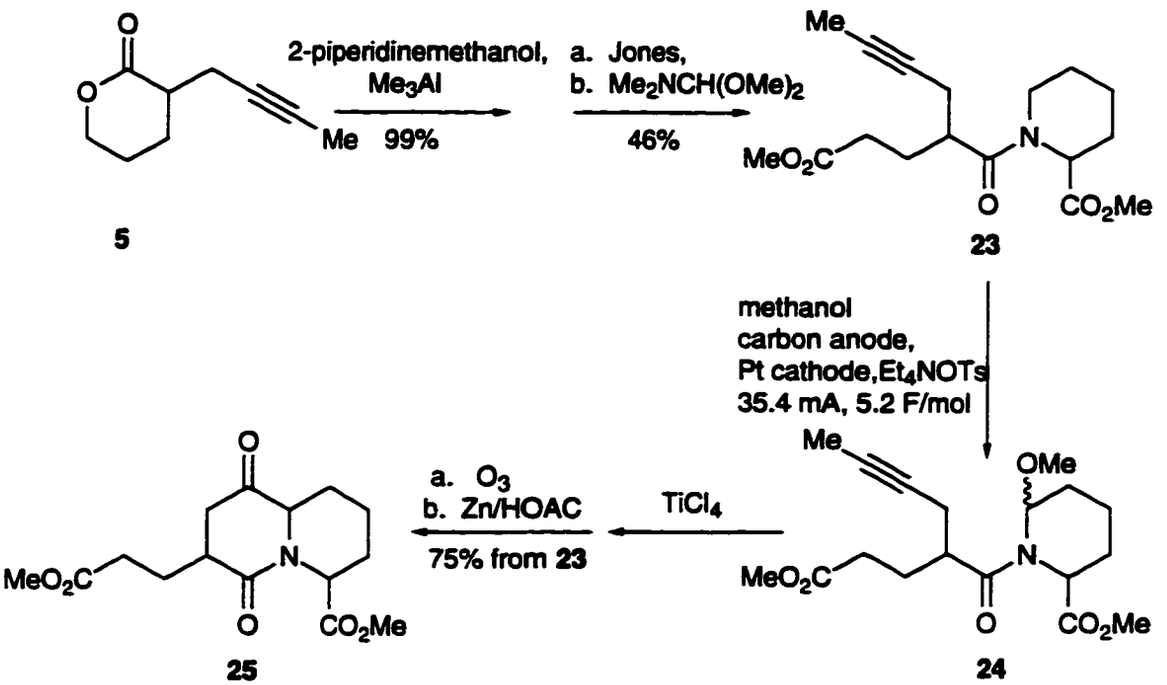

**Scheme 5**

**(±)-A58365B**

For the synthesis of (±)-A58365B, a nearly identical procedure was used in order to convert the electrolysis substrate **23**, derived from pipecolic acid, into the required 1-aza-2,5-dioxobicyclo[4.4.0]decane ring skeleton.

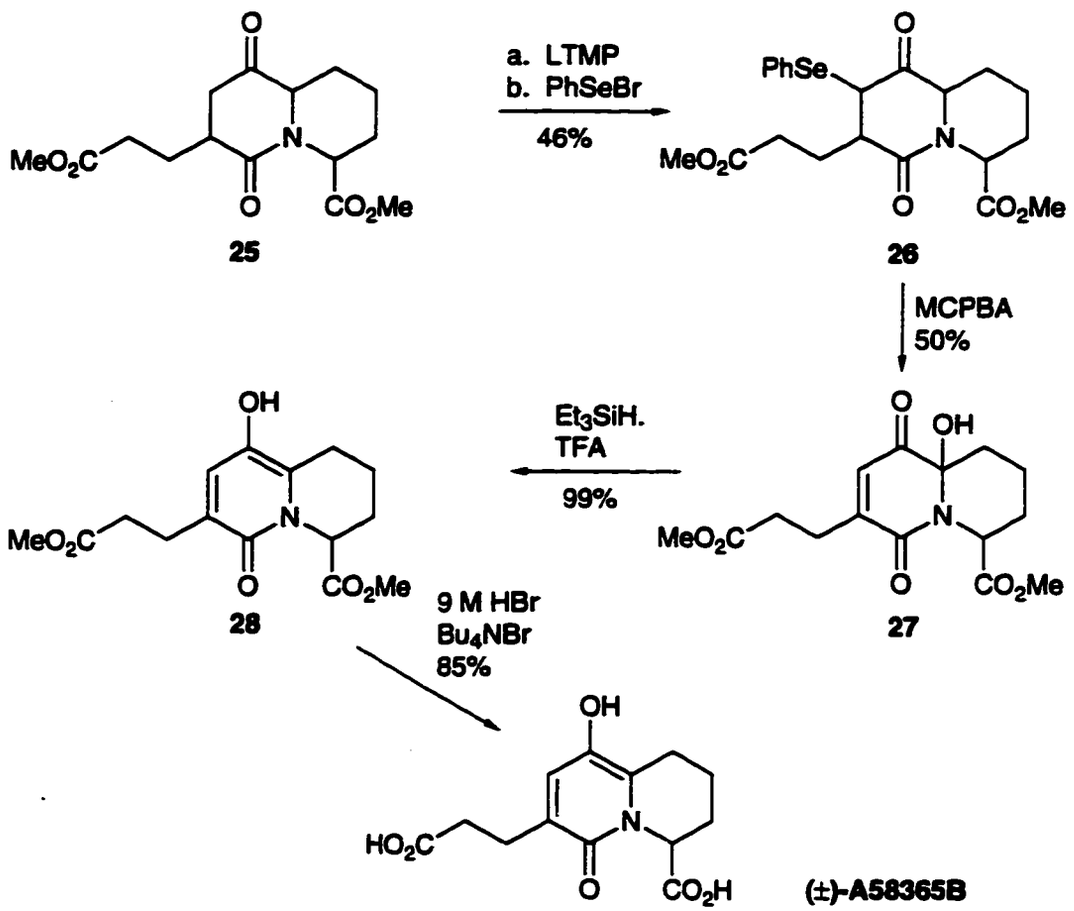
Key intermediate **23** for the anodic amide oxidation was prepared using the same chemistry as described above for the preparation of substrate **17**. Then anodic amide oxidation,

cyclization induced by titanium tetrachloride, and ozonolysis led to compound **25** (**Scheme 6**).




**Scheme 6**

The ketone **25** was treated with lithium 2,2,6,6-tetramethylpiperidide as the base, and the resulting enolate was quenched with benzeneselenenyl bromide; the selenated product **26** was obtained. Treatment of **26** with MCPBA led to formation of product **27**. This over-oxidized product **27** could be reduced to the desired compound **28** by using triethylsilane and TFA. The synthesis was completed by treatment of **28** with 9 N HBr, so as to obtain the natural product (±)-A58365B (**Scheme 7**).

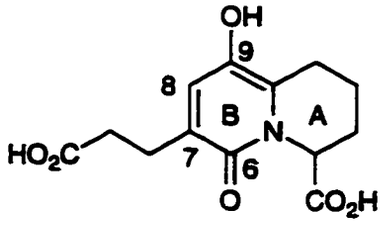

a. LTMP
b. PhSeBr
46%
PhSe
MeO2C
CO2Me
25
26
MCPBA
50%
Et3SiH.
TFA
99%
OH
28
27
9 M HBr
Bu4NBr
85%
HO2C
CO2H
(±)-A58365B

**Scheme 7**

## (II) Results and Discussion

### Part 1 Attempted Synthetic Approaches to (±)-A58365B.

*Synthetic Plan*

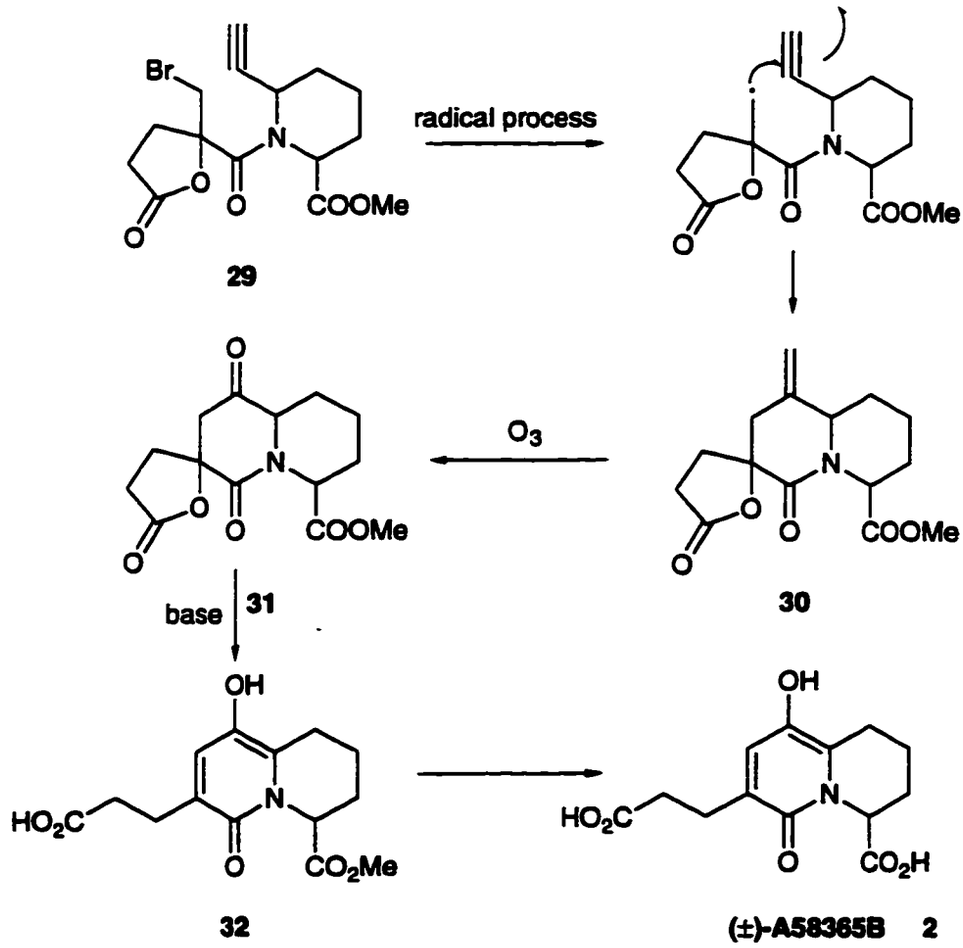



**(±)-A58365B 2**

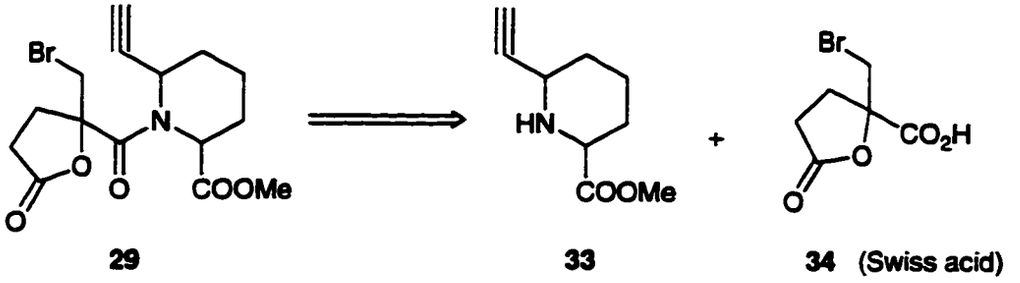
The structure of (±)-A58365B (compound **2**) does not appear to be especially complicated, but synthetic work, both our own and that done earlier,[15,16] revealed a number of unexpected difficulties. In particular, generation of the C(7)-C(8) double bond of **2** is not at all straightforward because ring A is also susceptible to desaturation. Therefore, routes that call for introduction of that double bond late in the synthesis do not seem to be highly promising. After appreciable exploratory work, we were led to the use of a radical process to construct ring B, in a sequence by which the C(7)-C(8) unsaturation is introduced early — although in the disguised form of a spirolactone. Considering all of these factors, we decided to build the molecule **29**.

We hoped that the acetylenic lactone **29**, representing the basic features of the target, including the propionic side chain, could be cyclized by a radical process to produce

the exocyclic olefin **30**. Ozonolysis of olefin **30**, followed by opening of lactone **31** and hydrolysis of the mono-methyl ester **32** should then lead to the natural product (±)-A58365B (**Scheme 8**). Our plan was to synthesize the key intermediate **29** from acetylene amine **33** and the known acid **34** (which we call the "Swiss acid")[17,18] (**Scheme 9**).



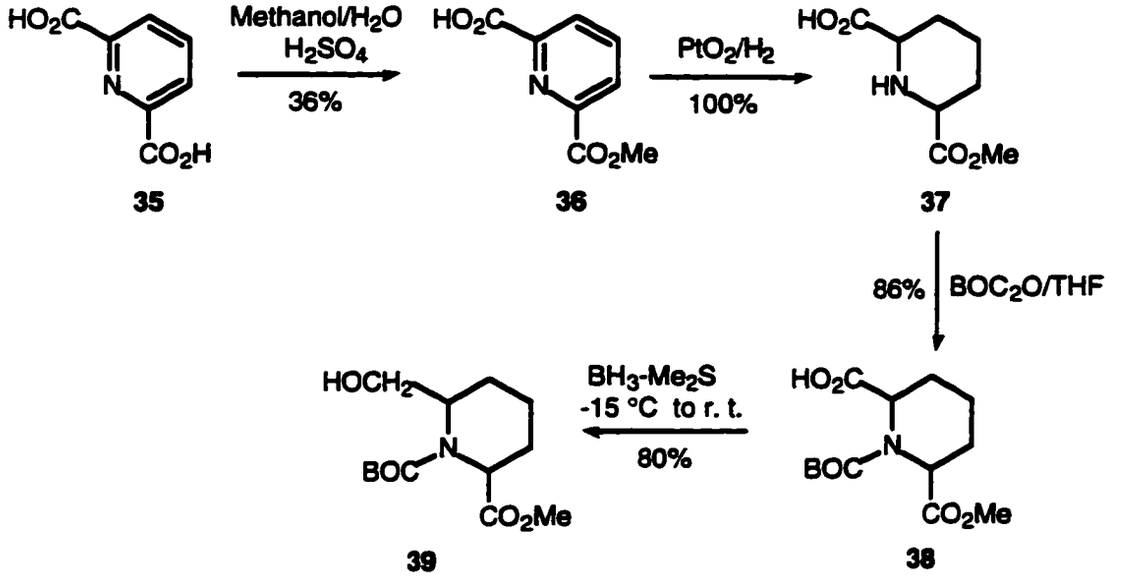

**Scheme 8**




29 33 34 (Swiss acid)

**Scheme 9**

*First Approach*



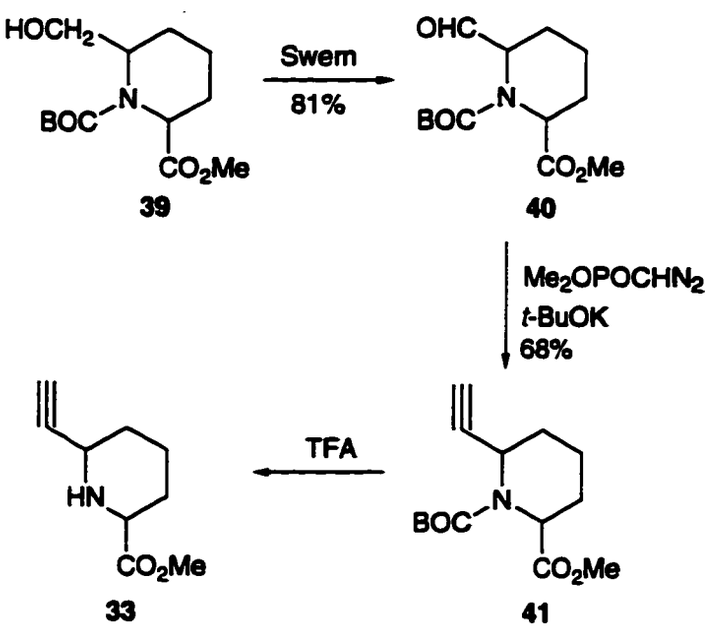

35 36 37 39 38

**Scheme 10**

Preparation of acetylenic amine **33** proceeded without incident. We started with commercial pyridine 2,6-dicarboxylic acid (**35**). When this was treated with a mixture of methanol and water in the presence of sulfuric acid, mono-methyl ester **36** and the corresponding bis-methyl ester were formed in 36% and 30% yield, respectively. Saturation of the aromatic ring of compound **36** was done by hydrogenation in the

presence of $PtO_2$ as catalyst, and the amino acid **37** was obtained in almost quantitative yield. Refluxing the amino acid **37** with di-*tert*-butyl dicarbonate ($BOC_2O$) in THF led to formation of the protected amino acid **38**.

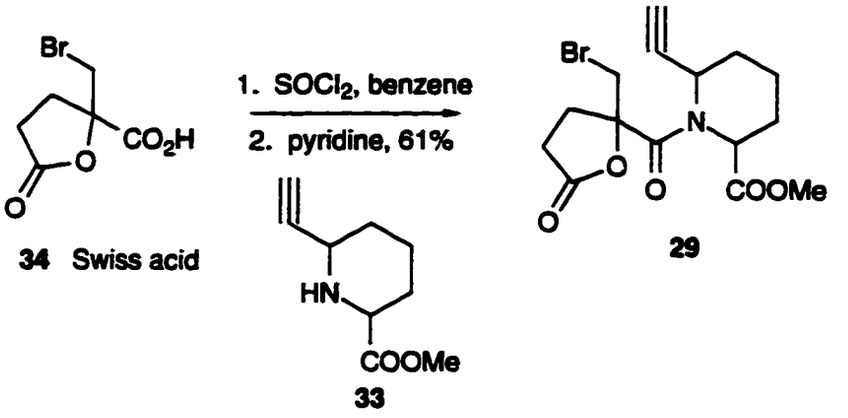
Some difficulty was encountered in reducing acid **38** to alcohol **39**. Following a literature[19] procedure, we used borane-tetrahydrofuran – a standard method for reducing an acid to the corresponding alcohol – but we did not isolate any product in our case. Then borane-dimethyl sulfide[20] was tried, but only a 30% yield of the desired compound **39** was obtained. Unlike many other alcohols, compound **39** was difficult to detect by TLC, and so it was difficult to monitor the reaction. Many experiments were done in an effort to improve the yield, and it was eventually found that the reaction is best done in the presence of excess borane-dimethyl sulfide at -15 °C to room temperature. At least 2 mole of reducing reagent are required in order to compensate for complexation of one equivalent of the reagent by the nitrogen. When done under optimum conditions, it is possible to isolate **39** in 80% yield. The reaction is also very sensitive to the quality of the reagent, and more than 2 mol of reagent are required if the reagent is not fresh (**Scheme 10**).




**Scheme 11**

Alcohol **39** was oxidized by the Swern method and two isomers of aldehyde **40** were obtained (81%) in a ratio of 15:1. The chromatographically faster-running isomer was the major product, and only this material was used in further synthetic work. Next, acetylene **41** was made from aldehyde **40** (major isomer) following a general methodology reported in the literature[21,22] According to this method, the reagent dimethyl diazomethylphosphonate was prepared and purified by distillation under vacuum. We found that the reagent tended to explode during distillation (fortunately done on a small scale!). For safety reasons, the crude reagent was used in our work, and acetylene **41** was obtained in 75% yield. The reaction product **41** and the starting material **39** had the same $R_f$ on TLC when 3:7-EtOAc-hexane was used. Finally, the acetylenic amine **33** was obtained in good yield after

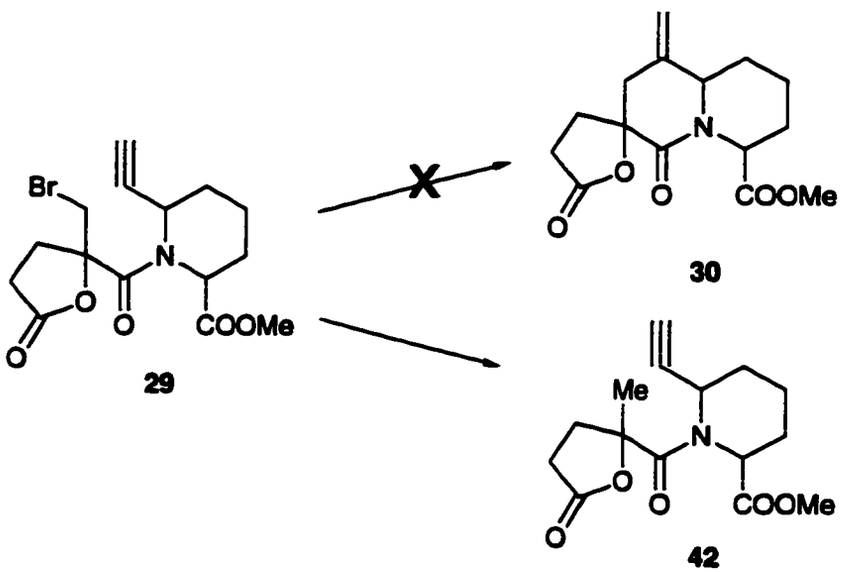
deprotection of the nitrogen (**Scheme 11**).




**Scheme 12**

In coupling amine **33** and the Swiss acid, we first tried DCC as the coupling agent, but did not isolate any of the desired product. Usually, primary amines are used in DCC coupling reactions, but in our case, the amine **33** is secondary and, therefore, less reactive. In addition, Swiss acid **34** is very hindered, and this would make the coupling reaction more difficult. Coupling of the two subunits was eventually achieved by treating amine **33** with the acid chloride derived from the Swiss acid, and the desired product **29** was obtained (61%) as a mixture of two isomers, which could not be separated by chromatography (**Scheme 12**).

Unfortunately, radical cyclization of **29** did not proceed as we had expected. Under a variety of different conditions (**Scheme 13**), none of the cyclized compound **30** was observed, and only the reduced compound **42** was isolated.

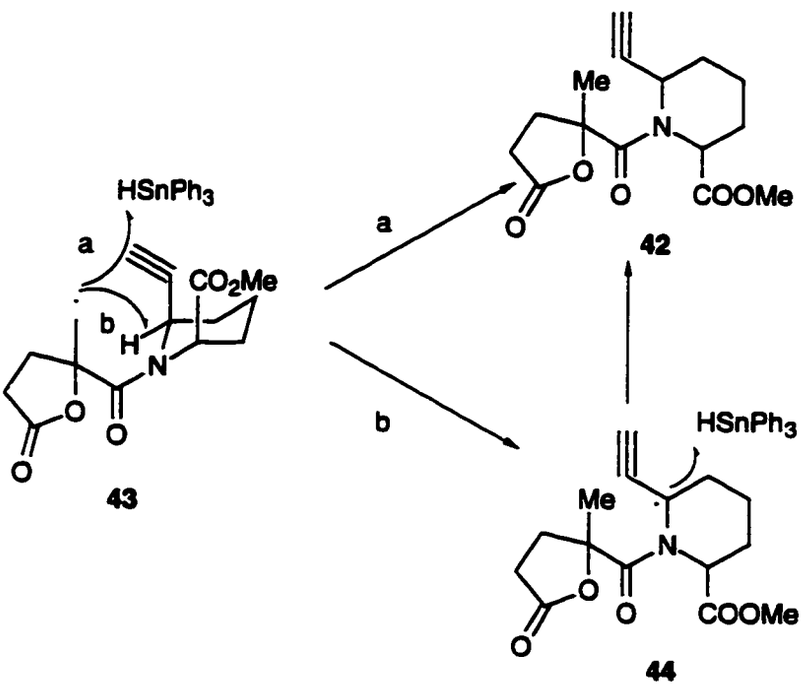



| Radical conditions | |
|---|---|
| $Ph_3SnH$, AIBN | benzene ( reflux, slow addition) |
| $Ph_3SnH$, AIBN | toluene (reflux, slow addition) |
| $Bu_3SnH$, AIBN | benzene ( reflux, slow addition) |
| $Bu_3SnH$, AIBN | toluene (reflux, slow addition) |
| $Ph_3SnH$, $Et_3B$ | benzene (r. t.) |

**Scheme 13**

Formation of the reduction product might be due to the conformation of **29**. Based on the experimental result, we assume that the acetylene group is in the axial conformation. When radical **43** is generated, it abstracts hydrogen from triphenyltin hydride, or gives radical **44** by intramolecular hydrogen-transfer – a process which is often a competitive side reaction in six-*exo* cyclizations.[23] Radical **44** would be stabilized by two resonance structures involving the acetylene and nitrogen. Both pathways (see *a* and *b* in **Scheme 14**) lead to formation of compound **42**, and so we

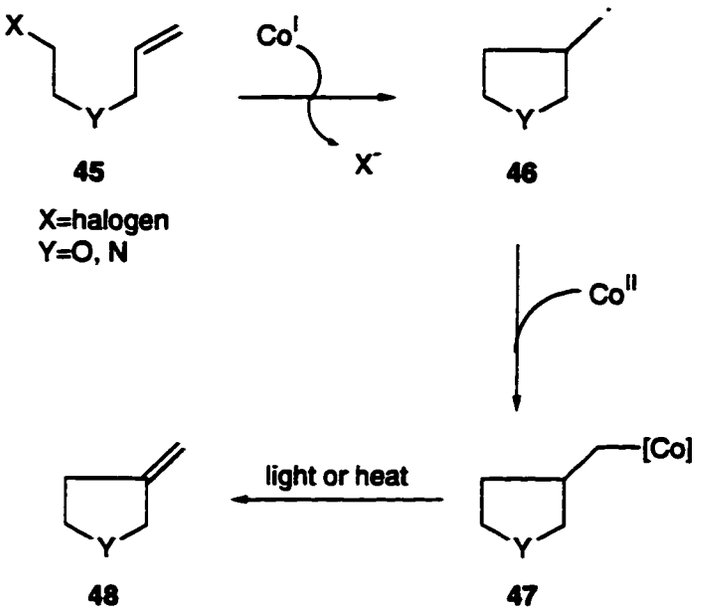
decided to embark on another approach to our target molecule.




**Scheme 14**

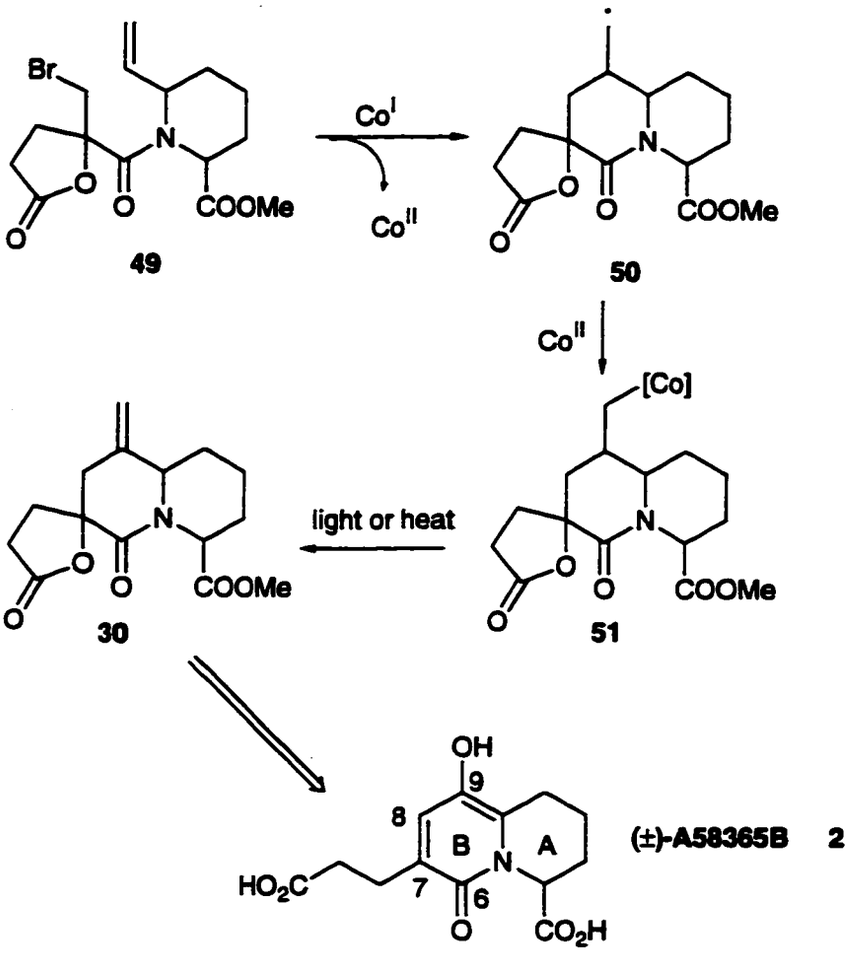
*Second Approach*

Cobalt-mediated radical cyclization has been reported to be a powerful synthetic method to form C-C bonds.[24-30] These reactions proceed via electron transfer from a cobalt(I) species to the carbon-halogen bond in the substrate (**45**), followed by (i) intramolecular cyclization, (ii) *in situ* trapping of the product radical center **46** with Co(II), and (iii) dehydrocobaltation (1,2-elimination) (**Scheme 15**).



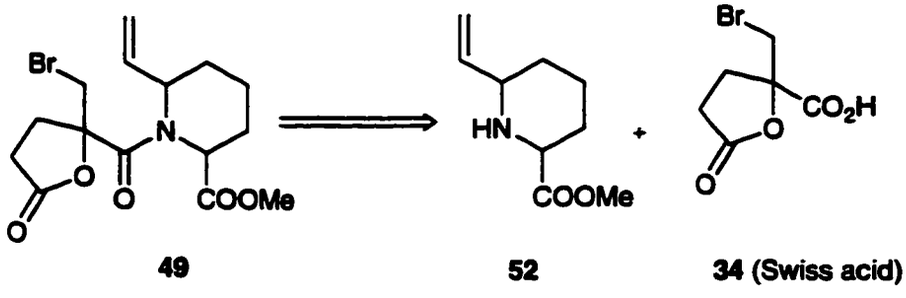

**Scheme 15**

In our second approach, we decided to try this method for construction of ring B in A58365B (**2**). This synthetic strategy would require building the lactone olefin **49**. Intramolecular radical cyclization, brought about by use of Co(I), followed by trapping of the radical intermediate, would form the organocobalt compound **51**. Dehydrocobaltation of **51** by either irradiation or heating could generate the exocyclic olefin **30**, from which the natural product **2** should be accessible, after ozonolysis and treatment with base (**Scheme 16**).



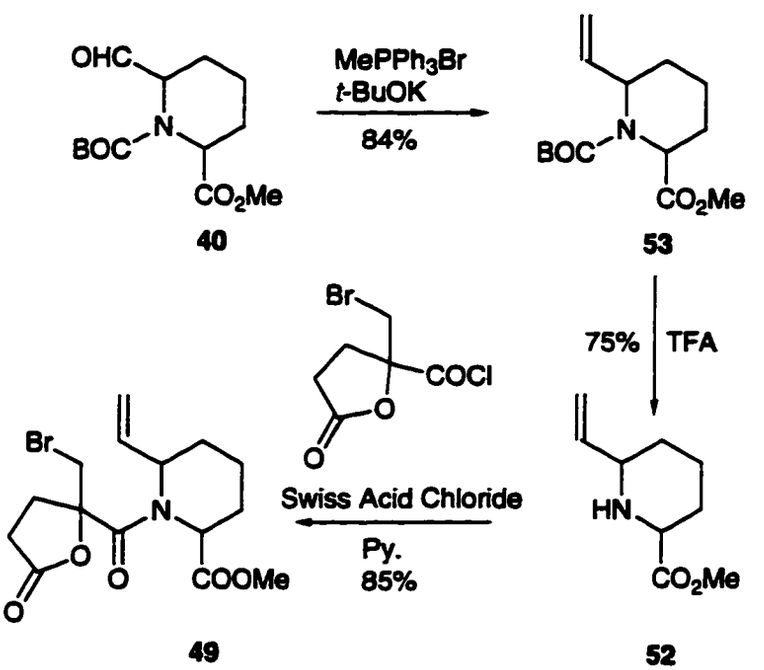

**Scheme 16**

As can be seen, compound **49** can be disconnected into two simple precursors, Swiss acid **34** and amine **52** (**Scheme 17**).



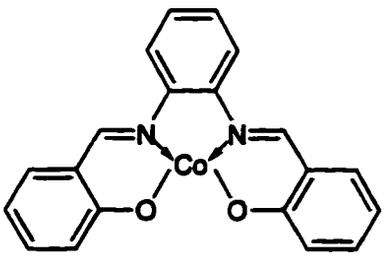

**Scheme 17**

Amine **52** was synthesized by a two-step procedure. Aldehyde **40** (major isomer) was converted into olefin **53** by Wittig reaction (84%), and then the BOC group was removed by the action of TFA (75%). Coupling of amine **52** and Swiss acid chloride led to formation of **49** (85%) as two fractions. These can be separated by chromatography (**Scheme 18**).

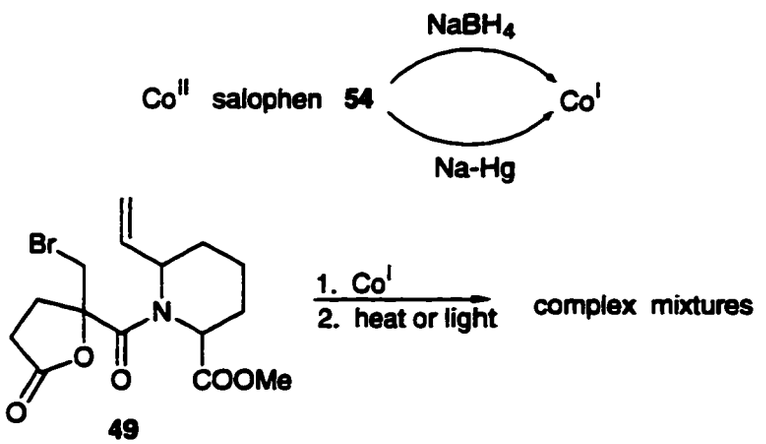



**Scheme 18**

The individual isomers of **49** were treated with Co(I), generated by reaction of Co(II) salophen **54**[31] and reducing reagents, such as $NaBH_4$[32] or sodium amalgam.[33] After a reaction period of 16 hours in the dark, the intermediate was either heated or irradiated, but only complex mixtures were obtained from this experiment (**Scheme 19**).

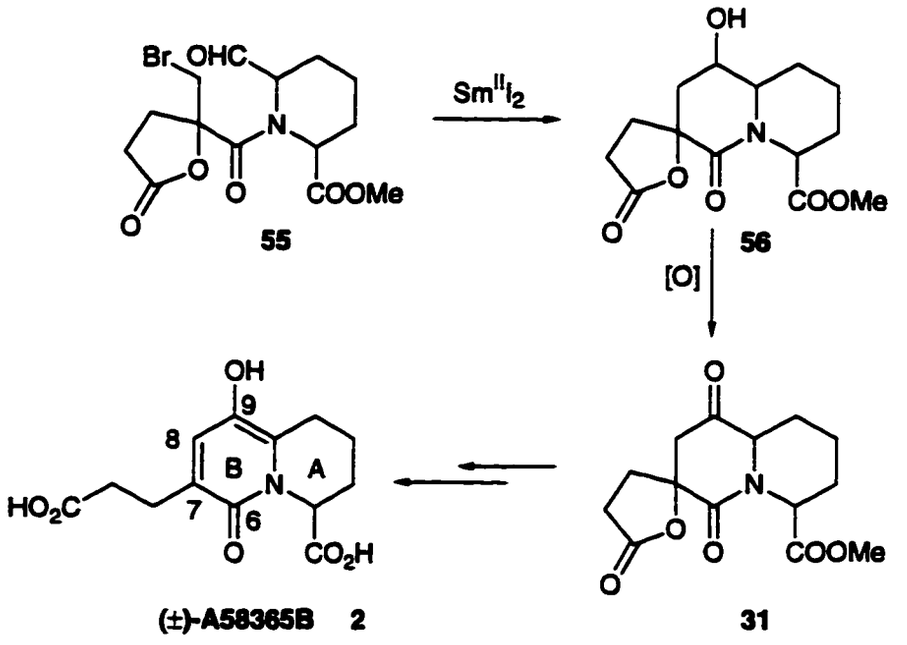


$Co^{II}$ salophen **54**



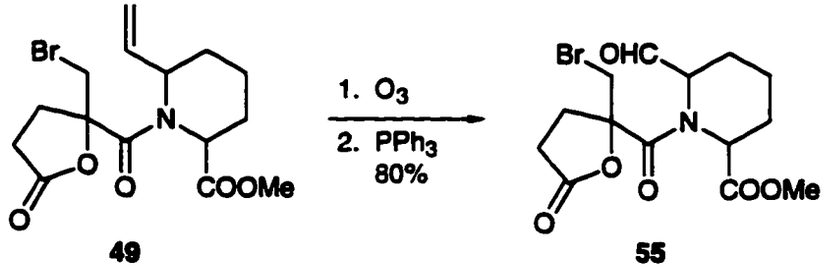

**Scheme 19**

A different, but related, procedure was explored to form ring B. For this strategy, aldehyde **55** was required. Sm(II)-mediated[34-37] cyclization of aldehyde **55**, followed by oxidation, could led to ketone **31**, which should be convertible into A58365B (**2**) in two steps (**Scheme 20**).




**Scheme 20**

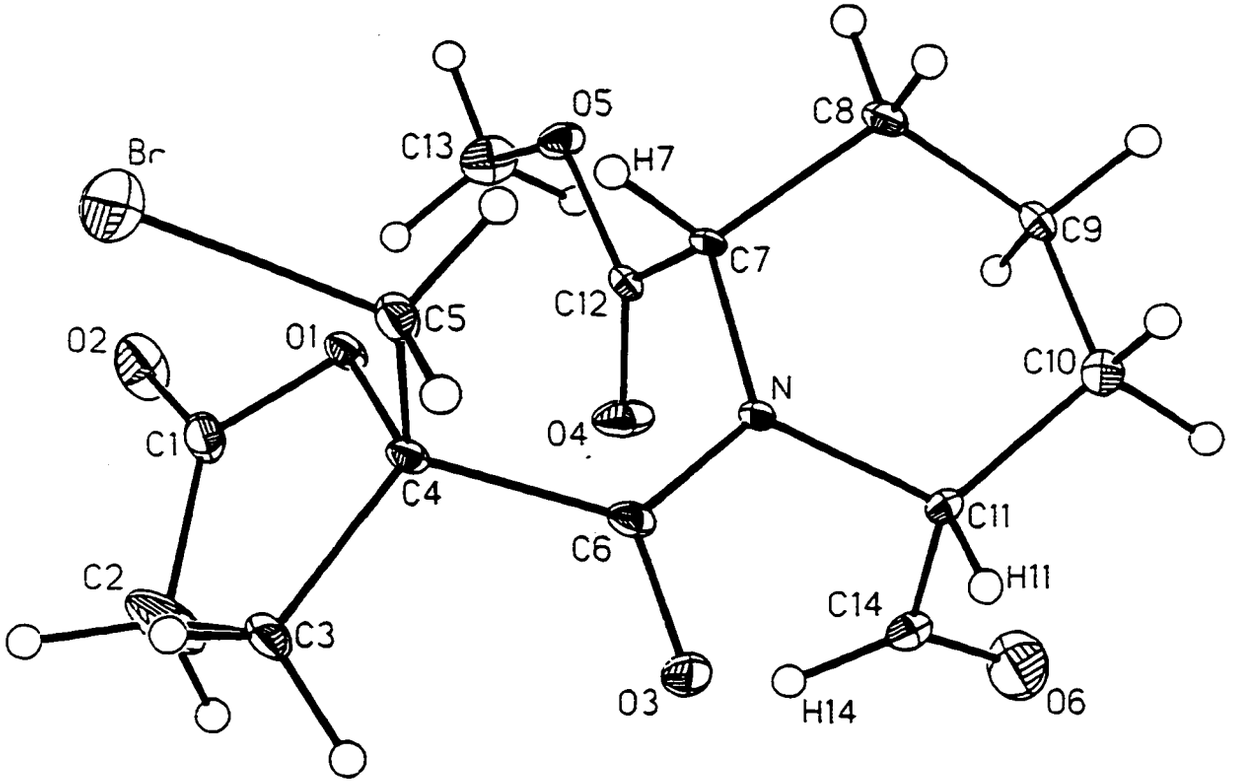
The two isomers of aldehyde **55** were obtained from **49** by ozonolysis (80%), the isomer ratio being 1:3 (**Scheme 21**). The chromatographically slower-running isomer (major product) of **55** was a mixture of rotamers and very unstable. The chromatographically faster-running isomer was just a single compound, and could be crystallized from 1:1 EtOAc-hexane.

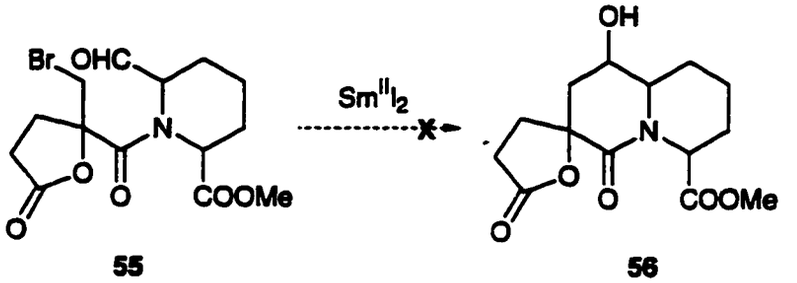



**Scheme 21**

X-ray analysis of this material (the faster-running

isomer of **55**) revealed that both ester and aldehyde groups were *cis* to each other and also that both of them occupied an axial conformation.



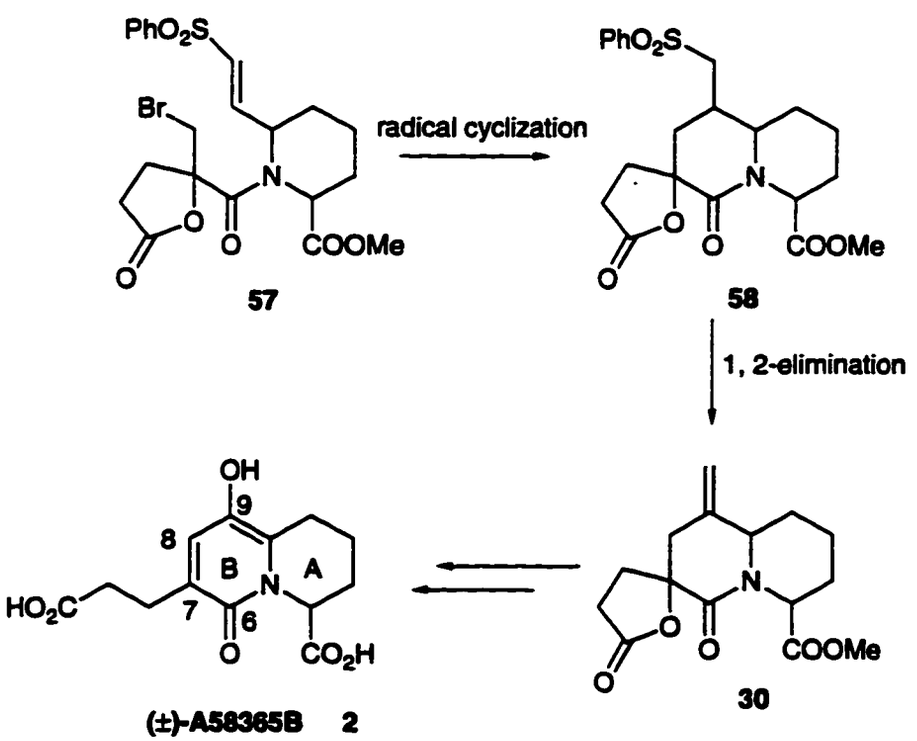

**55** **56**

**Scheme 22**

The individual isomers of **55** were treated with $SmI_2$, but only complex mixtures were obtained (**Scheme 22**), and we realized, of course, that this approach was not promising.

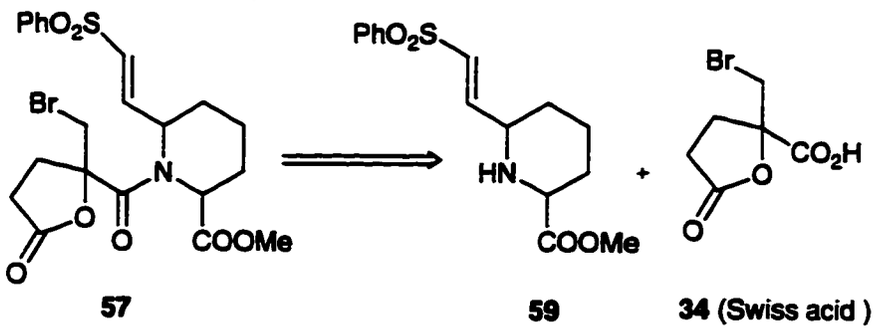
*Third Approach*

As discussed above, all attempts to make B ring in compound **2** were unsuccessful, and we next considered the possibility of radical cyclization, by using substrate **57**. As shown in **Scheme 23**, 6-*exo* radical cyclization of **57**, followed by 1,2-elimination, would lead to olefin **30**, which could subsequently be elaborated into A58365B (**2**).



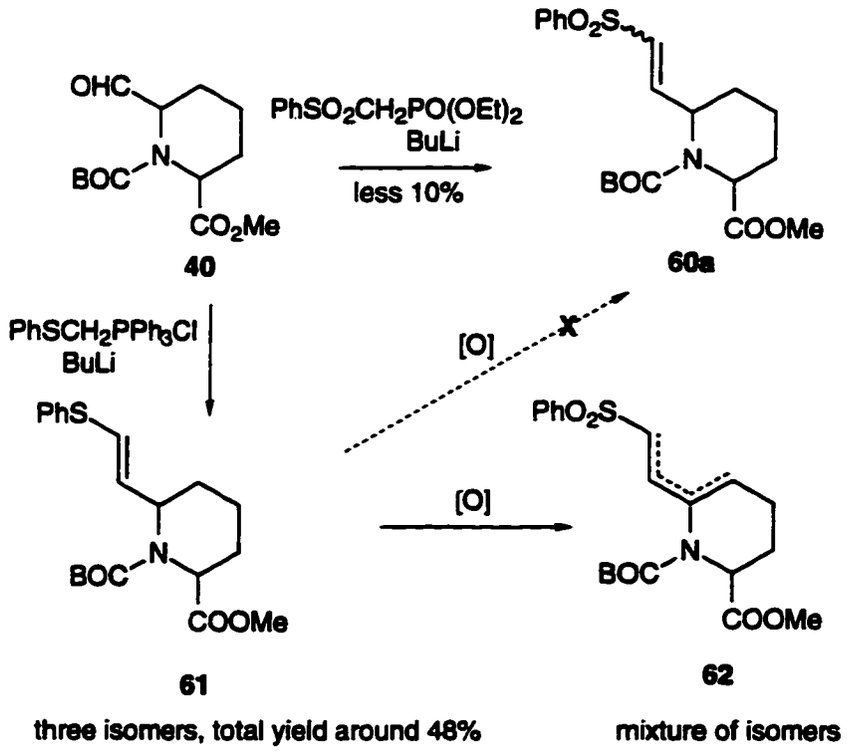

**Scheme 23**

From a retrosynthetic standpoint, compound **57** could be built by joining amine **59** and Swiss acid **34** (**Scheme 24**).




**Scheme 24**

Amine **59** appears to have a very simple structure, but our attempts to make it were not successful.

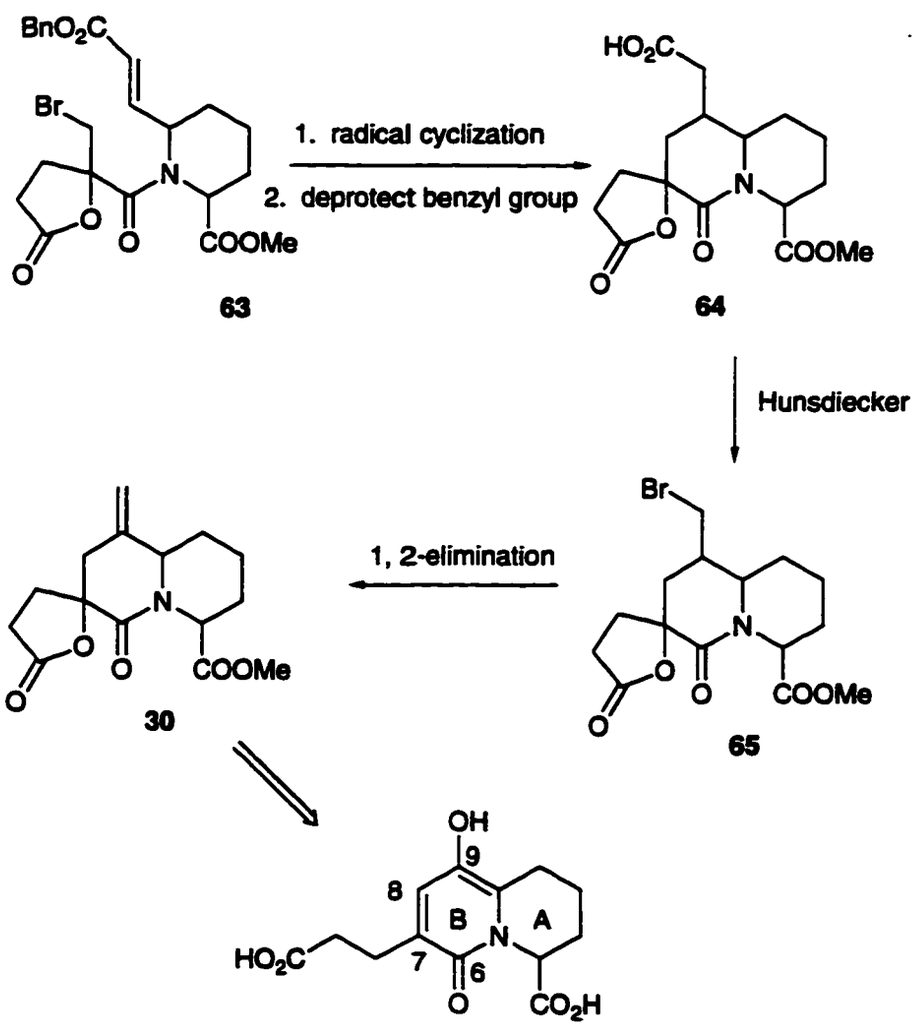



**Scheme 25**

We tried to prepare compound **60a** by the Horner-Emmons method,[38] but less than 10% of the desired compound was

obtained. We also attempted an alternative pathway, by generating compound **61** first, and then converting it into **60**. Unfortunately, the oxidation step did not appear to give us the desired product (the sulfone) because of double bond migration (**Scheme 25**).

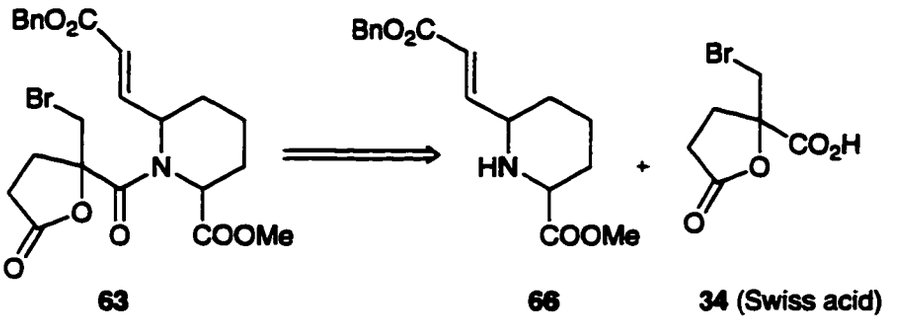
Another approach to form ring B is related to the chemistry of **Scheme 23**, and is summarized in **Scheme 26**.




**(±)-A58365B 2**

**Scheme 26**

We hoped that radical cyclization of precursor **63**, followed by deprotection of the benzyl group, would lead to carboxylic acid **64**. Conversion of **64** into **65** would then be done by the Hunsdiecker method, and 1,2-elimination of **65** could then provide us with the desired olefin **30** (**Scheme 26**). It seemed that radical precursor **63** could be assembled from two components, amine **66** and Swiss acid **34** (**Scheme 27**).



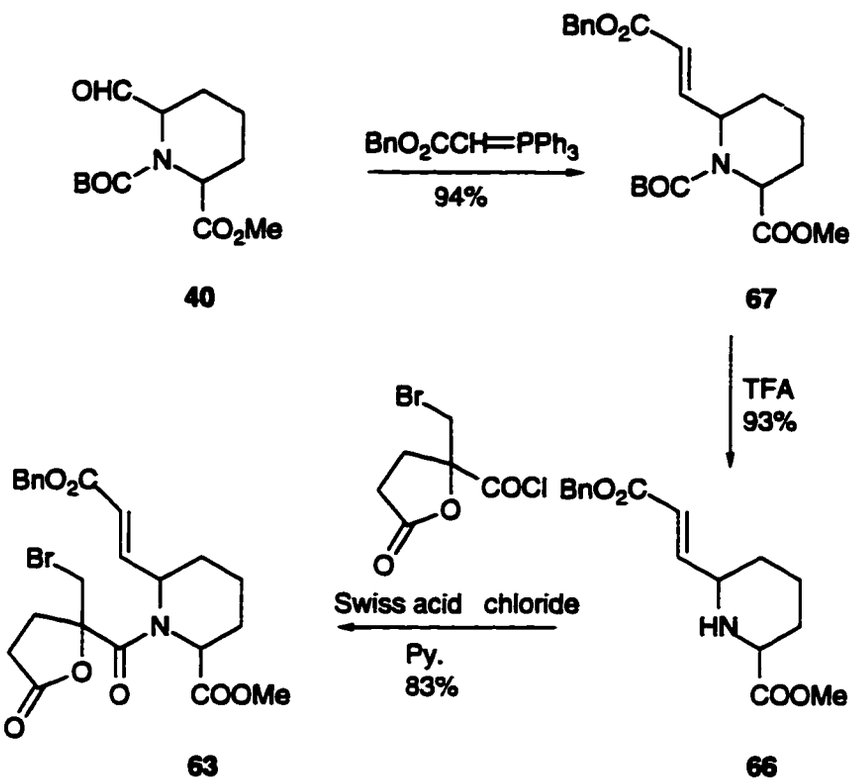

**63** **66** **34 (Swiss acid)**

**Scheme 27**

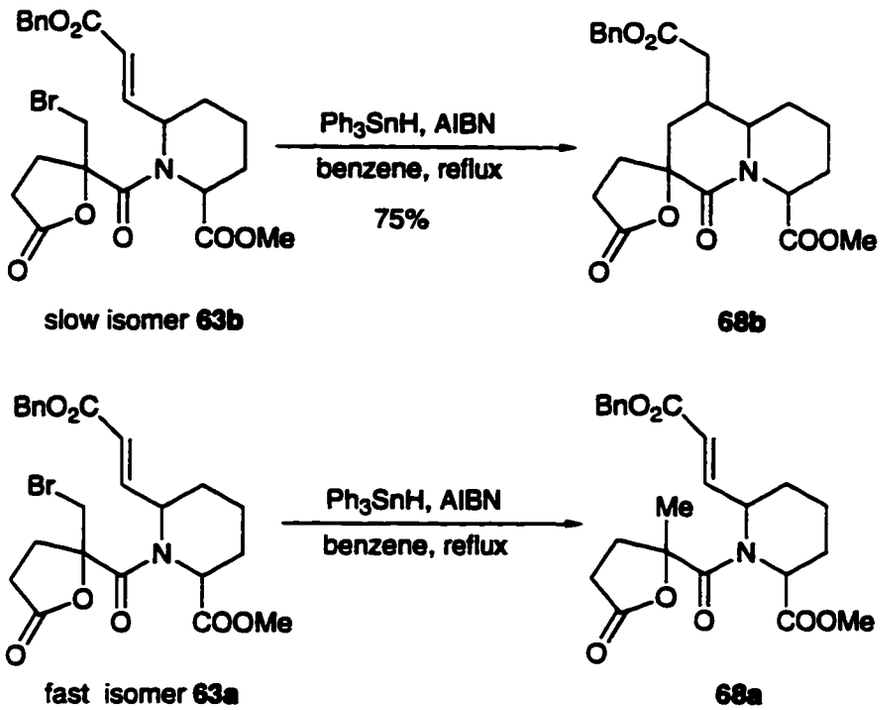
**Scheme 28** shows the route leading to **63**. Aldehyde **40** (major isomer) was treated with dry $BnOOCCH{=}PPh_3$, prepared from a 1 N solution of sodium hydroxide and $BnOOCCH_2PPh_3Br$, followed by azeotropic drying with benzene. The conjugated benzyl ester **67** was generated in 94%.[39,40]

Removal of the BOC group of **67** was accomplished by treatment with dry TFA (93%). After that, coupling of amine **66** and Swiss acid chloride led to formation of the desired product **63** as two chromatographically separable isomers in a ratio of 4:6 (total yield 83%) (**Scheme 28**). The chromatographically slower-running material was the major

isomer. Based on the $^{1}H$ and $^{13}C$ NMR spectra, the faster-running isomer was a single compound, and the other one was a mixture of rotamers.



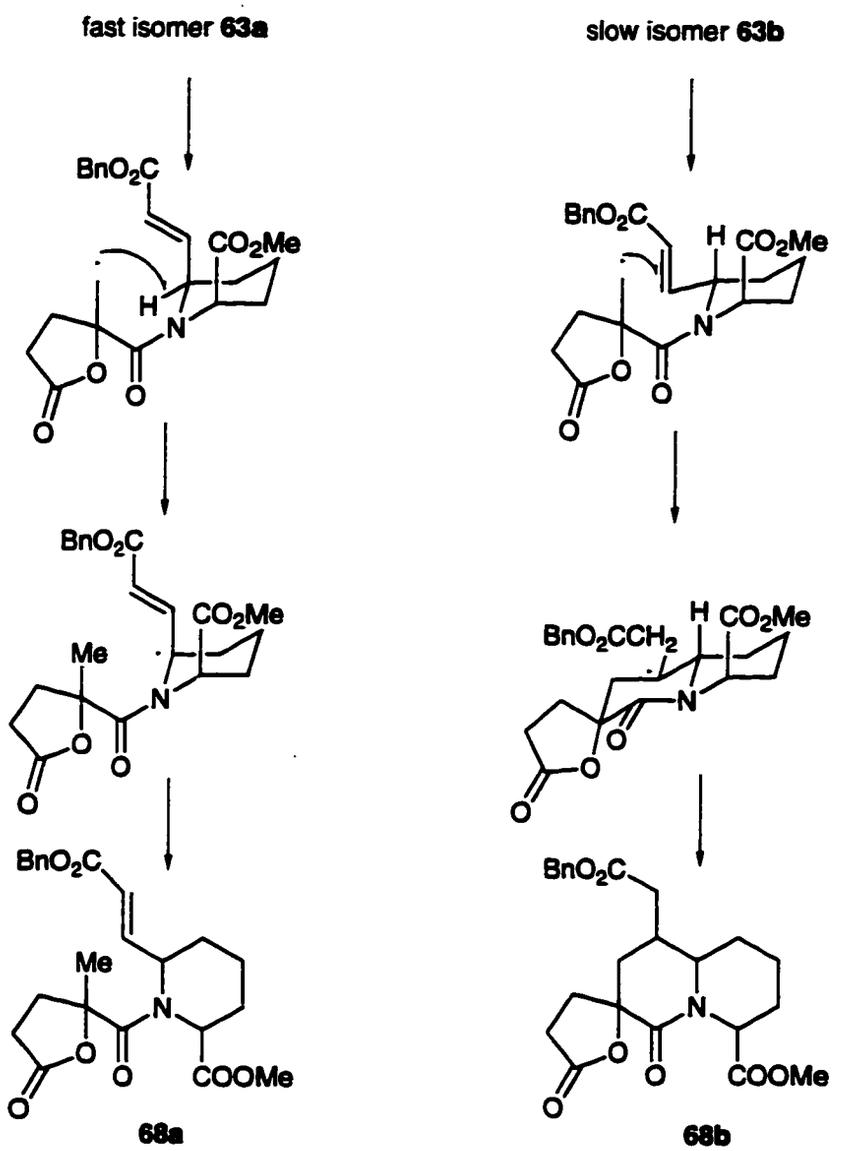

**Scheme 28**




**Scheme 29**

However, when the individual fractions of **63** were treated with triphenyltin hydride and AIBN under standard thermal conditions, the ring closure product **68b** was obtained only from the slower-running material **63b** (in 75% yield), and the faster-running isomer produced only the reduction product **68a** (**Scheme 29**).

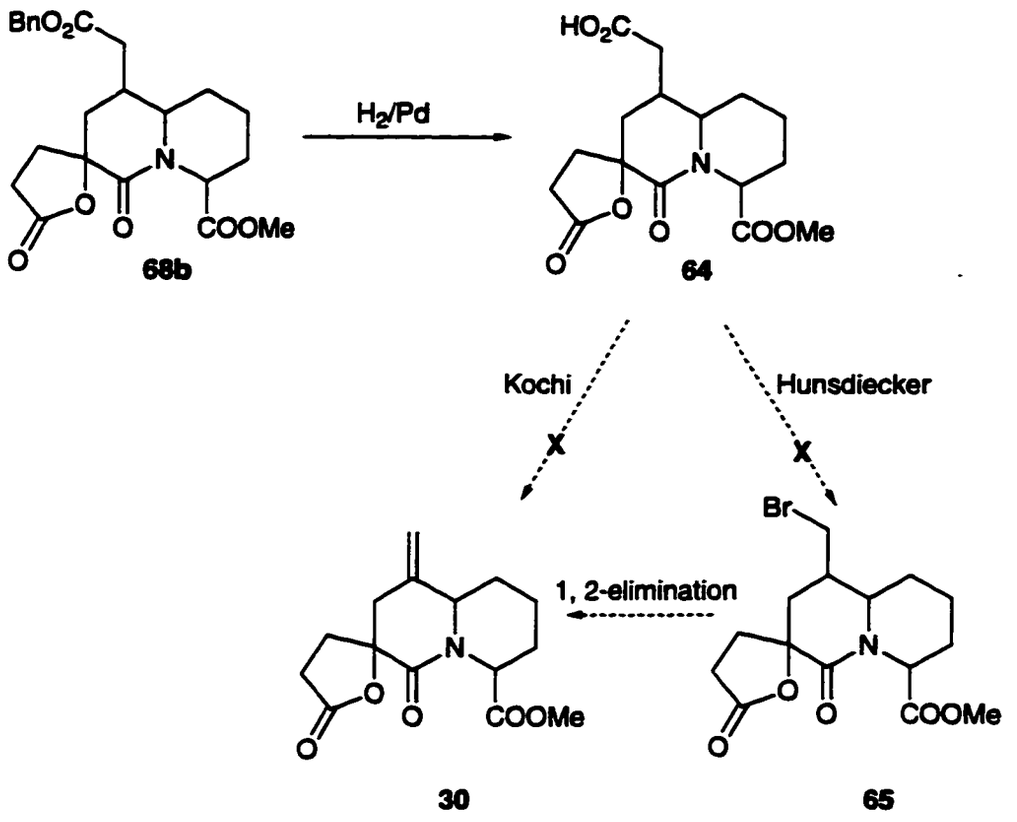
Based on the experimental results and the X-ray structure of aldehyde **55**, we believe that the relative stereochemistry of the conjugated benzyl ester and methyl ester in compound **63** is as shown in **Scheme 30**, for the two isomers.




**Scheme 30**

On this basis, if the conjugated benzyl ester in the faster-running isomer is in the axial conformation, then intramolecular hydrogen transfer occurs and leads to the reduced product **68a**. However, in the slower-running isomer, when this group is in an equatorial conformation, intramolecular hydrogen transfer is impossible as judged by inspection of Dreiding models, and radical cyclization occurs

to form the desired product **68b** (**Scheme 30**). As compound **66** is a single substance, isomerization must have occurred in the coupling step **66** → **63**, see **Scheme 28**).



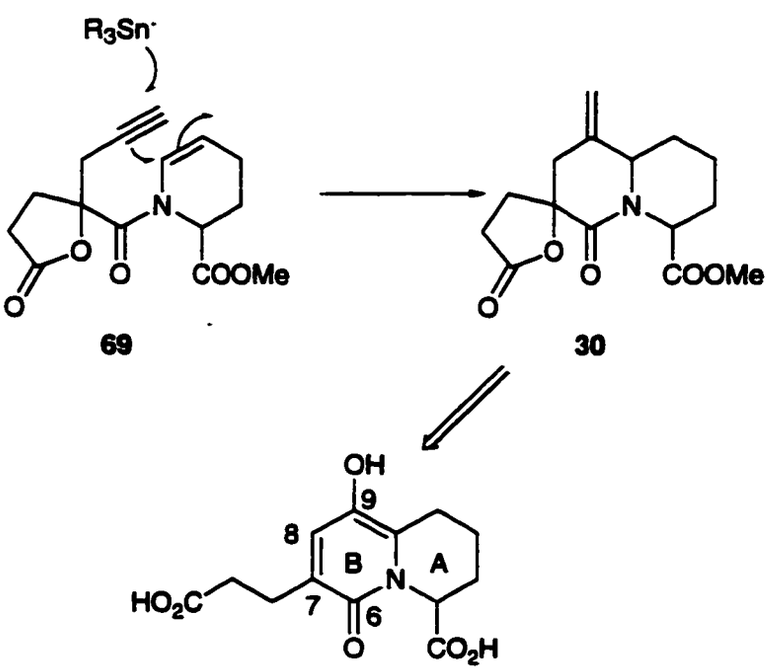

**Scheme 31**

Debenzylation of **68b** under standard conditions ($H_2$/Pd) afforded the carboxylic acid **64**, but all efforts to make the olefin **30** by Kochi's method[41,42] or to make **65** by Hunsdiecker reaction[43] were fruitless, and only complex mixtures were obtained (**Scheme 31**). This route was therefore also abandoned, and we embarked on an alternative which, in the event, led nicely to the desired racemic natural product.

## Part II – The Successful Route to (±)-A58365B.

*Synthetic Plan*

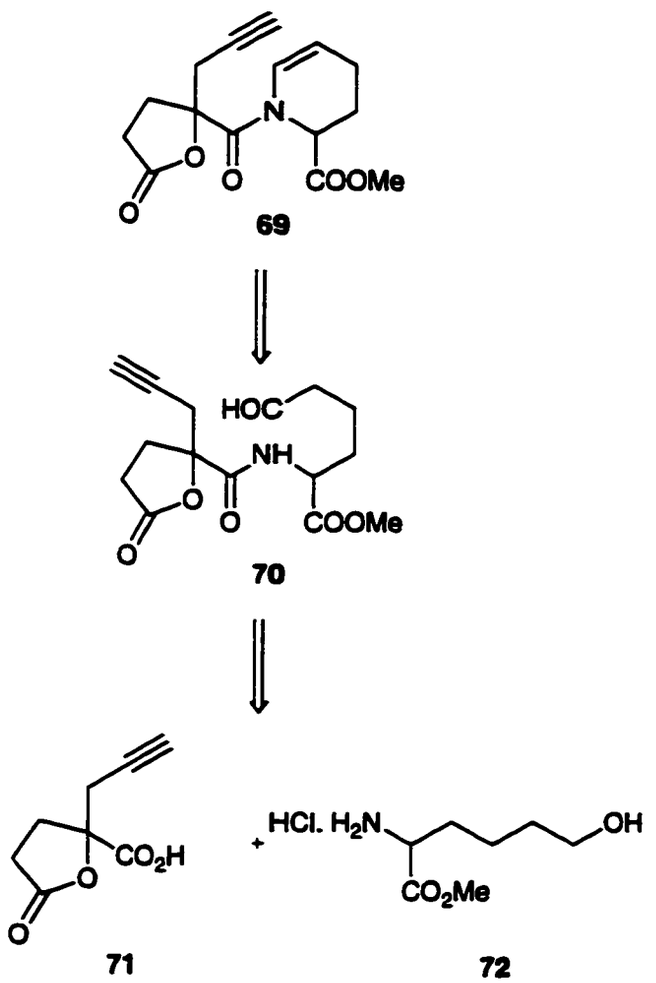
As indicated before, the structure of (±)-A58365B **2** does not appear to be especially complicated, but all our own extensive efforts to make it – those described above, as well as some others – had not been successful. We were eventually led to an approach in which the C(7)-C(8) unsaturation was introduced in the disguised form of a spirolactone, and ring B was formed by a process based on enyne radical cyclization (**Scheme 32**).




**Scheme 32**

Retrosynthetic analysis for the required intermediate

**69**, itself assembled from two pieces – lactone acid **71** and ε-hydroxynorleucine methyl ester **72** – is shown in **Scheme 33**.

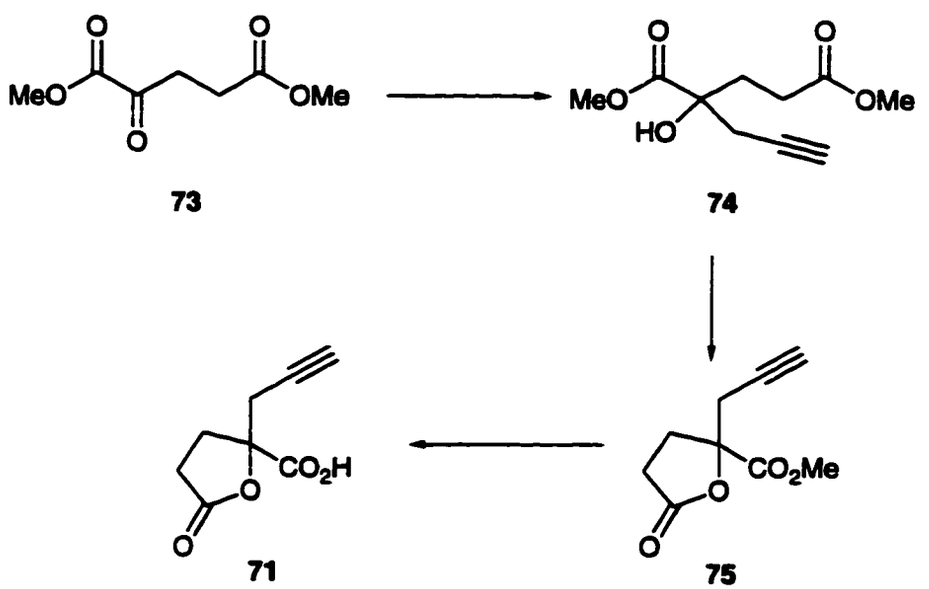



**Scheme 33**

Compound **71** represents all the carbons that make up the C(6)-C(9) segment of the natural product, including the propionic side chain. The ring A portion of (±)-A58365B was constructed from ε-hydroxynorleucine methyl ester[44] which had all the required atoms.

*Synthesis of Lactone Carboxylic Acid* **71**

In our attempt to make the lactone carboxylic acid **71**, we planned to synthesize tertiary alcohol **74**, which, we hoped could be elaborated into **71** by lactonization and hydrolysis (**Scheme 34**).

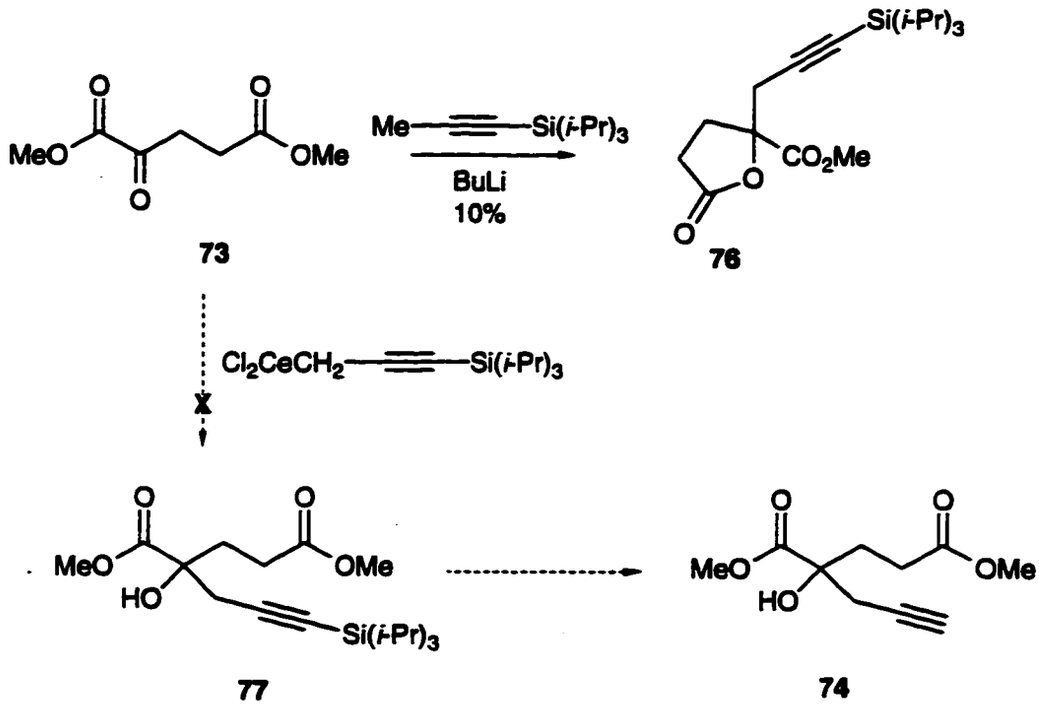



**73** **74** **71** **75**

**Scheme 34**

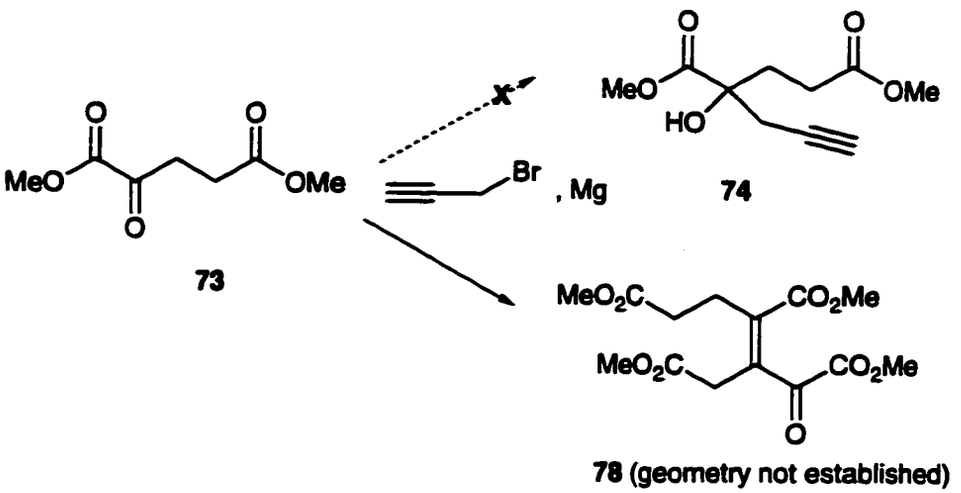
Converting **73** into **74** proved to be a very difficult task. Four methods were tried for the synthesis of alcohol **74**. The first one involved adding lithio-1-(triisopropylsilyl)propyne[45] to dimethyl α-ketoglutarate **73**, itself prepared from methanol and α-ketoglutaric acid in the presence of a catalytic amount of acid. Surprisingly lactone **76** (Scheme 35) was obtained directly, but the reaction was not useful for us due to the low yield (10%). In our second attempt, the cerium salt of 3-(triisopropylsilyl)propyne was generated following a literature procedure.[46] We hoped the

acetylide would add to the carbonyl group of **73** and generate **77**, but only a complex mixture was obtained from this reaction (**Scheme 35**).

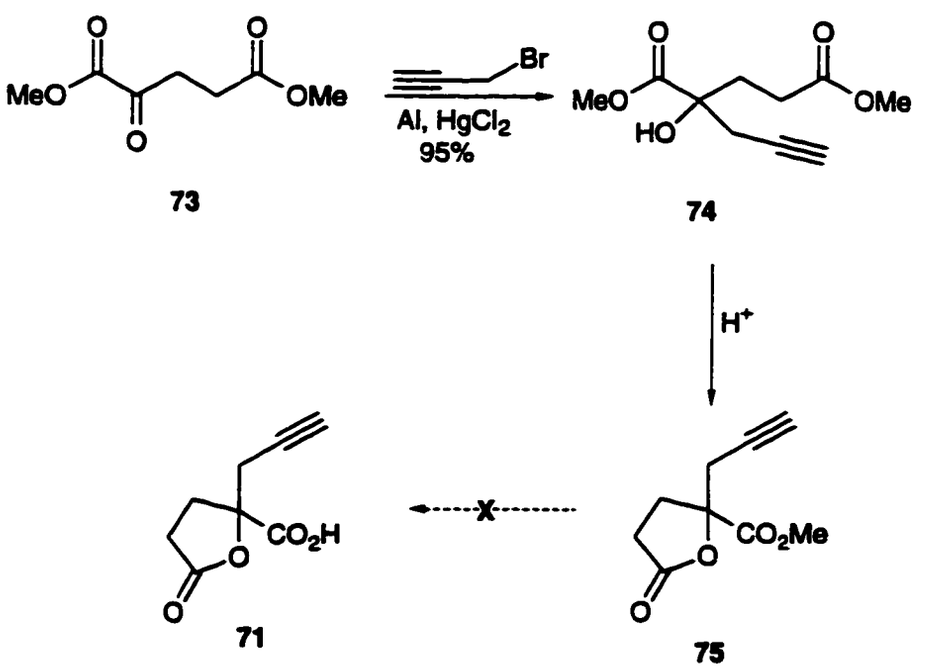



**scheme 35**

Use of a Grignard reagent was considered next.[47] Unfortunately, the starting material simply dimerized to form compound **78** (**Scheme 36**).




**Scheme 36**

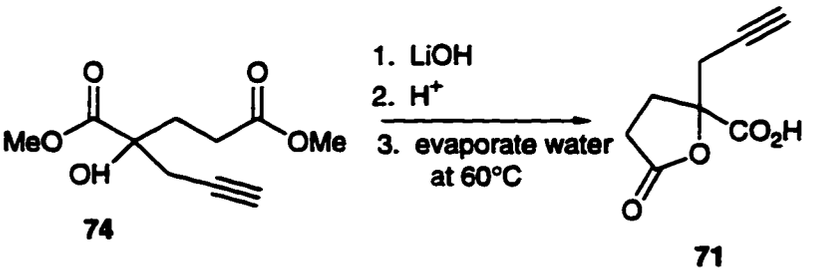



**scheme 37**

To our delight, we then found that the three-carbon side chain could be introduced by addition of propargylaluminum sesquibromide[48] solution to **73** in dry THF at -78 °C. Compound **74** was obtained in good yield (95%). Lactonization

did not pose any problem, but hydrolysis of methyl ester **75** was not successful. Many methods were tried to hydrolyze **75** into **71** [LiOH,[49] $(Bu_3Sn)_2O$,[50] $Me_3SiCl/NaI$[51] and $Ba(OH)_2$[52], but all of them gave complex mixtures (**Scheme 37**).

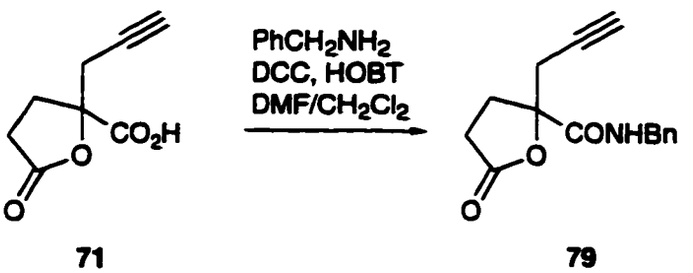
However, we eventually found that ester hydrolysis, liberation of the free hydroxy diacid by ion-exchange chromatography using Amberlite IR-120 (acid form), followed by evaporation of the resulting aqueous solution at 65 °C, directly converted the hydroxy diester **74** into lactone acid **71** in good yield (95%) (**Scheme 38**).




**74** **71**

**Scheme 38**

In order to confirm that the reaction in **Scheme 38** gave us lactone acid **71** and not the di-acid, we prepared the benzylamide derivative. In this reaction, the standard coupling method was followed, and **79** was obtained in 85% yield (**Scheme 39**). Now we were confident that we had the required lactone acid **71** in hand.



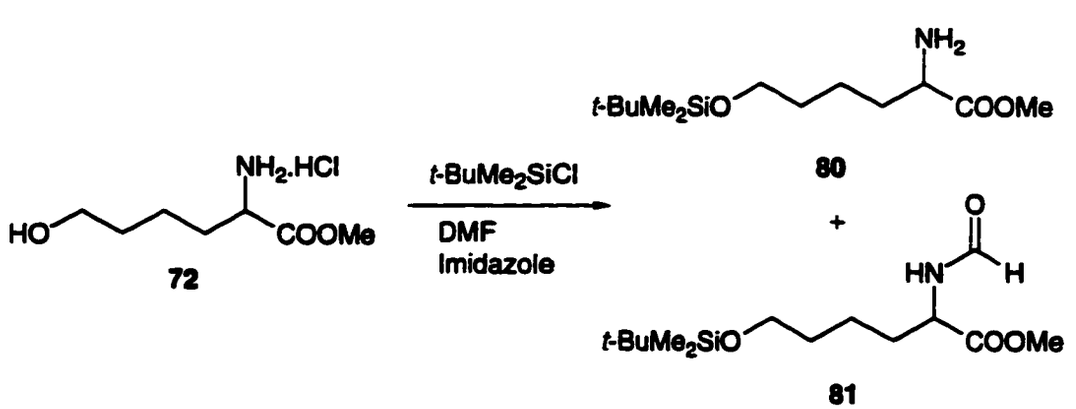

**71** **79**

**Scheme 39**

*Coupling of Lactone Acid* ***71*** *and ε-Hydroxynorleucine Methyl Ester* ***72***

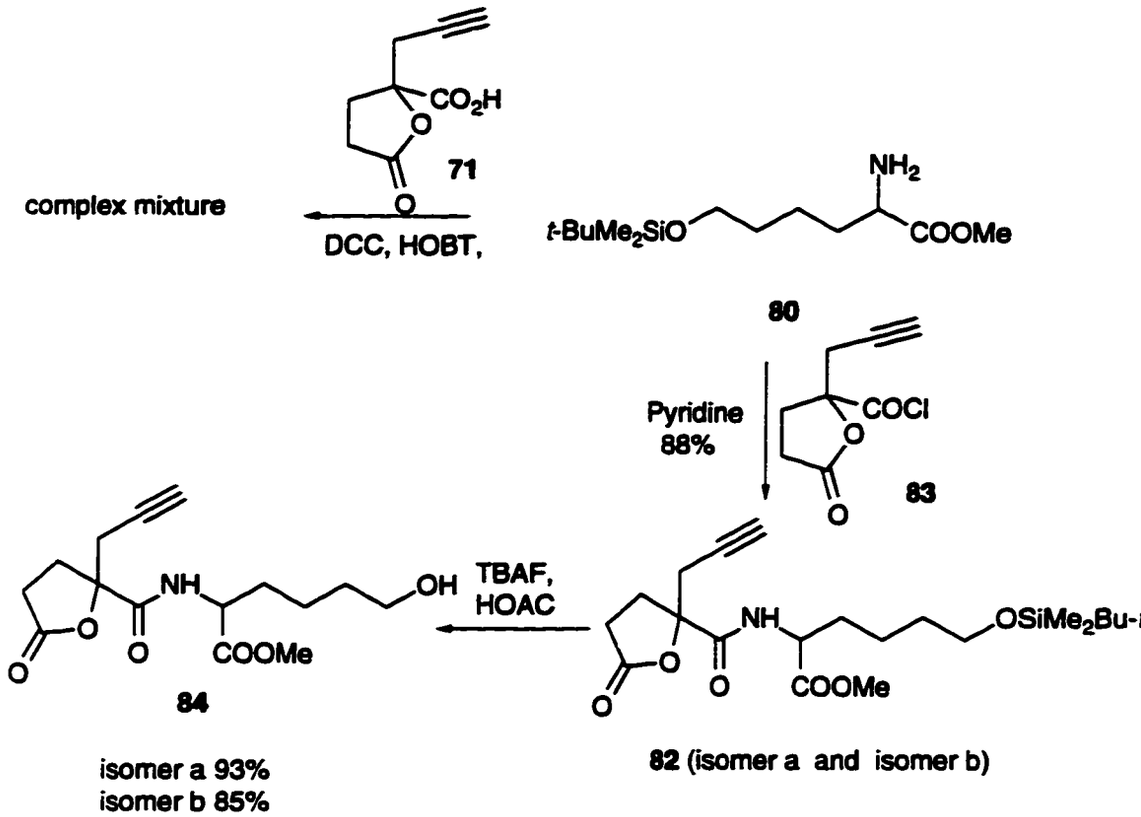
Three strategies were tried for coupling the lactone acid **71** and ε-hydroxynorleucine methyl ester hydrochloride salt **72**, itself prepared by treating ε-hydroxynorleucine with excess $Me_3SiCl$ in dry methanol.

In our first attempt, **72** was silylated in order to protect the free hydroxyl group, but the desired compound **80** was obtained in less than 38% yield along with the byproduct **81** (**Scheme 40**).




**72** **80** + **81**

**Scheme 40**

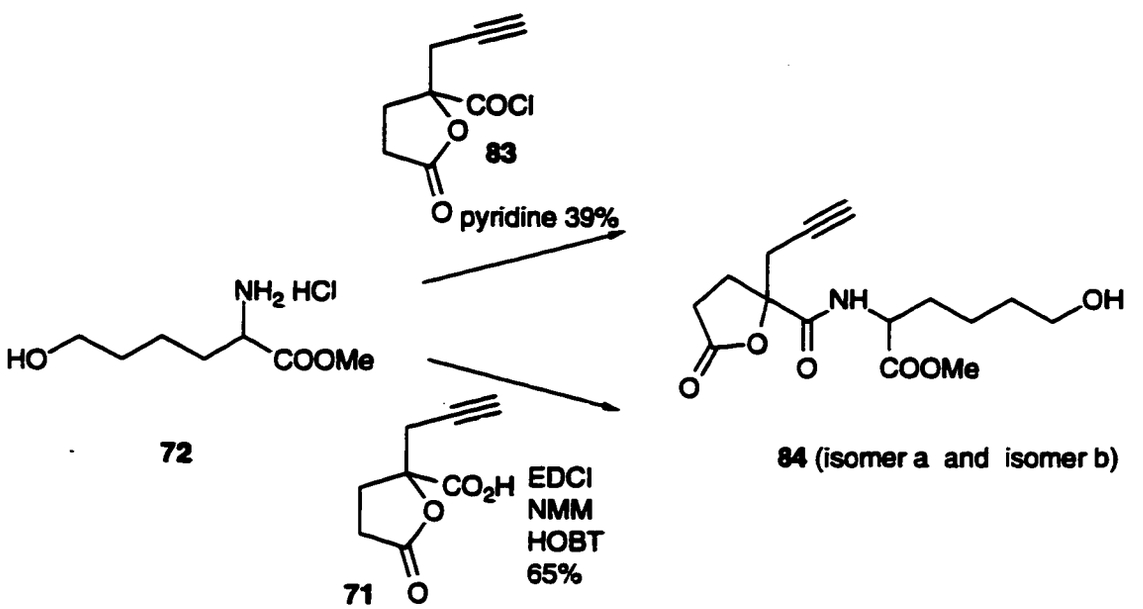



**Scheme 41**

Coupling of **71** and **80** under mild conditions (DCC, HOBT) gave a complex mixture, and, at this point, we decided to try more vigorous conditions. Reaction of **80** with lactone acid chloride **83** produced the coupled compound **82** as mixture of two isomers (88%), **82a** (major) and **82b** (minor) in a ratio of 7:3. Exposure of the single isomer **82** to TBAF/AcOH/THF gave the expected compound **84** (**Scheme 41**).

Two other methods were also explored in order to increase the yield of alcohol **84**. Without protecting the free OH group, treatment of **72** with acid chloride **83** in the presence of pyridine or triethylamine gave **84** in 39% yield.

However, coupling of **71** and **72** proceeded most efficiently under another set of standard conditions (*N*-methylmorpholine, HOBT, EDCI, DMF),[53] a mixture (6:4) of diastereoisomeric amides **84a** (major) and **84b** (minor) being obtained in 65% yield (based on ε-hydroxynorleucine).

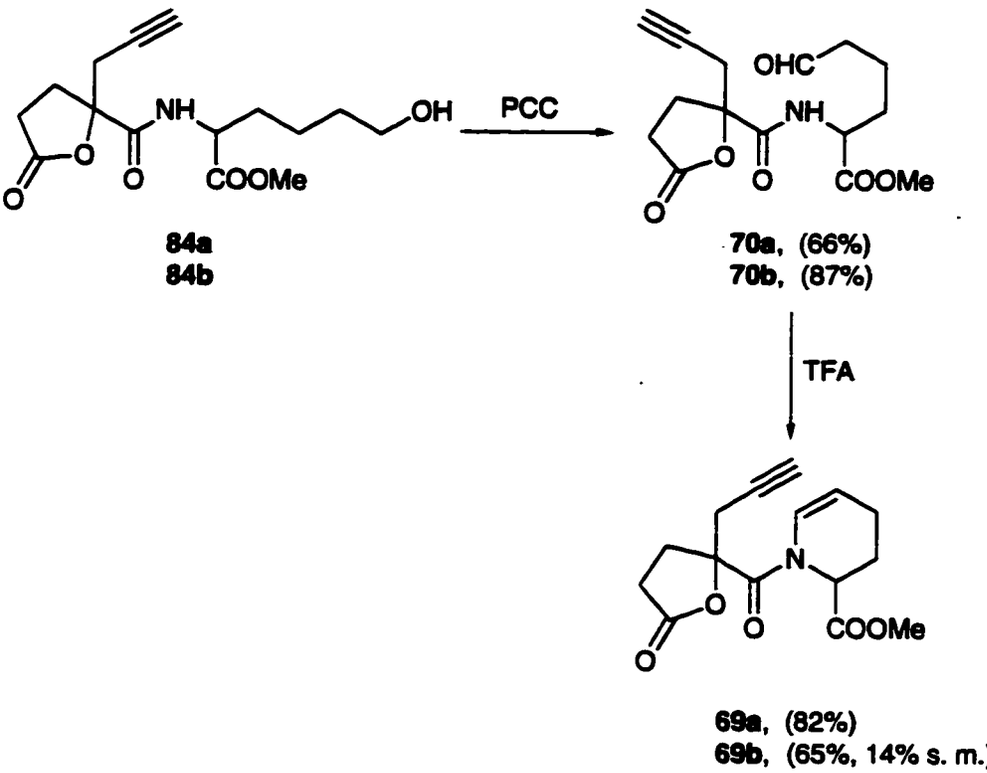



**Scheme 42**

*Synthesis of Intermediate **69***

All that remained to reach the key intermediate **69** was to oxidize alcohol **84** and then cyclize the resulting aldehyde **70** (**Scheme 43**). Our initial plan called for Swern oxidation of **84**, but only 20% of **70a** and 30% of **70b** were obtained from the individual isomers of **84**, respectively. Fortunately, isomers **84a** and **84b** could be individually oxidized by PCC to the corresponding aldehydes, (**84a** → **70a**, 66%; **84b** → **70b**, 87%), and these were cyclized[44] [**70a** → **69a**, 82%; **70b** →

**69b**, 65%, after correction for recovered starting material (14%)] by exposure to freshly distilled TFA in the presence of 4Å molecular sieves, the reaction taking 4 h in the case of **70a**, and 1 h with **70b**.




**84a**
**84b**

**70a**, (66%)
**70b**, (87%)

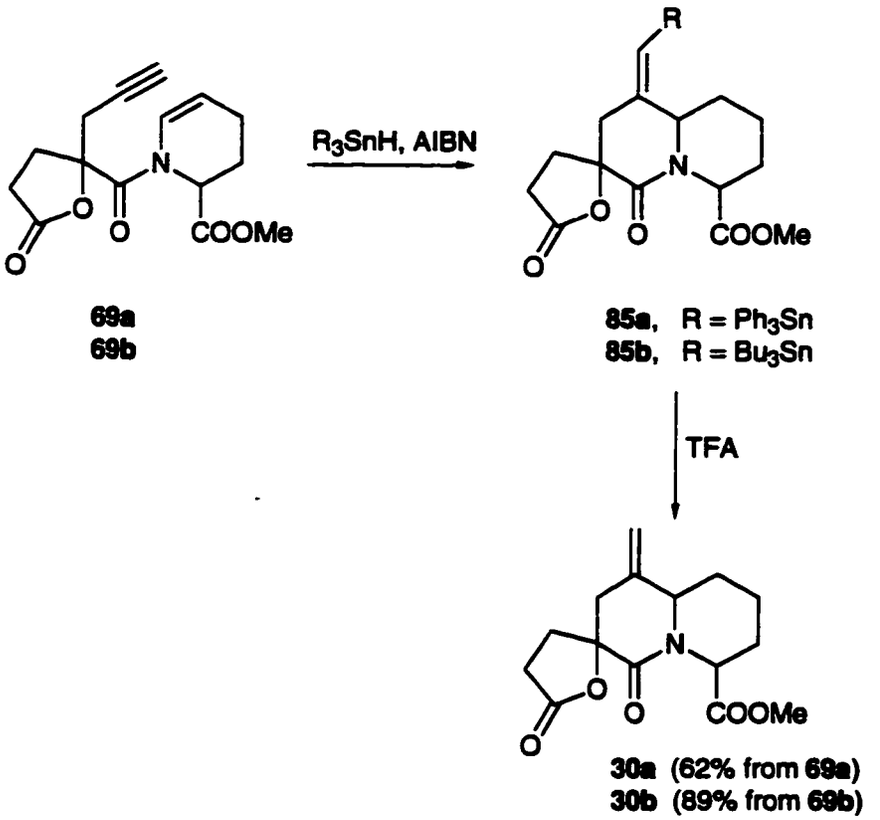
**69a**, (82%)
**69b**, (65%, 14% s. m.)

**Scheme 43**

*Synthesis of Olefin **30** from Radical Cyclization Products*

Now, the stage was set for closure of ring B by stannane addition to the alkyne, followed by cyclization of the resulting vinyl radical onto the proximal terminus of the enamine double bond.[54-57] Individual toluene solutions of AIBN and $Ph_3SnH$ were added over 2 minutes to a refluxing solution of **69a** in the same solvent. The desired product **85a** (79%) was obtained from this experiment, while

cyclization of **69b** under similar conditions, but using $Bu_3SnH$, gave **85b** (89%). Use of $Bu_3SnH$ with **69a** was much less efficient in either refluxing toluene or benzene. It may be significant that **69a** exists as two rotamers at room temperature, while **69b**, which closes efficiently ($Bu_3SnH$, refluxing, toluene), does not. The $^1H$ NMR spectrum of **69a** shows broad signals at 85 °C, but coalesced signals at 100 °C.

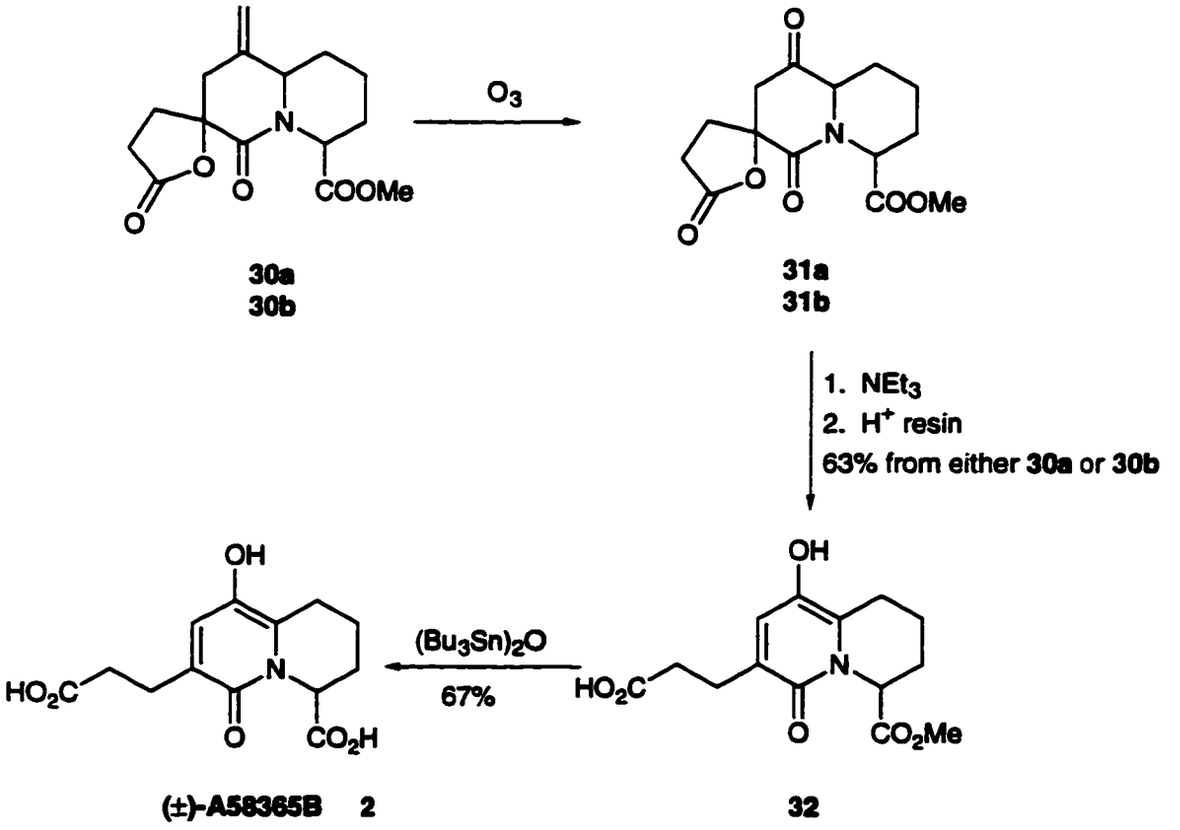



**Scheme 44**

Thorough purification of **85a** and **85b** was difficult because of persistent tin species, but protodestannylation gave **30a** (TFA, 12 h at room temperature, 2 h at 60 °C; 62%

from **69a**) and **30b** (TFA, 5 h at room temperature; 89% from **69b**). Both cyclization-destannylation products **30a** and **30b** were single compounds although, of course, of different stereochemistry. However, both served equally well for the last steps of the synthesis (**Scheme 45**).

*Completion of the Synthesis of (±)-A58365B (**2**)*



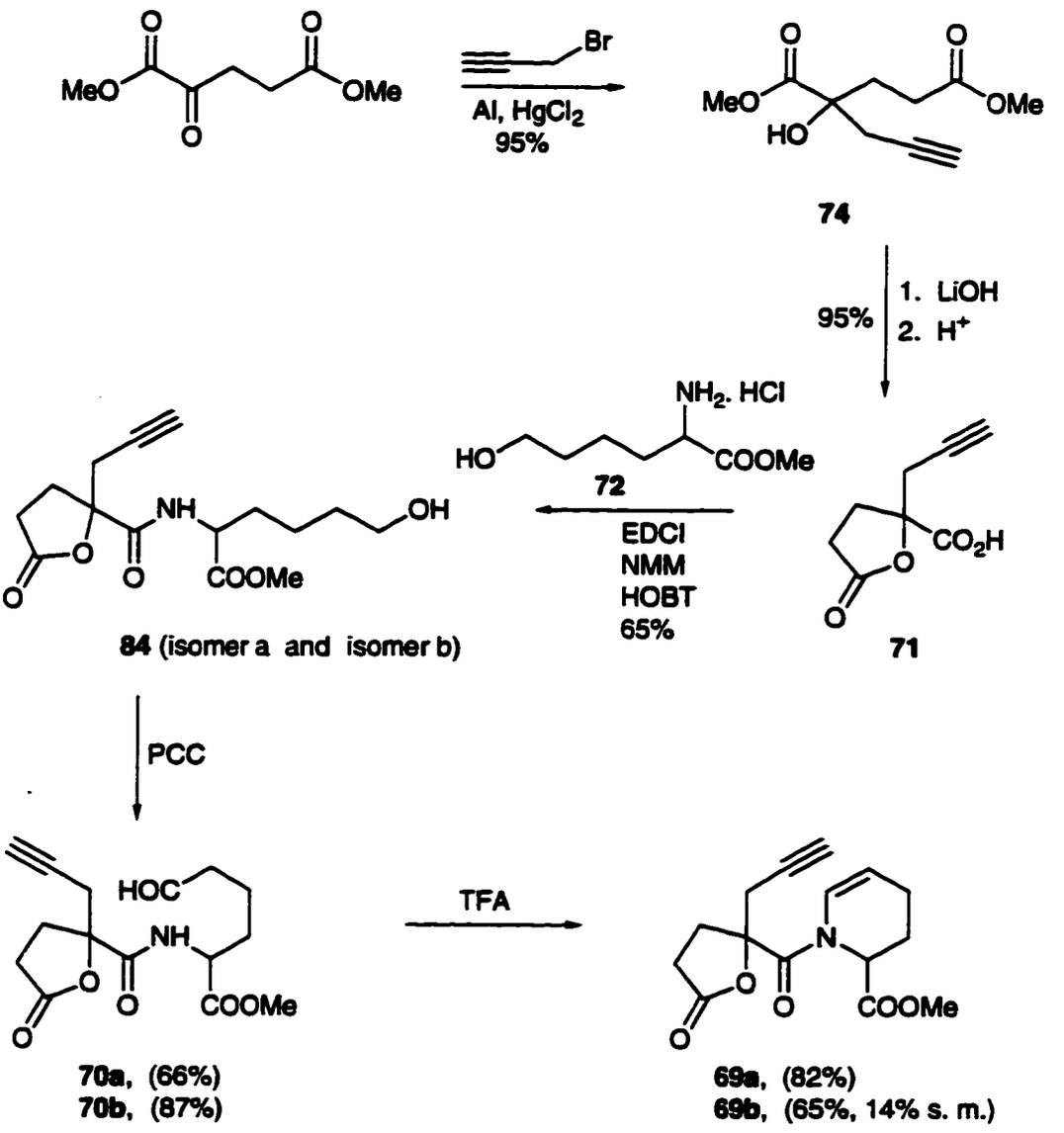

**Scheme 45**

Ozonolysis (**30a** → **31a**; **30b** → **31b**) gave the corresponding ketones and, without isolation, exposure to triethylamine (THF, 60°C, 2 h) served both to introduce the

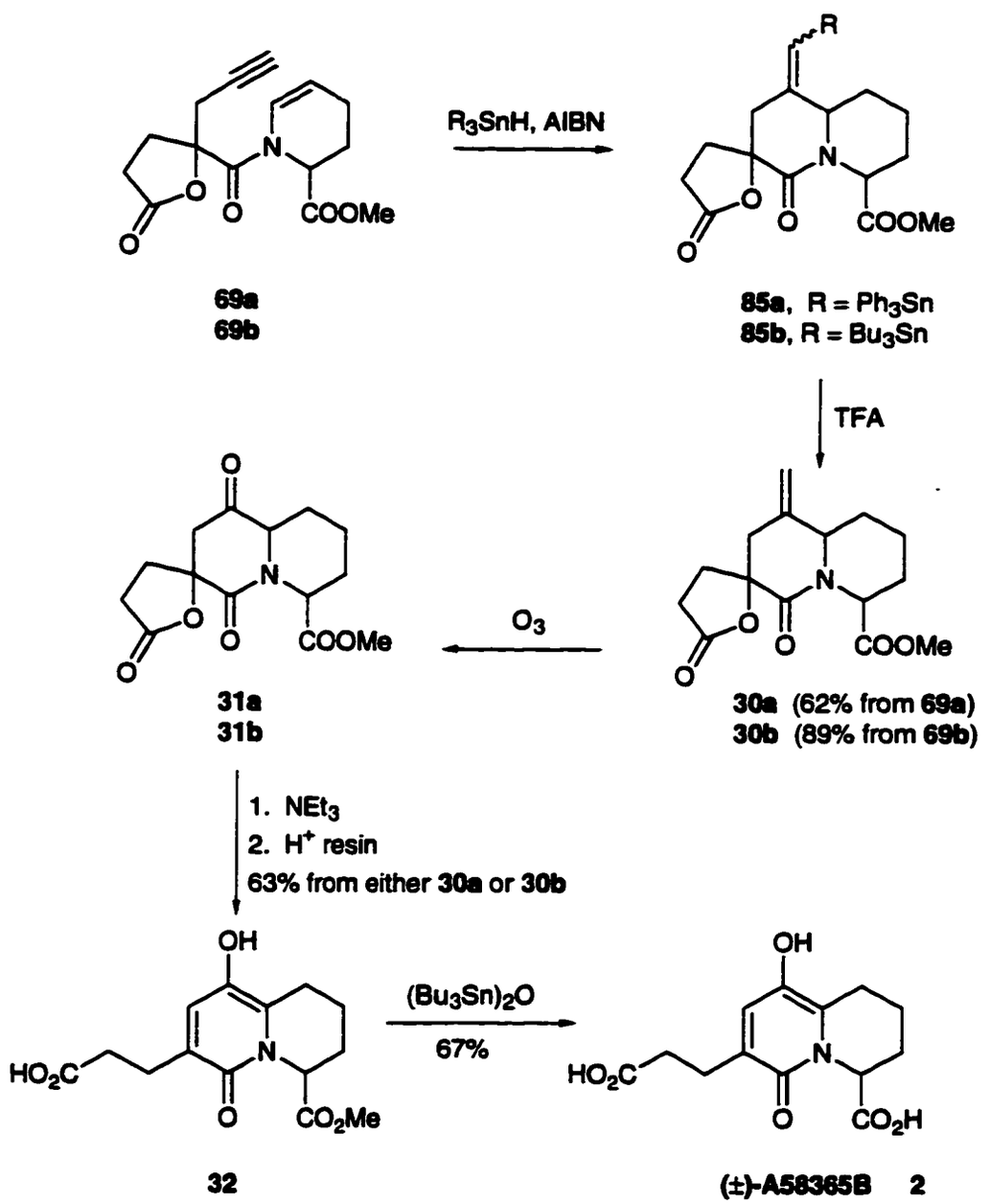
critical C(7)-C(8) double bond and release the propionic acid side chain in 63% overall yield from either **30a** or **30b**. Finally, ester hydrolysis, using $(Bu_3Sn)_2O$[58] in refluxing benzene for 3 days, gave crystalline (±)-A58365B **2** in 67% (mp 209-213 °C, from water) (**Scheme 45**).

## Conclusion

(±)-A58365B **2**, an inhibitor of angiotensin-converting enzyme, was synthesized[59] from two subunits, spiro lactone **71**, which represents all the carbons that make up the C(6)-C(9) segment of the natural product, including the propionic side chain, and ε-hydroxynorleucine methyl ester **72**, which not only has all of the required atoms of ring A, but also could be used without prior hydroxyl protection. Ring B was constructed by a process based on enyne radical cyclization (**69ab** → **30ab**). Our synthesis of (±)-A58365B **2** (7.8% over 10 steps) is summarized in **Scheme 46** and **Scheme 47**.


MeO
OMe
Br
Al, HgCl2
95%
HO
74
95%
1. LiOH
2. H+
NH2. HCl
HO
COOMe
72
EDCI
NMM
HOBT
65%
CO2H
71
NH
OH
COOMe
84 (isomer a and isomer b)
PCC
HOC
NH
COOMe
70a, (66%)
70b, (87%)
TFA
N
COOMe
69a, (82%)
69b, (65%, 14% s. m.)

**Scheme 46**



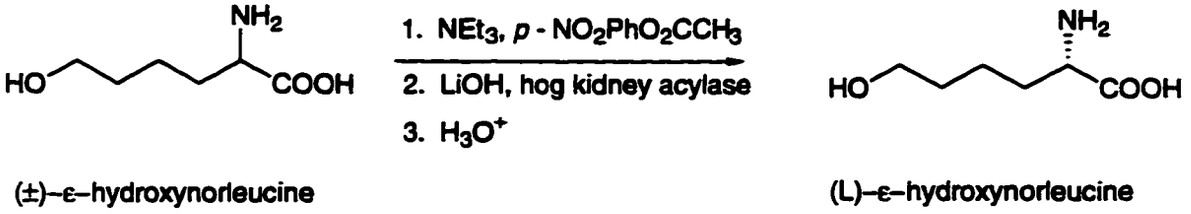

**Scheme 47**

## Synthesis of (-)-A58365B

Our initial plan was based on the fact that racemic A58365B could be synthesized from (±)-ε-hydroxynorleucine. Consequently, optically pure material should be obtained

following an identical route, but using (L)-ε-hydroxylnor-leucine as the starting material.

In order to test this hypothesis we repeated the synthetic route developed for the racemic form, but using the optical pure amino acid (L)-ε-hydroxynorleucine, which was obtained by enzymatic resolution, according to a literature procedure[60] (**Scheme 48**).

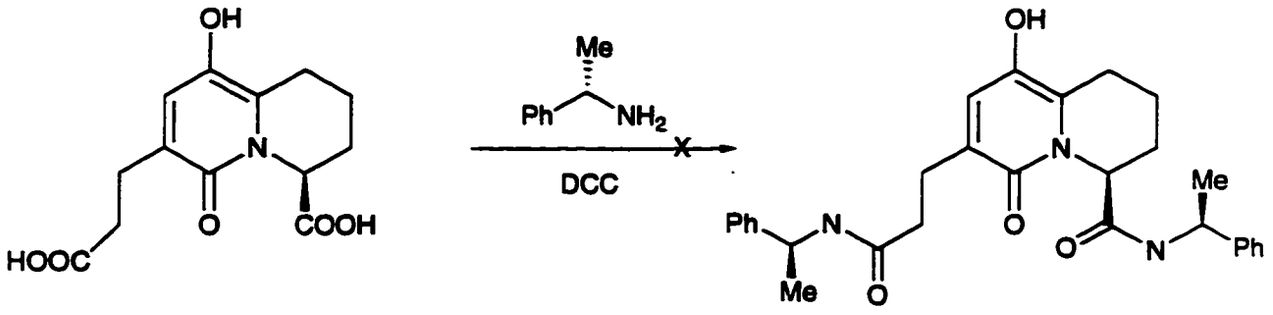



**Scheme 48**

The synthesis was completed in a fashion identical to the one described earlier for the racemic material (see **Schemes 46** and **47**). The final compound had $[\alpha]_D^{21}$ = -114 ° (c 0.16, $H_2O$); the literature[11] value is $[\alpha]_D^{25}$ = -141 ° (c 0.16, $H_2O$). The difference between the observed and literature values might suggest that the stereogenic center had undergone a small amount of epimerization during the synthesis. However, this difference could also be attributed to the different experimental conditions under which the optical rotations were measured. In order to determine the exact ee% of the final product, several experiments were

carried out, as follows.

Our first attempt was to make the amide derivative **86** from **2** by using chiral amine (*S*)-α-methylbenzylamine (**Scheme 49**). Unfortunately, compound **2** decomposed during attempts (use of DCC) to form the amide.

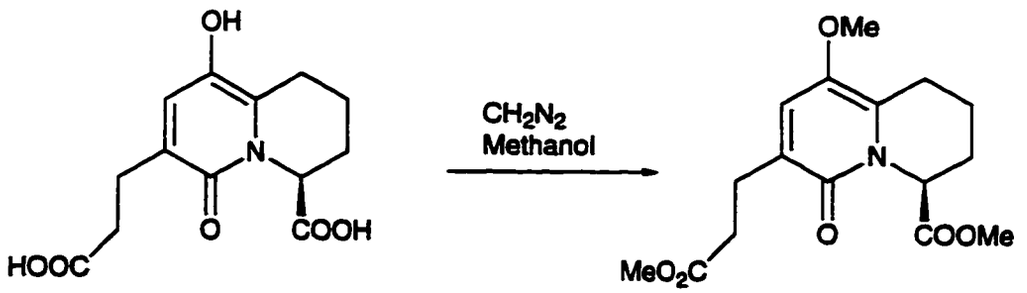



**2** **86**

**Scheme 49**

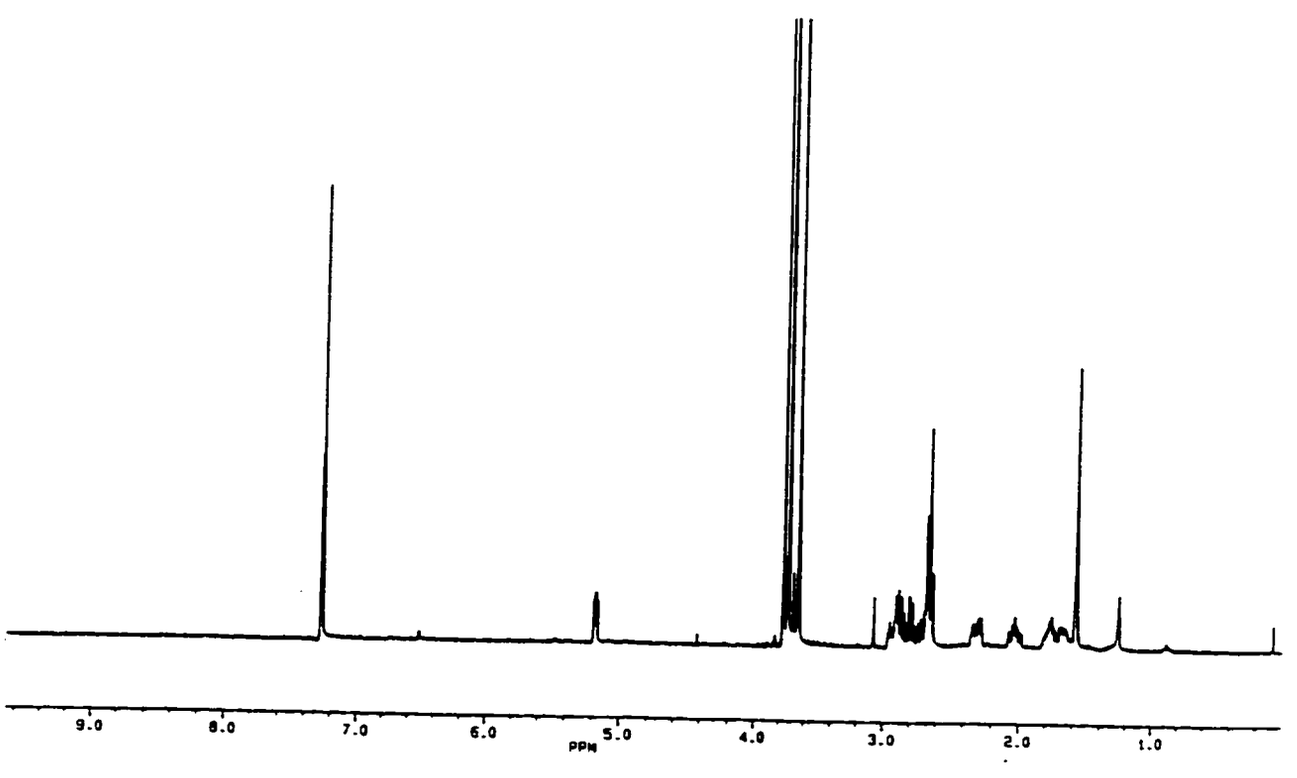
Our next attempt was to prepare the trimethyl derivative of **2**, by following the literature procedure[13] (**Scheme 50**), and then we could apply an $^1H$ NMR chiral shift reagent [Eu(hfc)$_3$] to determine the ee%. This experiment was informative and the $^1H$ spectra are shown below. In the racemic form of **2** (spectrum b), the three methyl groups were shifted into the six peaks, but for optically active material only three sharp signals, corresponding to these methoxy groups were observed (spectrum c). We can conclude that optically active natural product **2** was obtained in high ee. However, we are unable to exactly quantify the ee, and we plan to examine our material by HPLC, using a chiral column

packing.

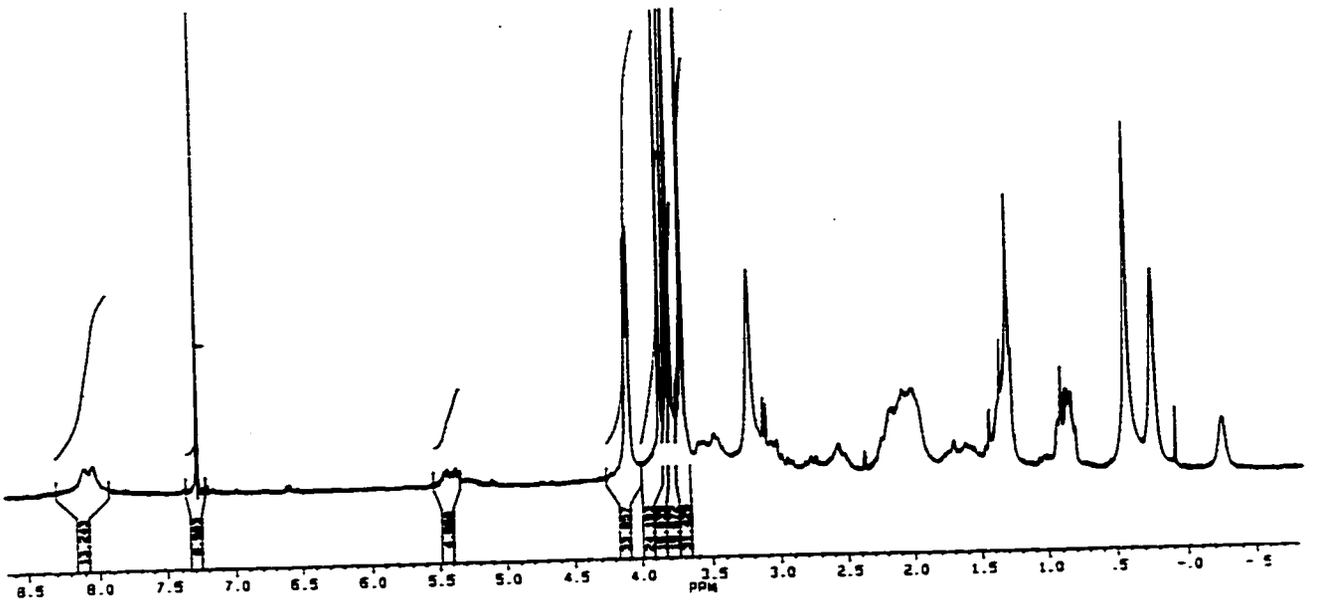



2 87

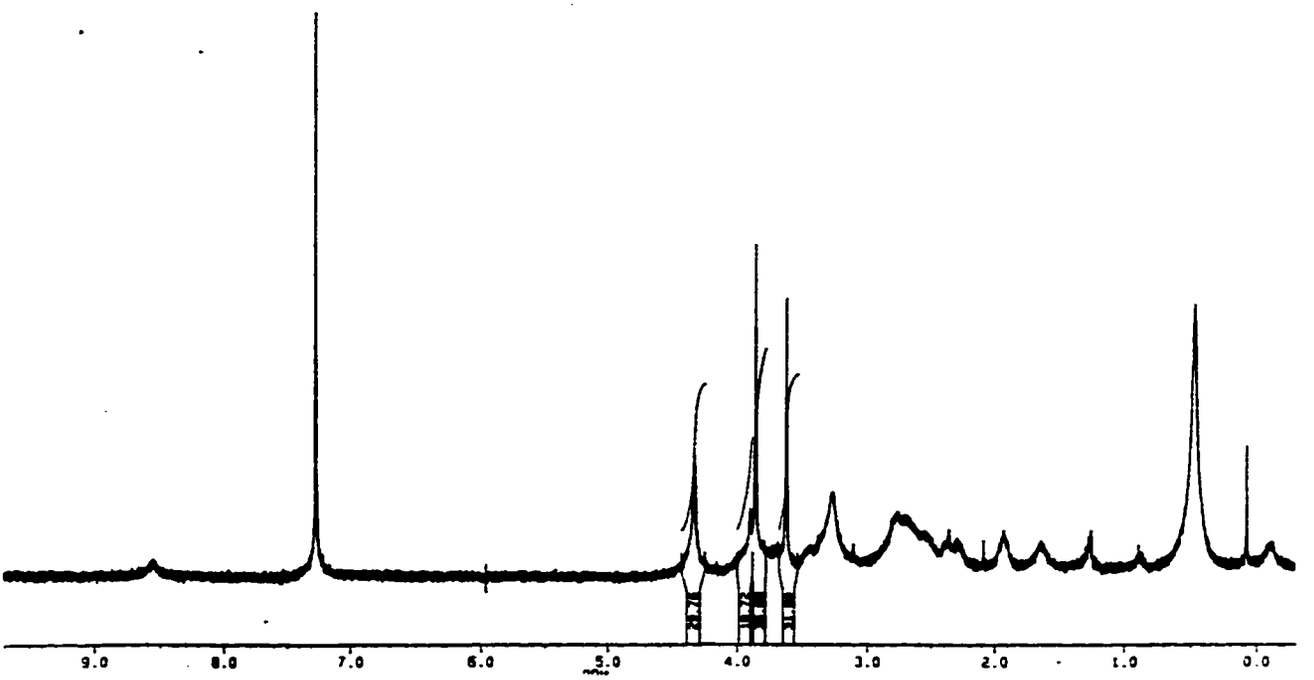
**Scheme 50**




**a. $^1H$ NMR of Trimethyl Derivative of(-)-A58365B without chiral shift reagent**




**b. $^1$H NMR of Trimethyl Derivative of(±)-A58365B with chiral shift reagent**




**c. $^1$H NMR of Trimethyl Derivative of(-)-A58365B with chiral shift reagent**

## (III) Experimental Section

### General experimental procedures

Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst[61] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30 °C, using a rotary evaporator.

Melting points were determined on a Kofler block melting point apparatus.

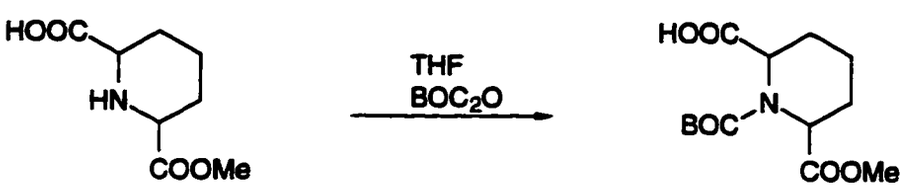
Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

C-18 Reverse phase silica gel (60 mesh, 10% C-18 capped with TMS, Lot 1-AB-76) (Catalogue # S4525) was obtained from Toronto Research Chemicals Inc., 4483 Chesswood Dr., Downsview, Ontario M3J 2C3 (telephone: 416-638-9696).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl. Dry PhH was distilled from Na. Dry $CH_2Cl_2$, MeOH, pyridine, DMF, and were distilled from $CaH_2$, the last two solvents being distilled under water pump vacuum. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

The symbols s', d', t', and q' used for $^{13}C$ NMR spectra indicate 0, 1, 2, or 3 attached protons.

**1-(t-Butoxycarbonyl)hexahydro-6-(methoxycarbonyl)-2-pyridinecarboxylic acid (38).**

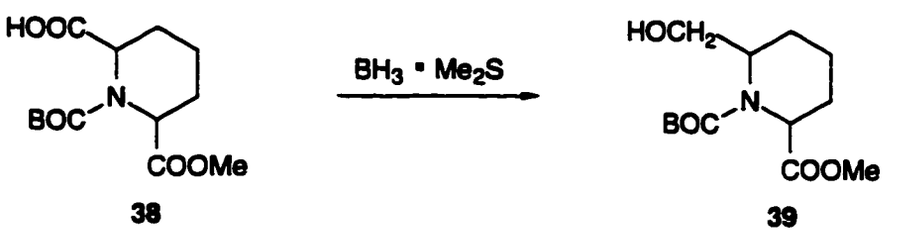



**37** **38**

BOC-anhydride (5.4 g, 24.71 mmol) was added to a suspension of amino acid **37** (3.9 g, 20.9 mmol) in dry THF (60 mL). The resulting mixture was refluxed for 48 h under Ar and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 20 cm), using 1:9 MeOH-$CHCl_3$, gave pure ($^1H$ NMR 400 MHz) **38** as a colorless oil (5 g, 83% yield): FTIR ($CH_2Cl_2$ cast) 1700, 1741, 1801 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.4-1.6 (br signal, 10 H), 1.6-1.7 (br, 1 H), 1.7-2.1 (br, 2 H), 2.1-

2.4 (br, 2 H), 3.8-4 (br, 3 H), 4.6-4.9 (br, 2 H) (the carboxyl H was not observed; possibly it was an very broad signal); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) δ 16.65 (t'), 25.8 (t'), 26.5 (t'), 27.9 (q'), 52.9 (d'), 53.65 (d'), 56.03 (q'), 82.5 (s'), 154.9 (s'), 174.5 (s'), 178.6 (s'); exact mass *m/z* calcd for $C_{12}H_{20}NO_4$ (M - COOH) 242.1391, found 242.1389.

**Methyl 1-(*t*-Butoxycarbonyl)hexahydro-6-(hydroxymethyl)-2-pyridinecarboxylate (39).**

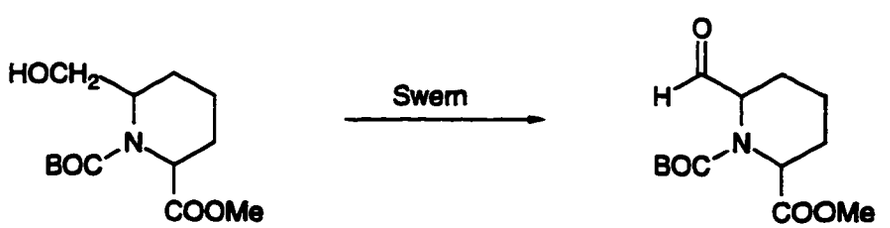



**38** **39**

A mixture of acid **38** (2.9 g, 10.10 mmol) and dry THF (20 mL) was cooled in an ice-salt bath (-14 °C), and $BH_3 \cdot Me_2S$ (2 M in THF, 11 mL, 22.01 mmol) was added over a period of 15 min (evolution of $H_2$). Stirring was continued for 16 h, the ice-salt bath being allowed to reach room temperature. The reaction mixture was hydrolyzed by dropwise addition of water (10 mL) at 0 °C (stirring). No hydrogen evolution was observed, indicating complete utilization of the $BH_3 \cdot Me_2S$. The aqueous phase was treated with $K_2CO_3$ (6 g) and the THF phase was separated. The aqueous phase was extracted with $Et_2O$ (3 x 50 mL). The combined ether extracts were washed with brine (3 x 20 mL) and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica

gel (3 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1$H NMR, 200 MHz) **39** (2.2 g, 80%): FTIR ($CH_2Cl_2$ cast) 1693, 1734, 1750, 3471 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) δ 1.4-1.6 (br, 11 H), 1.6-1.8 (m, 3 H), 2-2.2 (br, 1 H), 3.1 (t, *J* = 7 Hz, 1 H), 3.5 (t, *J* = 7 Hz, 2 H), 3.8 (s, 3 H), 4.3-4.4 (m, 1 H), 4.7-5 (br, 1 H); $^{13}$C NMR ($CD_2Cl_2$, 50.3 MHz) δ 17.1 (t'), 25.0 (t'), 26.4 (t'), 28.4 (q'), 51.9 (d'), 52.7 (d'), 53.6 (q'), 63.6 (t'), 80.5 (s'), 156.2 (s'), 175.5 (s'), exact mass *m/z* calcd for $C_{13}H_{23}NO_5$ 273.1572, found 273.1571.

**Methyl 1-(*t*-Butoxycarbonyl)-6-formylhexahydro-2-pyridinecarboxylate (40).**




**39** **40a, 40b**

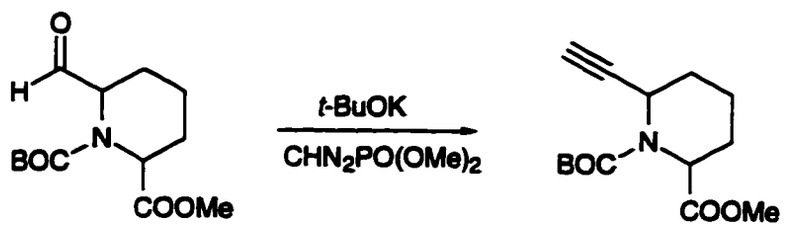
Freshly distilled DMSO (1.9 mL, 26.76 mmol) was added slowly (Ar atmosphere) to a cooled (-78 °C) and stirred solution of $(COCl)_2$ (1.2 mL, 13.76 mmol) in dry $CH_2Cl_2$ (15 mL). There was immediate gas evolution. Stirring was continued and, after 0.5 h, the alcohol **39** (1.76 g, 6.45 mmol) in dry $CH_2Cl_2$ (5 mL) was added dropwise. Stirring was continued for 2 h at -78 °C, and then $Et_3N$ (3.5 mL, 25.11 mmol) was added dropwise. The cooling bath was removed, stirring was continued for 3 h, and the mixture was then

quenched with water (30 mL), and extracted with $CHCl_3$ (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:4 EtOAc-hexane, gave two isomers in ratio 15:1 [faster-running isomer (**40a**) on TLC, 1.32 g; slower-running isomer (**40b**) on TLC, 87 mg; total yield 81%].

The pure ($^1H$ NMR, 200 MHz) faster-running isomer (**40a**) had: FTIR 1699, 1729, 1743, 2868 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 200 MHz) δ 1.1-1.3 (br, 1 H), 1.3-1.6 (br, 11 H), 1.6-1.8 (m, 1 H), 1.9-2.1 (br, 1 H), 2.2-2.4 (br, 1 H), 3.7 (s, 3 H), 4.4-4.6 (br, 1 H), 4.7-4.9 (br, 1 H), 9.7-9.8 (br, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 MHz) δ 17.4 (t'), 22.7 (t'), 26.8 (t'), 28.3 (q'), 52.4 (q'), 58.9 (d'), 58.9 (d'), 81.4 (s'), 155.7 (s'), 173.7 (s'), 201.96 (d'); exact mass *m/z* calcd for $C_{12}H_{20}NO_4$ (M - CHO) 242.13924, found 242.13254.

The slower-running isomer (**40b**) had: $^1H$ NMR ($CD_2Cl_2$, 200 MHz) δ 1.1-1.5 (br, 11 H), 1.6-1.8 (br, 3 H), 2.1-2.2 (br d, 1 H), 3.6 (s, 3 H), 3.8-4.0 (br, 1 H), 4.6-4.7 (br d, 1 H), 9.2-9.4 (m, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 MHz) (mixture of rotamers) δ 18.6 (t'), 25.7 (t'), 26.8 (t'), 28.2 (q'), 52.38 (q'), 54.43 (d'), 55.97 (d'), 61.42 (d'), 61.7 (d'), 82.00 (s'), 157.7 (s'), 173.1 (s'), 196.9 (d'), 197.9 (d'); exact mass *m/z* calcd for $C_{12}H_{20}NO_4$ (M - CHO) 242.13924, found 242.13912.

**Methyl 1-(*t*-Butoxycarbonyl)-6-ethynylhexahydro-2-pyridinecarboxylate (41).**

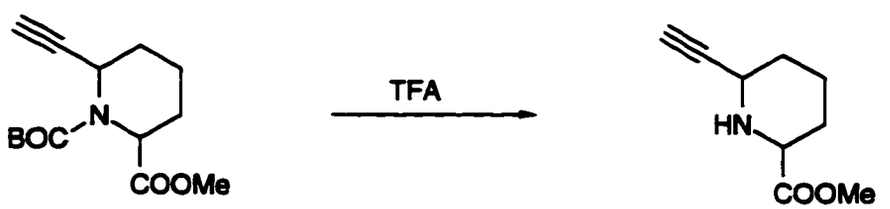



**40** **41**

A stirred slurry of *t*-BuOK (300 mg, 2.67 mmol) in dry THF (3 mL) was cooled to -78 °C under Ar. A solution of dimethyl (diazomethyl)phosphonate (383 mg, 2.54 mmol) in THF (1 mL) was added dropwise over 2 min and the mixture was stirred for 5 min. During this time, the color of the mixture changed from pale yellow to brown. A solution of aldehyde **40** (518 mg, 1.91 mmol) in THF (2 mL) was added over 1 min. $N_2$ was evolved immediately. The resulting solution was stirred at -78 °C for 12 h, the cooling bath was removed, and stirring was continued for an additional 4 h. The mixture was then quenched with water (50 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (2 x 3 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 3:17 EtOAc-hexane, gave **41** as a pure ($^1H$ NMR, 200 MHz), white powder (380 mg, 75%): FTIR ($CH_2Cl_2$ cast) 1701, 1738, 3265 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 200 MHz) $\delta$ 1.4 (s, 10 H), 1.5-1.9 (m, 5 H), 2.2 (d, $J$ = 2 Hz, 1 H), 3.7 (s, 3 H), 4.7-4.85 (br, 1 H), 4.9-

5.05 (br, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 MHz) (mixture of rotamers) δ 16.9 (t', two peaks), 25.3 (t'), 28.3 (q'), 31.0 (t'), 42.6 (d', two peaks), 51.5 (q', two peaks), 55.5 (d'), 71.4 (s'), 80.7 (d'), 81.3 (s', two peaks), 155.0 (s', two peaks), 172.2 (s', two peaks); exact mass *m/z* calcd for $C_{14}H_{21}NO_4$ 267.14706, found 267.14520.

**Methyl 6-Ethynylhexahydro-2-pyridinecarboxylate (33).**

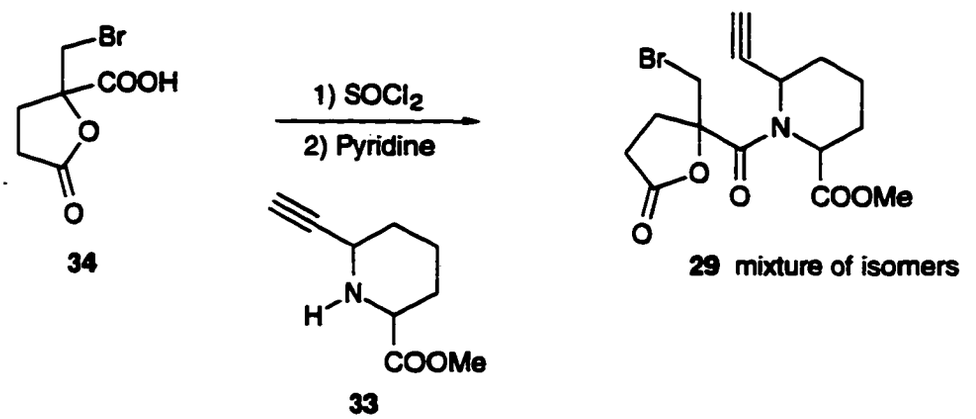



**41** **33**

TFA (2.5 mL, 32.45 mmol) was added to a cooled (0 °C, ice bath) and stirred solution of the acetylene **41** (207 mg, 0.77 mmol) in $CH_2Cl_2$ (3 mL). The cold bath was removed, and stirring was continued for 4 h. The solvent was evaporated, the residue was dissolved in EtOAc (20 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), water (2 x 10 mL) and brine (1 x 20 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave the desired product **33** (120 mg, 92%) as a colorless oil: FTIR ($CHCl_3$, cast) 1696, 1739, 3290 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 200 MHz) δ 1.4-1.6 (m, 3 H), 1.8-2.0 (m, 3 H), 2.25-2.34 (br d, *J* = 2 Hz, 2 H), 3.23-3.30 (m, 1 H), 3.45-

3.52 (m, 1 H), 3.7 (s, 3 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 MHz) δ 24.3 (t'), 28.7 (t'), 32.9 (t'), 48.0 (d'), 52.1 (d'), 58.9 (q'), 70.5 (d'), 173.2 (s') (one acetylenic signal is not observed under the conditions used to measure the spectrum); exact mass *m/z* calcd for $C_9H_{13}NO_2$ 167.09464, found 167.09383.

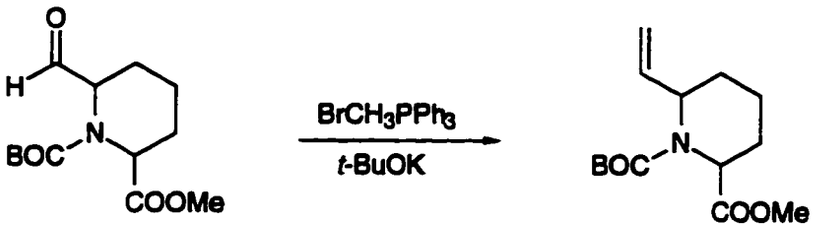
**Methyl 1-[[2-(Bromomethyl)tetrahydro-5-oxo-2-furanyl]-carbonyl]-6-ethynylhexahydro-2-pyridinecarboxylate (29).**




$SOCl_2$ (1.8 mL, 24.66 mmol) was added to a suspension of Swiss acid **34** (562 mg, 2.52 mmol) in dry PhH (4 mL) and the mixture was refluxed with stirring for 2 h (Ar atmosphere), cooled and evaporated to dryness, with protection from moisture. The resulting freshly prepared acid chloride in $CH_2Cl_2$ (2 mL) was added to a stirred and cooled (0 °C) mixture of amine **33** (374 mg, 2.25 mmol), pyridine (0.7 mL, 8.65 mmol) and $CH_2Cl_2$ (4 mL) (Ar atmosphere). The cold bath was left in place and stirring was continued overnight. The solution was then evaporated. The residue was dissolved in EtOAc (30 mL),

washed with 1N HCl solution (4 x 10 mL), water (3 x 10 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 7:3 hexane-ethyl acetate, gave **29** as a mixture of isomers (500 mg, 61%): exact mass *m/z* calcd for $C_{15}H_{18}{}^{81}BrNO_5$ 373.03479, found 373.03591; calcd for $C_{15}H_{18}{}^{79}BrNO_5$ 371.03683, found 371.03749. Because the material is a mixture of isomers, we can not get good $^{13}C$ and $^{1}H$ NMR spectra.

**Methyl 1-(*t*-Butoxycarbonyl)-6-ethenylhexahydro-2-pyridinecarboxylate (53).**



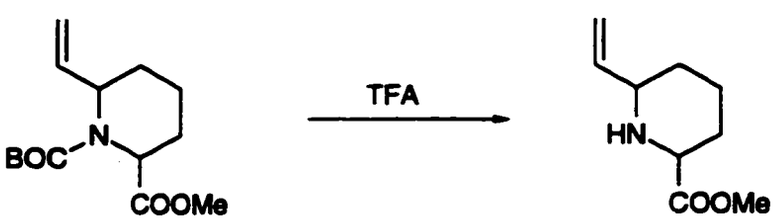

**40** **53**

For this experiment, *t*-BuOK was weighed in a glove bag filled with Ar. $Ph_3PCH_3Br$ was dried under good oil pump vacuum at 60 °C (oil bath), and dioxane was dried by refluxing over Na.

*t*-BuOK (333 mg, 2.96 mmol) was suspended in dry dioxane (10 mL), and $Ph_3PCH_3Br$ (1.05 g, 2.93 mmol) was added in small portions from a side-arm addition tube (Ar atmosphere). The reaction mixture was stirred for 1 h at 50 °C (oil bath), then cooled to room temperature. A solid was deposited. The liquid above the solid was added by cannula to a solution of

aldehyde **40** (600 mg, 2.22 mmol) in dry THF (10 mL), and the resulting solution was stirred for 24 h at room temperature (Ar atmosphere). The mixture was diluted with EtOAc (20 mL), washed with water (3 x 10 mL) and brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. The residue was suspended in distilled hexane (20 mL) and stored overnight in a refrigerator. The resulting white solid ($Ph_3PO$) was filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 3:17 EtOAc-hexane, gave **53** as a pure ($^1H$ NMR, 300 MHz), colorless oil (497 mg, 84%): FTIR ($CDCl_3$, cast) 1695, 1737, 2881, 2949, 2974 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.4 (s, 9 H), 1.5-1.7 (m, 4 H), 1.8-1.9 (m, 1 H), 2.2-2.3 (m, 1 H), 3.7 (s, 3 H), 4.56-4.62 (br, 1 H), 4.78-4.84 (m, 1 H), 5.0-5.2 (m, 2 H), 6.0-6.1 (m, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 MHz) δ 16.6 (t'), 26.2 (t'), 28.4 (t'), 28.5 (q'), 51.9 (d'), 52.7 (q'), 80.2 (s'), 114.6 (t'), 139.1 (d'), 155.7 (s'), 173.5 (s'); exact mass *m/z* calcd for $C_{14}H_{23}NO_4$ 269.16272, found 269.16215.

**Methyl 6-Ethenylhexahydro-2-pyridinecarboxylate (52).**

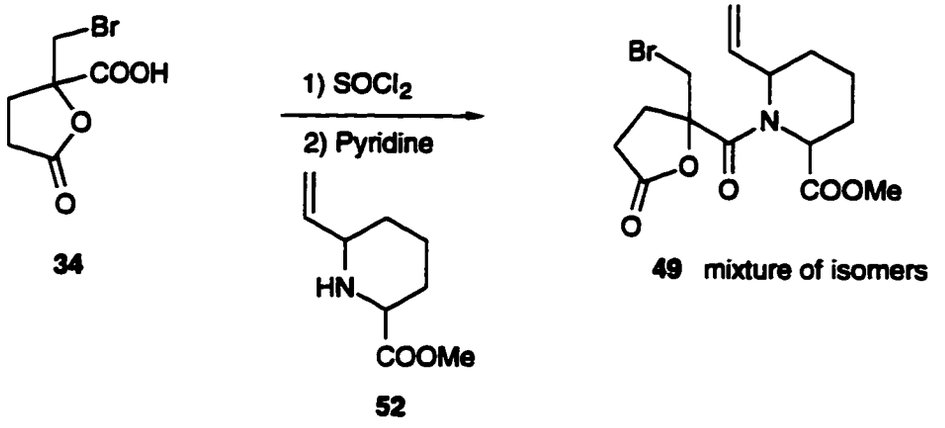



**53** **52**

TFA (2 mL, 25.96 mmol) was added to a stirred and cooled

(0 °C) solution of olefin **53** (1.3 g, 4.83 mmol) in dry $CH_2Cl_2$ (2 mL). The cold bath was left in place, and stirring was continued for 5 h. The solvent was then evaporated. The residue was dissolved in EtOAc (40 mL), washed with saturated aqueous $NaHCO_3$ (3 x 20 mL), water (2 x 20 mL) and brine (2 x 30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 3:7 EtOAc-hexane, gave pure **52** ($^1H$ NMR, 300 MHz) (610 mg, 75%): $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.2-1.3 (m, 1 H), 1.4-1.6 (m, 2 H), 1.7-1.8 (m, 1 H), 1.9-2.1 (m, 3 H), 3.1-3.2 (m, 1 H), 3.4-3.44 (dd, *J* = 13.5, 1.8 Hz, 1 H), 3.75-3.8 (m, 3 H), 5.0-5.05 (dd, *J* = 13.5, 3.6 Hz, 1 H), 5.2-5.25 (dd, *J* = 18, 3.6 Hz, 1 H), 5.9-5.95 (m, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 75.5 MHz) δ 24.7 (t'), 29.1 (t'), 32.3 (t'), 51.9 (d'), 59.3 (q'), 59.4 (d'), 113.9 (t'), 142.0 (d'), 173.8 (s'); exact mass *m/z* calcd for $C_9H_{15}NO_2$ 169.11028, found 169.11033. We did not get the FTIR.

**Methyl 1-[[2-(Bromomethyl)tetrahydro-5-oxo-2-furanyl]-carbonyl]-6-ethenylhexahydro-2-pyridinecarboxylate (49).**



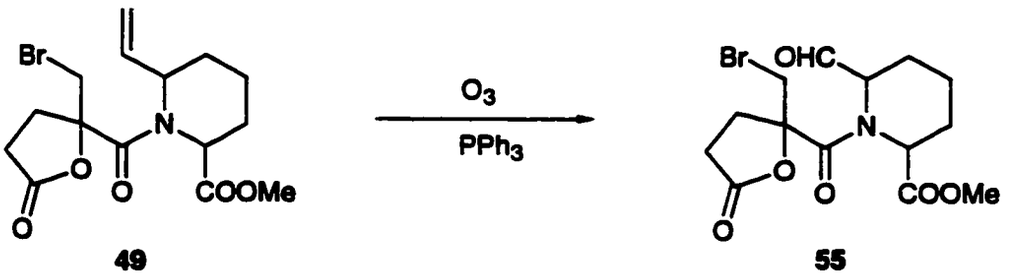

**34** **52** **49** mixture of isomers

$SOCl_2$ (2.3 mL, 25.13 mmol) was added to a suspension of Swiss acid **34** (740 mg, 3.32 mmol) in dry PhH (15 mL), and the mixture was stirred and refluxed for 2 h (Ar atmosphere). The solution was then cooled to room temperature and evaporated to dryness. Dry pyridine (0.54 mL, 6.61 mmol) and the freshly prepared acid chloride in PhH (5 mL) were added sequentially to a stirred and cooled (ice bath) solution of amine **52** (510 mg, 3.01 mmol) in PhH (10 mL) (Ar atmosphere). The ice bath was left in place, and stirring was continued overnight. The mixture was diluted with EtOAc (50 mL), washed with 1 N HCl (4 x 20 mL), water (3 x 20 mL) and brine (2 x 30 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 7:3 hexane-EtOAc, gave **49** as two separable fractions (total yield 1.01 g, 85%).

The faster-running fraction (TLC) (minor reaction product) was a mixture of rotamers and/or isomers (394 mg): FTIR ($CHCl_3$ cast) 1130, 1685, 1737, 1794, 2950 $cm^{-1}$; exact mass *m/z* calcd for $C_{15}H_{20}{}^{79}BrNO_5$ 373.05249, found 373.05225. Because the material is a mixture of rotamers and/or isomers, satisfactory NMR data could not be obtained.

The slower-running fraction (TLC) (major reaction product) was also a mixture of rotamers and/or isomers (620 mg): FTIR ($CHCl_3$ cast) 1631, 1739, 1794, 2921, 2953; exact mass *m/z* calcd for $C_{15}H_{20}{}^{81}BrNO_5$ 375.05045, found 375.05042; calcd for $C_{15}H_{20}{}^{79}BrNO_5$ 373.05249, found 373.05259. Because the material is a mixture of rotamers and/or isomers, satisfactory NMR dates could not be obtained.

**Methyl 1-[[2-(Bromomethyl)tetrahydro-5-oxo-2-furanyl]-carbonyl]-6-formylhexahydro-2-pyridine-carboxylate (55).**




**49** **55**

Ozonized oxygen was passed into a stirred and cooled (-78 °C) solution of spirolactone **49** (mixture of two isomers, 90 mg, 0.24 mmol) in $CH_2Cl_2$ (5 mL) contained in a three-necked flask equipped with a reflux condenser (not connected to a

water supply) closed by a drying tube packed with Drierite, an inlet tube (for ozone), and a glass stopper. When the solution became pale blue, ozonization was stopped, and the excess of ozone was removed with a stream of oxygen. $Ph_3P$ (130 mg, 0.49 mmol) was tipped into the solution, the cooling bath was removed, and stirring was continued for 2 h. Evaporation of solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **55** (68 mg, 75%) as a mixture of two isomers.

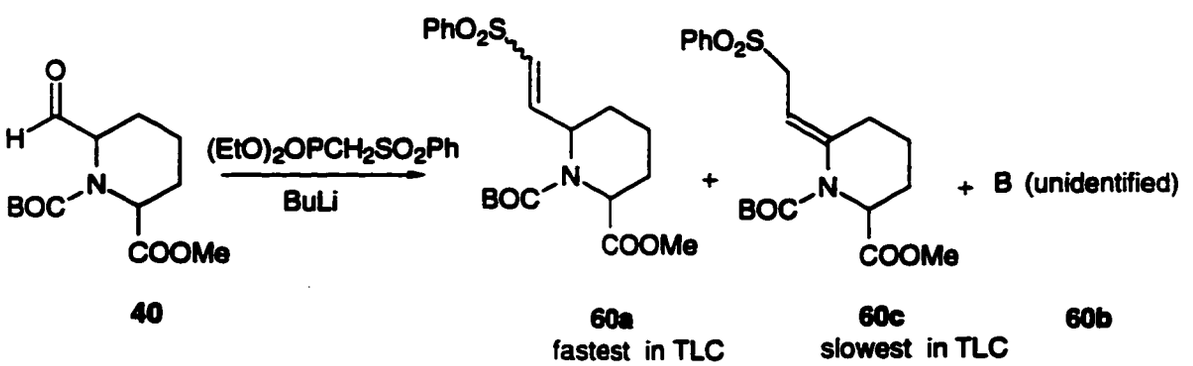
The chromatographically faster-running isomer (17 mg) crystallized from EtOAc and had: mp 149-151 °C; FTIR ($CHCl_3$, cast) 1637, 1731, 1796, 2867, 2954; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.4-1.7 (m, 3 H), 1.8-1.9 (m, 1 H), 2.3-2.5 (m, 3 H), 2.6-2.7 (m, 2 H), 3.1-3.2 (m, 1 H), 3.6 (d, 1 H), 3.7 (s, 3 H), 3.9-4.0 (dd, 1 H), 5.1-5.2 (m, 1 H), 5.4-5.5 (m, 1 H), 9.8 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) (mixture of rotamers or isomers) δ 16.9 (t'), 21.9 (t'), 26.5 (t'), 27.2 (t'), 27.4 (t'), 32.4 (t'), 33.4 (t'), 37.4 (t'), 49.5 (t'), 53.0 (d'), 56.1 (q'), 58.9 (d'), 87.9 (s'), 88.5 (s'), 170.5 (s'), 173.1 (s'), 173.9 (s'), 199.1 (d'); exact mass *m/z* calcd for $C_{13}H_{17}{}^{81}BrNO_5$ (M − CHO) 348.02698, found 348.02628; calcd for $C_{13}H_{17}{}^{79}BrNO_5$ 346.02902, found 346.02894.

The chromatographically slower-running isomer (51 mg, mixture of rotamers) was a colorless oil and had: FTIR ($CHCl_3$, cast) 1642, 1732, 1796, 2869, 2954 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) δ 1.3-1.8 (m, 3 H), 2.15-2.26 (m, 2 H), 2.34-

2.44 (m, 2 H), 2.5-2.8 (m, 2 H), 3.0-3.15 (m, 1 H), 3.6-4 (m, 5 H), 4.9-5.2 (br d, 1 H), 5.3-5.6 (br d, 1 H), 9.6-9.8 (d, 1 H); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) (mixture of rotamers) δ 16.7 (t'), 16.6 (t'), 21.8 (t'), 23.2 (t'), 25.9 (t'), 26.5 (t'), 27.3 (t'), 27.5 (t'), 27.9 (t'), 30.4 (t'), 31.3 (t'), 31.8 (t'), 32.7 (t'), 36.9 (t'), 39.196 (t'), 52.5 (q'), 52.9 (q'), 53.2 (d'), 55.5 (d'), 59.7 (d'), 60.7 (d'), 87.1 (s'), 87.5 (s'), 88.1 (s'), 169.9 (s'), 170.2 (s'), 170.4 (s'), 171.7 (s'), 172.4 (s'), 174.0 (s'), 174.5 (s'), 199.1 (d'), 199.7 (d'); exact mass *m/z* calcd for $C_{13}H_{17}{}^{81}BrNO_5$ (M − CHO) 348.02698, found 348.02731; calcd for $C_{13}H_{17}{}^{79}BrNO_5$ 346.02902, found 346.02896.

The structure of the fast-running isomer was confirmed by X-ray analysis (see appendix for details of the X-ray determination).

**Methyl 1-(*t*-Butoxycarbonyl)hexahydro-6-[2-(phenylsulfonyl)ethenyl]-2-pyridinecarboxylate (60a).**




**40** **60a** fastest in TLC **60c** slowest in TLC **60b**

BuLi (2.5 M in hexane, 1.1 mL, 2.75 mmol) was added slowly (Ar atmosphere) to a stirred and cooled (-78 °C)

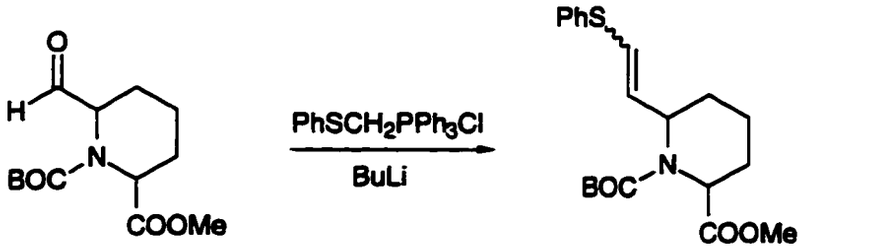
solution of $(EtO)_2POCH_2SO_2Ph$ (773 mg, 2.64 mmol) in dry THF (15 mL). This mixture was stirred for 1 h, and then aldehyde **40** (670 mg, 2.47 mmol) in dry THF (5 mL) was added dropwise. Stirring was continued for another 2.5 h, the cold bath was removed and, when the mixture had attained room temperature, saturated aqueous $NH_4Cl$ (30 mL)was added. The aqueous solution was extracted with $Et_2O$ (3 x 20 mL) and the combined organic extracts were washed with water (2 x 10 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:5 EtOAc-hexane, gave three pure compounds ($^1H$ NMR, 200 MHz): **60a** (fastest-running on TLC) 38 mg; **60c** (slowest-running on TLC) 230 mg; **60b** (unidentified structure) 410 mg; total yield 65% [**60b** has the same mass (mass spectrum) as **60a**].

Isomer **60a** had: $^1H$ NMR ($CD_2Cl_2$, 200 MHz) δ 1.30-1.40 (br, s, 9 H), 1.4-1.6 (m, 2 H), 1.8-2.0 (m, 3 H), 2.1-2.2 (m, 1 H), 3.7 (s, 3 H), 4.7-4.75 (dd, $J$ = 8, 2 Hz, 1 H), 5.7-5.9 (m, 1 H), 6.1-6.15 (dd, $J$ = 12, 2 Hz, 1 H), 7.1-7.15 (dd, $J$ = 12, 8 Hz, 1 H), 7.5-7.6 (m, 3 H), 8.0-8.2 (m, 2 H); $^{13}C$ NMR ($CD_2Cl_2$, 75.5 MHz) δ 17.17 (t'), 26.6 (t'), 28.4 (q'), 31.5 (t'), 48.7 (d'), 52.6 (q'), 54.5 (d'), 80.9 (s'), 127.6 (d'), 127.9 (d'), 129.5 (d'), 133.8 (d'), 141.6 (s'), 149.6 (d'), 155.7 (s'), 174.6 (s'); exact mass *m/z* calcd for $C_{16}H_{19}NO_6S$ (M - $C_4H_8$) 352.09332, found 353.09382.

Isomer **60c** had: $^1H$ NMR ($CD_2Cl_2$, 200 MHz) δ 1.1-1.2 (m, 2 H), 1.4 (s, 9 H), 1.6-1.9 (m, 3 H), 2.0-2.1 (m, 1 H), 3.7

(s, 3 H), 3.8-3.85 (dd, $J$ = 8, 4 Hz, 2 H), 4.7-4.8 (m, 1 H), 5.5 (t', $J$ = 8 Hz, 1 H), 7.5-7.7 (m, 3 H), 7.9-8.0 (m, 2 H); $^{13}C$ NMR ($CD_2Cl_2$, 75.5 MHz) $\delta$ 20.8 (t'), 26.2 (t'), 26.2 (t'), 28.3 (q'), 52.3 (q'), 55.9 (t'), 57.3 (d'), 81.3 (s'), 110.6 (d'), 129.0 (d'), 129.4 (d'), 133.9 (d'), 139.2 (s'), 141.9 (s'), 153.9 (s'), 172.2 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_4S$ (M - $C_4H_9CO_2$) 309.10349, found 309.10299.

**Methyl 1-(*t*-Butoxycarbonyl)hexahydro-6-[2-(phenylthio)ethenyl]-2-pyridinecarboxylate (61).**




**40** **61** three isomers

BuLi (2.5 M in hexane, 0.16 mL, 0.41 mmol) was added slowly to a stirred and cooled (-78 °C) solution of $PhSCH_2PPh_3Cl$ (170 mg, 0.41 mmol) in dry THF (1 mL). Stirring was continued for 1 h (Ar atmosphere) at -78 °C, and then aldehyde **40** (106 mg, 0.39 mmol) in THF (1 mL) was added dropwise. The cold bath was removed, stirring was continued for 4 h, and the mixture was diluted with $Et_2O$ (20 mL), washed with saturated aqueous $NH_4Cl$ (3 x 10 mL), water (3 x 10 mL) and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over

silica gel (1.5 x 20 cm), using 1:9 EtOAc-hexane, gave three isomers: isomer **61a** (fastest-running on in TLC) (11 mg); isomer **61b** (23 mg); isomer **61c** (slowest-running on TLC) (36 mg); total yield 48%.

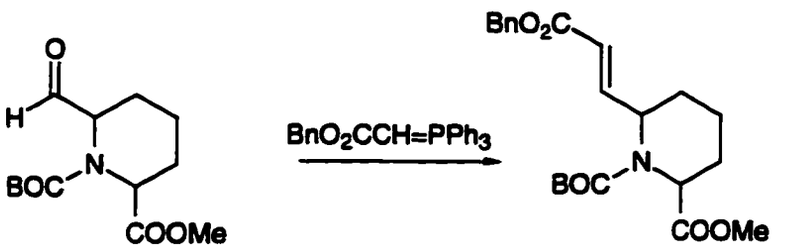
Isomer **61a** had: $^1$H NMR ($CD_2Cl_2$, 200 MHz) δ 1.4 (s, 9 H), 1.5-1.9 (m, 5 H), 2.23-2.33 (m, 1 H), 3.7 (s, 3 H), 4.78-4.82 (br s, 2 H), 6.0-6.2 (dd, *J* = 14, 8 Hz, 1 H), 6.3-6.5 (dd, *J* = 14, 0.8 Hz, 1 H), 7.2-7.4 (m, 5 H); $^{13}$C NMR ($CD_2Cl_2$, 75.5 MHz) δ 16.6 (t'), 26.2 (t'), 28.5 (q'), 28.5 (t'), 52.2 (q'), 52.4 (d'), 53.1 (d'), 80.4 (s'), 123.5 (d'), 126.7 (d'), 129.1 (d'), 129.4 (d'), 135.4 (d'), 136.6 (s'), 155.5 (s'), 173.4 (s'); exact mass *m/z* calcd for $C_{20}H_{27}NO_4S$ 377.16608, found 377.16538.

Isomer **61b** had: $^1$H NMR ($CD_2Cl_2$, 200 MHz) δ 1.4 (s, 9 H), 1.5-1.6 (m, 2 H), 2.7-2.9 (m, 3 H), 2.2-2.3 (m, 1 H), 3.7 (s, 3 H), 4.8 (dd, *J* = 6, 2 Hz, 1 H), 5.3-5.4 (m, 1 H), 6.2-6.4 (m, 2 H), 7.2-7.4 (m, 5 H); $^{13}$C NMR ($CD_2Cl_2$, 75.5 MHz) δ 17.1 (t'), 26.5 (t'), 28.5 (q'), 30.5 (t'), 50.7 (d'), 52.3 (d'), 53.1 (q'), 80.4 (s'), 122.5 (d'), 176.7 (d'), 129.3 (d'), 129.4 (d'), 134.4 (d'), 136.7 (s'), 155.7 (s'), 174.1 (s', two signals); exact mass *m/z* calcd for $C_{20}H_{27}NO_4S$ 377.16608, found 377.16589.

Isomer **61c** [a mixture of rotamers ($^1$H NMR)] had: $^1$H NMR ($CD_2Cl_2$, 200 MHz) δ 1.3-1.5 (br s, 9 H), 1.5-1.8 (m, 4 H), 1.8-2.8 (m, 2 H), 3.7 (s, 3 H), 4.2-4.4 (m, 1 H), 4.7-4.9 (m, 1 H), 5.8-6.0 (m, 1 H), 6.2-6.3 (m, 1 H), 7.2-7.4 (m, 5 H); $^{13}$C NMR ($CD_2Cl_2$, 75.5 MHz) δ 16.3 (t'), 17.3 (t'), 28.4 (q'),

28.6 (t'), 52.1 (q'), 55.1 (d'), 55.5 (d'), 80.7 (s'), 122.2 (d'), 122.7 (d'), 126.6 (d'), 129.3 (d'), 129.4 (d'), 134.3 (d'), 136.6 (s'), 173.6 (s'); exact mass *m/z* calcd for $C_{20}H_{27}NO_4S$ 377.16608, found 377.17008.

**Methyl 6-[2-(Benzyloxycarbonyl)ethenyl]-1-(*t*-butoxycarbonyl)hexahydro-2-pyridinecarboxylate (67).**




**40** **67**

Aqueous NaOH (2 N, 40 mL) was added to a solution of $BnOOCCH_2PPh_3Br$ (986 mg, 2.00 mmol) and $CHCl_3$ (40 mL) in a separatory funnel, and the mixture was shaken gently for 5 min. The organic solution was dried ($MgSO_4$) and evaporated. The residue ($BnOOCCH{=}PPh_3$) was kept under oil pump vacuum for 5 min and then dissolved in dioxane (10 mL). Aldehyde **40** (444 mg, 1.638 mmol) in dioxane (4 mL) was added to the above solution of $BnOOCCH{=}PPh_3$, and the mixture was stirred and heated in an oil bath set 90 °C. Stirring was continued for 4 h and the resulting solution was then cooled to room temperature. Evaporation of the solvent gave a white residue which was suspended in distilled hexane (20 mL) and kept overnight in a refrigerator. The resulting solid ($Ph_3PO$) was

filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:9 EtOAc-hexane, gave pure **67** ($^1$H NMR, 400 MHz) (620 mg, 94%): FTIR ($CH_2Cl_2$, cast) 1653, 1696, 1722, 2950, 2973 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.4 (s, 9 H), 1.45-1.53 (m, 2 H), 1.67-1.72 (m, 2 H), 1.84 (d, *J* = 12 Hz, 1 H), 2.24 (d, *J* = 12 Hz, 1 H), 3.6 (s, 3 H), 4.78-4.85 (br s, 2 H), 5.2 (s, 2 H), 5.89 (d, *J* = 12 Hz, 1 H), 7.01-7.15 (dd, *J* = 12, 6 Hz, 1 H), 7.38-7.43 (m, 5 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 16.2 (t'), 25.7 (t'), 27.6 (t'), 28.2 (q'), 51.2 (d'), 51.9 (q'), 52.8 (d'), 65.9 (t'), 80.7 (s'), 120.9 (d'), 128.2 (d'), 128.5 (d'), 136.1 (s'), 148.4 (d'), 155.2 (s'), 166.2 (s'), 172.8 (s'); exact mass *m/z* calcd for $C_{18}H_{21}NO_6$ (M - $C_4H_8$) 347.13690, found 347.13648.

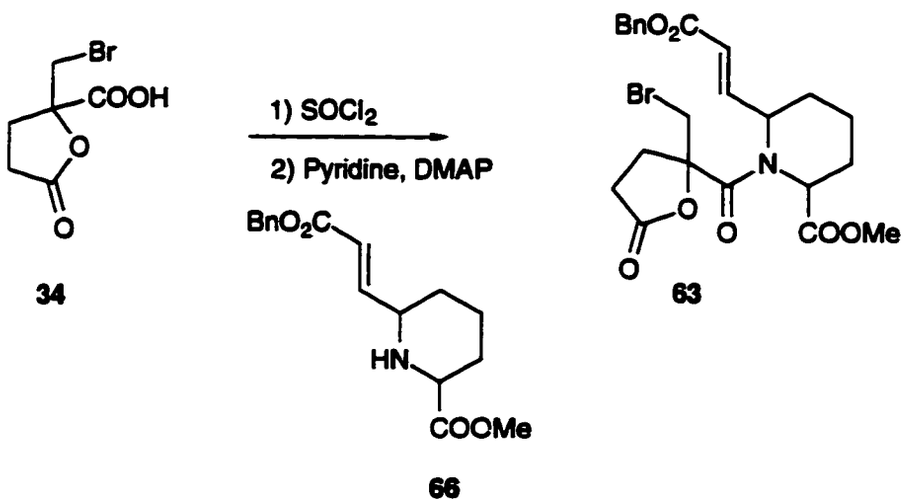
**Methyl 6-[2-(Benzyloxycarbonyl)ethenyl]hexahydro-2-pyridinecarboxylate (66).**


**67** **66**

TFA (1 mL) was added to a stirred and cooled (0 °C) solution of **67** (134 mg, 0.33 mmol) in dry $CH_2Cl_2$ (1 mL). The ice bath was removed, stirring was continued for 5 h, and the

solvent was then evaporated. The residue was dissolved in EtOAc (20 mL) and the organic solution was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), water (2 x 20 mL) and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 400 MHz) **66** (90 mg, 93%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 1656, 1621, 1737, 2855, 2948, 3350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.2-1.3 (m, 1 H), 1.4-1.6 (m, 2 H), 1.7 (d, $J$ = 12 Hz, 1 H), 1.95-2.0 (m, 2 H), 2.0 (d, $J$ = 12 Hz, 1 H), 3.3-3.4 (m, 1 H), 3.4 (dd, $J$ = 12, 3.6 Hz, 1 H), 3.7 (s, 3 H), 5.2 (s, 2 H), 6.1 (d, $J$ = 14 Hz, 1 H), 7.0 (dd, $J$ = 14, 6 Hz, 1 H), 7.4-7.7 (m, 5 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) $\delta$ 24.1 (t'), 28.4 (t'), 31.2 (t'), 51.9 (d'), 51.1 (d'), 58.6 (q'), 66.1 (t'), 120.0 (d'), 128.0 (d'), 128.1 (d'), 128.5 (d'), 135.9 (s'), 150.2 (d'), 166.1 (s'), 173.0 (s'); exact mass *m/z* calcd for $C_{17}H_{20}NO_4$ (M - 1) 302.13922, found 302.13909; calcd for $C_{15}O_{18}NO_2$ (M − COOMe) 244.13376, found 244.13385.

**Methyl 6-[2-(Benzyloxycarbonyl)ethenyl]hexahydro-1-[[2-(bromomethyl)tetrahydro-5-oxo-2-furanyl]carbonyl]-2-pyridinecarboxylate (63).**




34 66 63

$SOCl_2$ (1 mL, 13.71 mmol) was added to a stirred suspension of acid **34** (423 mg, 1.89 mmol) in dry PhH (10 mL). The mixture was refluxed and stirred for 2 h (Ar atmosphere), and then cooled to room temperature and evaporated to dryness. The freshly prepared acid chloride in PhH (5 mL) was added at room temperature (Ar atmosphere) to a solution of amine **66** (330 mg, 1.089), pyridine (0.4 mL, 4.91 mmol), and DMAP (10 mg, 0.08 mmol) in PhH (10 mL). The mixture was stirred overnight at room temperature, diluted with EtOAc (50 mL), and then washed with 1 N HCl (4 x 20 mL), water (3 x 20 mL) and brine (2 x 30 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 7:3 hexane-EtOAc, gave the product as two isomers: isomer **63a** (faster-running on TLC) (240 mg) and

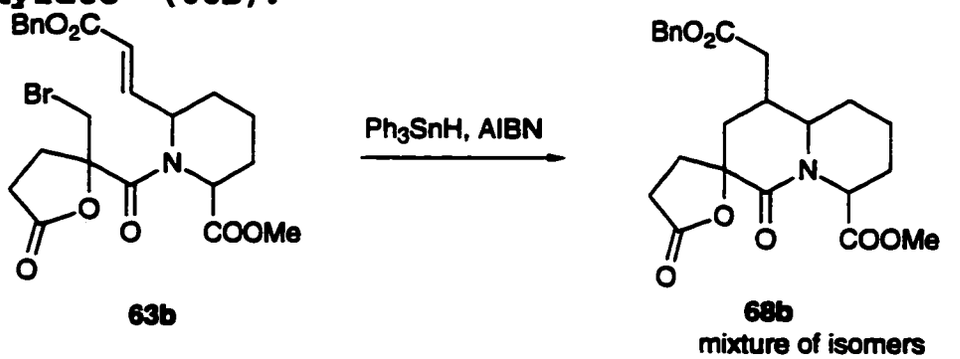
isomer **63b** (slower-running on TLC) (220 mg) (total yield 83%).

Isomer **63a** (faster-running on TLC) was a pure ($^1$H NMR, 400 MHz) single compound: FTIR ($CH_2Cl_2$, cast) 1636, 1720, 1737, 2872, 2951, 3007, 3032 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.56-1.61 (m, 2 H), 1.78-1.81 (m, 2 H), 2.05 (d, $J$ = 12 Hz, 1 H), 2.34-2.4 (m, 1 H), 2.45 (d, $J$ = 12 Hz, 1 H), 2.55-2.6 (m, 2 H), 3.0-3.1 (m, 1 H), 3.6 (s, 3 H), 3.7-4.1 (m, 2 H), 5.2 (s, 2 H), 5.34-5.42 (br, 1 H), 5.45-5.53 (m, 1 H), 6.0 (d, $J$ = 12 Hz, 1 H), 7.1-7.2 (dd, $J$ = 12, 6 Hz, 1 H), 7.34-7.42 (m, 5 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 16.0 (t'), 26.1 (t'), 27.2 (t'), 27.6 (t'), 33.1 (t'), 38.2 (t'), 50.9 (d'), 52.7 (d'), 54.7 (q'), 66.3 (t'), 88.2 (s'), 121.9 (d'), 128.3 (d'), 128.6 (d'), 135.9 (s'), 146.8 (d'), 165.9 (s'), 169.6 (s'), 172.1 (s'), 174.2 (s'); exact mass $m/z$ calcd for $C_{23}H_{26}{}^{81}BrNO_7$ 509.08722, found 509.08761; calcd for $C_{23}H_{26}{}^{79}BrNO_7$ 507.08926, found 507.08986; $C_{21}H_{23}{}^{81}BrNO_5$ (M – COOMe) 450.07391, found 450.07476; calcd for $C_{21}H_{23}{}^{79}BrNO_5$ 448.07596, found 448.07673.

Isomer **63b** (slower-running on TLC) was a mixture of rotamers and had: FTIR ($CH_2Cl_2$ cast) 1640, 1684, 1721, 1738, 1796, 2951, 3008 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.6-1.7 (m, 1 H), 1.7-1.9 (m, 3 H), 2.0-2.1 (m, 1 H), 2.3-2.8 (m, 4 H), 3.0-3.1 (m, 1 H), 3.50 and 3.60 (two s, 3 H), 3.7-4.1 (m, 2 H), 5.15-5.22 (br, 3 H), 5.34-5.44 (br 1 H), 6.0-6.2 (dd, $J$ = 18, 6 Hz, 1 H), 6.9-7.1 (m, 1 H), 7.36-7.44 (m, 5 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 15.8 (t'), 15.9 (t'), 24.5 (t'), 25.5 (t'), 26.6 (t'), 27.7 (t'), 27.9 (t'), 28.0 (t'), 31.7 (t'),

32.9 (t'), 37.3 (t'), 51.7 (d'), 52.36 (q'), 52.6 (q'), 53.5 (d'), 54.6 (d'), 66.4 (t'), 87.5 (s'), 88.1 (s'), 122.6 (d'), 128.2 (d'), 128.5 (d'), 135.9 (s'), 145.8 (d'), 147.5 (d'), 165.6 (s'), 169.7 (s'), 171.3 (s'), 171.5 (s'), 174.1 (s'); exact mass *m/z* calcd for $C_{23}H_{26}{}^{81}BrNO_7$ 509.08722, found 509.08811; calcd for $C_{23}H_{26}{}^{79}BrNO_7$ 507.08926, found 507.08936; calcd for $C_{21}H_{23}{}^{81}BrNO_5$ (M − COOMe) 450.07391, found 450.07459; calcd for $C_{21}H_{23}{}^{79}BrNO_5$ (M − COOMe) 448.07596, found 448.07637.

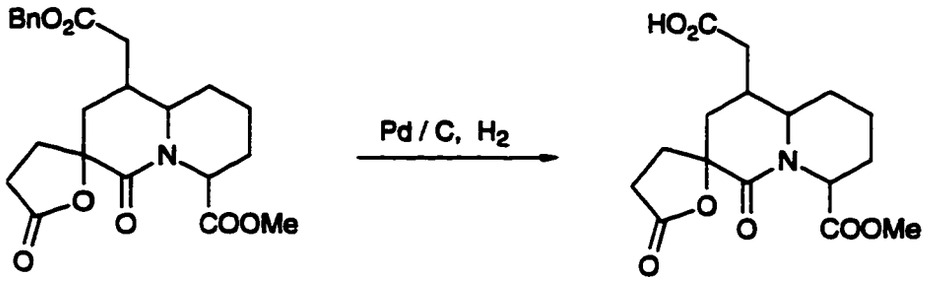
**Methyl 1'-[(Benzyloxycarbonyl)methyl]octahydro-4',5-dioxospiro[furan-2(3*H*), 3'(4'*H*)-[2*H*]quinolizine]-6'-carboxylate (68b).**




$Ph_3SnH$ (225 mg, 0.67 mmol) in PhH (10 mL) and AIBN (6 mg, 0.04 mmol) in PhH (10 mL) were added simultaneously over 5 h, by syringe pump, to a stirred and refluxing solution of **63b** (220 mg, 0.43 mmol) in PhH (5 mL). After the addition, refluxing was continued for another 10 h and the mixture was then cooled and evaporated. Flash chromatography (done twice) over silica gel (2 x 20 cm), using 1:1 EtOAc-hexane, gave **68b** (139 mg, 75%) as a mixture of isomers: exact mass

*m/z* calcd for $C_{23}H_{27}NO_7$ 429.17874, found 429.17786; calcd for $C_{21}H_{24}NO_5$ (M - COOMe) 370.16544, found 370.16515; calcd for $C_{14}H_{18}NO_5$ (M - $CH_2COOBn$) 280.11850, found 280.11790. We can not get $^1H$ and $^{13}C$ due to the mixture of isomers.

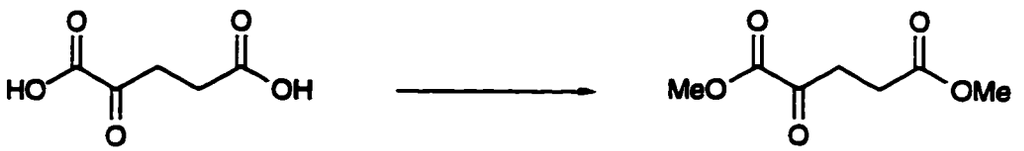
**Methyl 1'-[Carboxymethyl]octahydro-4',5-dioxospiro-[furan-2(3*H*),3'(4'*H*)-[2*H*]quinolizine]-6'-carboxylate (64).**




**68b** **64**

Benzyl ester **68b** (34 mg, 0.08 mmol) was hydrogenated (60 psi) overnight in EtOAc over Pd/C (10 mg). The catalyst was filtered off and the solvent was evaporated to leave **64** as a white foam (22 mg, 85%): FTIR ($CDCl_3$, cast) 1699, 1717, 1735, 1782, 3500, 2990 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) 1.5-1.8 (m, 7 H), 1.9-2.1 (m, 3 H), 2.2-3.9 (m, 6 H), 3.1 (d, 6 Hz, 1 H), 3.7 (s, 3 H); exact mass *m/z* calcd for $C_{16}H_{21}NO_7$ 339.13181, found 339.13136; calcd for $C_{14}H_{18}NO_5$ (M - COOMe) 280.11850, found 280.11841. An informative $^{13}C$ NMR spectrum could not be obtained because of the presence of several isomers.

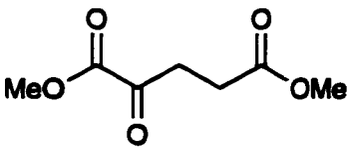
**Dimethyl α-Ketoglutarate (73).**



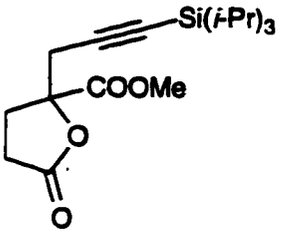
**73**

A round bottomed flask equipped with a Dean-Stark apparatus was charged with α-ketoglutaric acid (5 g, 34 mmol), $TsOH.H_2O$ (580 mg, 3.31 mmol), dry MeOH (5 mL, distilled from Mg) and dry PhMe (10 mL). The solution was refluxed for 5 h, cooled and poured into saturated aqueous $NaHCO_3$ (250 mL). The aqueous solution was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 50 mL), water (3 x 50 mL) and brine (2 x 50 mL), and dried ($MgSO_4$). Evaporation of solvent gave pure (400 $^1H$ NMR) **73** as colorless oil (3.5 g, 59%): FTIR ($CH_2Cl_2$ cast) 1735, 2850, 2957 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.65 (t, $J$ = 6 Hz, 2 H), 3.15 (t, $J$ = 6 Hz, 2 H), 3.65 (s, 3 H), 3.85 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 27.3 (t'), 34.1 (t'), 51.8 (q'), 52.9 (q'), 160.8 (s'), 172.3 (s'), 192.2 (s'); exact mass $m/z$ calcd for $C_7H_{10}O_5$ 174.05283, found 174.05249.

**Methyl Tetrahydro-5-oxo-2-[(3-triisopropylsilyl)-2-propynyl)]furancarboxylate (76).**




73

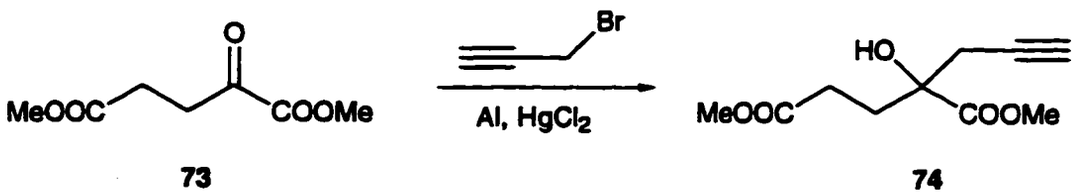




76

BuLi (1.6 M in hexane, 0.4 mL, 0.64 mmol) was added to a stirred and cooled (-20 °C) solution of 1-(triisopropylsilyl)propyne (82 mg, 0.42 mmol) and THF (1 mL). The mixture was stirred 20 min at -20 °C and then cooled to -78 °C (Ar atmosphere). Dimethyl α-ketoglutarate (106 mg, 0.611 mmol) in THF (1 mL) was added dropwise, and stirring was continued for 6 h at -78 °C (Ar atmosphere). The cooling bath was removed, the solution was quenched with saturated aqueous $NH_4Cl$ (10 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organic extracts were washed with water (3 x 5 mL) and brine (2 x 10 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:8 EtOAc-hexane, gave pure ($^1H$ NMR 300 MHz) **76** as a colorless oil (15 mg, 10%): $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.9-1.1 (br. 21 H), 2.45-2.50 (m, 2 H), 2.56-2.60 (m, 2 H), 2.95 (d, *J* = 2.7 Hz, 2 H), 3.85 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 11.2 (d'), 18.6 (q'), 28.3 (t'), 28.7 (t'), 29.6 (t'), 53.2 (q'), 84.338 (s'), 85.4 (s'), 100.6 (s'), 170.8 (s'), 175.3 (s'); exact mass *m/z* calcd for

$C_{15}H_{23}O_4Si$ ($M - CHMe_2$) 295.13657, found 295.13658.

**Dimethyl 2-Hydroxy-2-[2-(propynyl)]pentanedioate (74).**

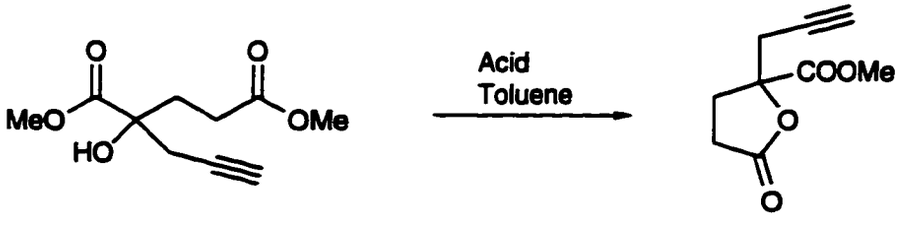



73 74

A mixture of Al powder (84 mg, 3.11 mmol) and $HgCl_2$ (5 mg, 0.02 mmol) in dry THF (3 mL) was stirred vigorously for 1 h (Ar atmosphere) in a three-necked flask fitted with a reflux condenser, and closed by septa. Most of the solvent was then withdrawn by syringe from the resulting shiny Al, and fresh THF (3 mL) was injected. The mixture was warmed in an oil bath set at 40 °C, and propargyl bromide (363 mg, 3.05 mmol) in THF (1 mL) was then added slowly with vigorous stirring and at such a rate that the THF did not boil. The addition took *ca.* 10 min. After the addition, stirring at 40 °C was continued until a dark gray solution was obtained (*ca.* 1 h). The solution of propargyl aluminum sesquibromide was cooled to room temperature, and added by cannula at a fast dropwise rate to a stirred and cooled (-78 °C) solution of dimethyl 2-ketoglutarate (158 mg, 0.90 mmol) in THF (5 mL). Stirring at -78 °C was continued for 4 h, and the mixture was then poured into ice-water (100 mL), and extracted with $Et_2O$ (4 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Flash

chromatography of the residue over silica gel (2 x 16 cm), using 3:7 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) **74** (185 mg, 95%) as a colorless oil: FTIR (KBr) 3502, 3286, 1739 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) δ 2.05-2.10 (m, 3 H), 2.15-2.26 (m, 1 H), 2.4-2.5 (m, 1 H), 2.5-2.63 (ABX, $J_{AB}$ = 16.9, $J_{AX}$ = 2.7, $J_{BX}$ = 2.7 Hz, 2 H), 3.52 (s, 1 H), 3.65 (s, 3 H), 3.78 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) 28.6 (t'), 30.2 (t'), 32.8 (t'), 51.8 (q'), 53.2 (q'), 71.6 (s'), 75.8 (d'), 78.4 (s'), 173.3 (s'), 174.8 (s'); exact mass *m/z* calcd for $C_9H_{11}O_4$ (M - $OCH_3$) 183.06573 found 183.06573.

**Methyl Tetrahydro-5-oxo-2-[2-(propynyl)]furan-carboxylate (75).**

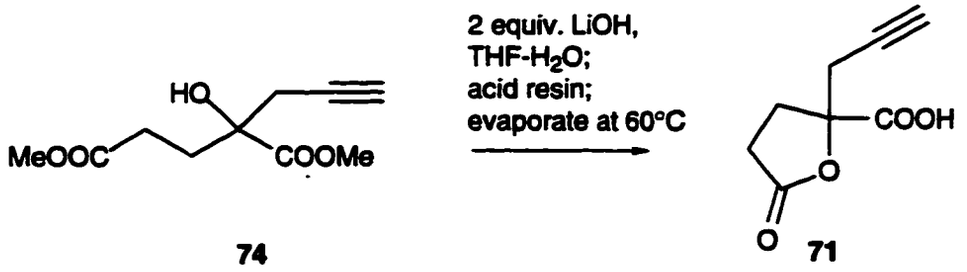



**74** **75**

A three-necked 100-mL round bottomed flask equipped with a Dean-Stark apparatus and condenser was charged with **74** (1.610 g, 7.51 mmol), $TsOH.H_2O$ (181 mg, 0.95 mmol) and dry PhMe (70 mL). The solution was refluxed for 3 h, cooled to room temperature, and poured into saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), water (3 x 20 mL) and brine (2 x

30 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **75** as colorless oil (900 mg, 66%): FTIR ($CHCl_3$, cast) 1743, 1787, 3283 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.1 (t, $J$ = 2.3 Hz, 1 H), 2.5-2.6 (m, 2 H), 2.7-2.8 (m, 2 H), 2.9 (narrow multiplet of ABX spectrum, 2 H), 3.8 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) $\delta$ 27.3 (t'), 28.2 (t'), 29.7 (t'), 53.3 (q'), 72.3 (d'), 84.0 (s'), 170.7 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_7H_7O_2$ (M - COOMe) 123.04460, found 123.04468.

**Tetrahydro-5-oxo-2-[2-(propynyl)]-2-furancarboxylic acid (71).**




74 71

Note that in the following experiment we do not know the order in which hydrolysis and lactonization occur.

LiOH (509 mg, 10.37 mmol) in water (2 mL) was added to a solution of diester **74** (1.00 g, 4.67 mmol) in THF (20 mL), and the mixture was stirred overnight at room temperature. Evaporation of the solvent gave what we assumed to be the dilithium salt, as a solid.

A column packed with Amberlite IR-120 ion-exchange resin

(20-50Å mesh, 2.5 x 16 cm) was washed with water until the eluent was colorless. The column was then washed successively with 2 N aqueous NaOH (4 bed volumes), water (until the eluent was neutral to pH paper), 2 N HCl (4 bed volumes), and finally with water (until the eluent was neutral to pH paper). The dilithium salt was dissolved in water (*ca.* 2-3 mL) and the solution was passed down the column, using water. The eluent was monitored with pH paper or by TLC (silica, 1:9 MeOH-$CHCl_3$). Evaporation of the combined acidic fractions (water pump, rotary evaporator, bath temperature 65-70 °C) gave lactone acid **71** (746 mg, 95%) as a pure ($^1$H NMR, 300 MHz), light yellow powder: FTIR (KBr) 1720 1770, 2500-3500 (br) $cm^{-1}$; $^1$H NMR ($D_2O$, 300 MHz) δ 2.45-2.70 (m, 3 H), 2.75-2.85 (m, 2 H), 2.9-3.1 (ABX, $J_{AB}$ = 16.9, $J_{AX}$ = 2.9, $J_{BX}$ = 2.9 Hz, 2 H); $^{13}$C NMR ($D_2O$, 75.5 MHz) δ 27.8 (t'), 29.0 (t'), 30.7 (t'), 73.3 (d'), 79.1 (s'), 86.9 (s'), 174.8 (s'), 180.5 (s'); exact mass *m/z* calcd for $C_5H_5O_4$ (M - $CH_2C{\equiv}CH$) 129.01878, found 129.01892; mass (FAB) *m/z* calcd for $C_8H_8O_4$ 168.15056, found (FAB) 168.9.

**N-Benzyl Tetrahydro-5-oxo-2-[2-(propynyl)]furan-carboxamide (79).**


**71** **79**

Lactone acid **71** (84 mg, 0.51 mmol) was dissolved in a mixture of dry DMF (1 mL) and dry $CH_2Cl_2$ (1 mL). HOBT (64 mg, 0.47 mmol) and benzylamine (49 mg, 0.46 mmol) were added, followed by DCC (97 mg, 0.47 mmol). The mixture was stirred overnight (Ar atmosphere) at room temperature, and the resulting solid was filtered off. The filtrate was diluted with EtOAc (20 mL) and washed with water (5 x 10 mL) and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **79** as a yellow oil (112 mg, 93%): FTIR ($CHCl_3$, cast) 1605, 1672, 1787, 3290, 3350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) δ 2.1-2.15 (m, 1 H), 2.45-2.5 (m, 2 H), 2.67-2.7 (m, 2 H), 2.9-2.95 (m, 2 H), 4.45-4.5(m, 2 H), 7.00-7.1 (br s, 1 H), 7.3-7.33 (m, 5 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 28.3 (t'), 28.6 (t'), 29.8 (t'), 43.5 (t'), 72.3 (d'), 85.6 (s'), 127.7 (d'), 127.8 (d'), 128.7 (d'), 137.3 (s'), 170.5 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_{15}H_{15}NO_3$ 257.10519, found 257.10513.

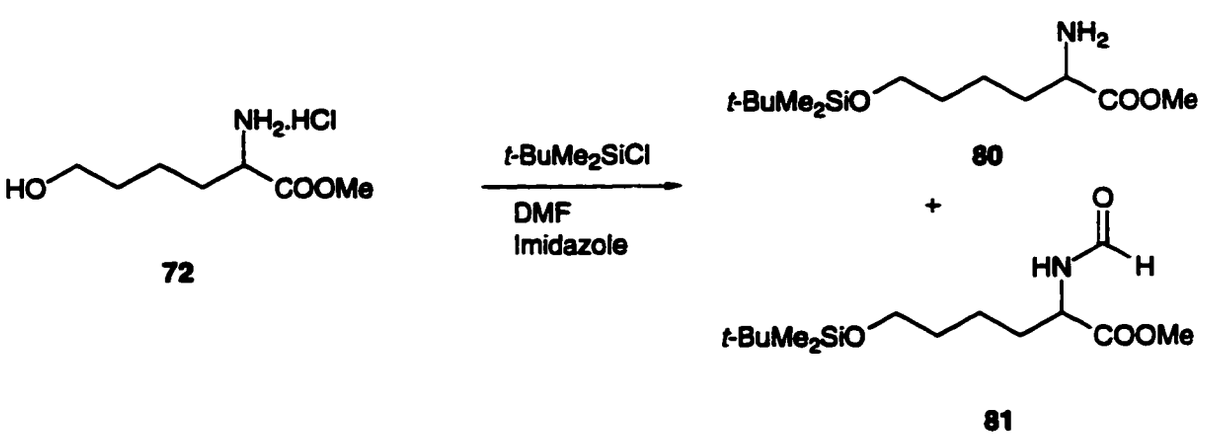
**6-Hydroxynorleucine Methyl Ester Hydrochloride (72).**


**72**

6-Hydroxynorleucine (1.06 g, 7.21 mmol) and then $Me_3SiCl$

(4.6 mL, 36.24 mmol) were added to dry MeOH (20 mL, freshly distilled from Mg), and the solution was stirred for 42 h at room temperature (protection from moisture by a tube filled with Drierite). The solvent was then evaporated. PhMe (20 mL) was added and evaporation was repeated. PhMe (20 mL) was added twice more and, after each addition, the solvent was evaporated. Finally, the residue was kept under good oil pump vacuum for 3 days to remove the last traces of solvent, and to afford the pure ($^1$H NMR, 300 MHz) **72** (1.42, 100%) as a colorless oil: $^1$H NMR ($D_2O$, 300 MHz) δ 1.5-1.6 (m, 2 H), 1.6-1.7 (m, 2 H), 2.0-2.1 (m, 2 H), 3.6 (t, *J* = 6.8 Hz, 2 H), 3.9 (s, 3 H), 4.2 (t, *J* = 6.8 Hz, 2 H); $^{13}$C NMR ($D_2O$, 100.6 MHz) δ 21.6 (t'), 30.3 (t'), 31.5 (t'), 53.6 (q'), 54.3 (d'), 61.9 (t'), 171.6 (s').

**6-[(*t*-Butyldimethylsilyl)oxy]norleucine Methyl Ester (80) and *N*-Formyl-6-[(*t*-butyldimethylsilyl)oxy]norleucine Methyl Ester (81).**



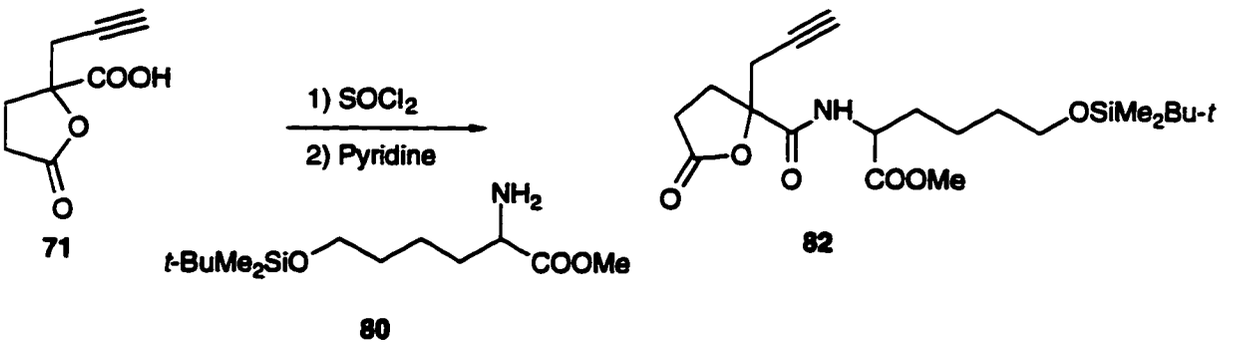
TBDMSCl (241 mg, 1.59 mmol) and imidazole (216 mg, 3.14 mmol) were added to a solution of **72** (310 mg, 1.57 mmol) in dry DMF (1 mL). Stirring was continued overnight (Ar atmosphere) and the mixture was diluted with $Et_2O$ (30 mL), washed with water (5 x 15 mL) and brine (3 x 10 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:1 EtOH:hexane, gave two compounds **80** (slower-running on TLC) (159 mg, 37%) and **81** (faster-running on TLC) (250 mg, 52%).

Compound **80** was a pure ($^1H$ NMR, 300 MHz), colorless oil ($^1H$ NMR, 300 MHz) and had: FTIR ($CHCl_3$, cast) 1698, 1702, 3384 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.05 (s, 6 H), 0.9 (s, 9 H), 1.4-1.5 (m, 2 H), 1.5-1.6 (m, 5 H), 1.8-1.7 (m, 1 H), 3.4 (dd, $J$ = 8.5, 7 Hz, 1 H), 3.6 (t, $J$ = 6.8 Hz, 2 H), 3.7 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) $\delta$ -5.4 (q'), 18.2 (s'), 21.8 (t'), 25.8 (q'), 32.4 (t'), 34.7 (t'), 51.7 (d'), 54.3 (q'), 62.7 (t'), 176.4 (s'); exact mass *m/z* calcd for $C_{13}H_{29}NO_3Si$ 275.19168, found 275.19198.

Compound **81** was a pure, colorless oil ($^1H$ 400 MHz) and had: FTIR ($CHCl_3$ cast) 1665, 1747, 3295 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.5 (s, 6 H), 0.9 (s, 9 H), 1.4-1.45 (m, 2 H), 1.5-1.53 (m, 2 H), 1.7-1.73 (m, 1 H), 1.9-1.93 (m, 1 H), 3.6-3.63 (m, 2 H), 3.7 (s, 3 H), 4.7-4.73 (m, 1 H), 6.2-6.23 (br, 1 H), 8.2 (s, 1 H); $^{13}C$ ($CDCl_3$, 75.5 MHz) $\delta$ -5.42 (q'), 18.2 (s'), 21.5 (t'), 25.8 (q'), 32.03 (t'), 32.05 (t'), 50.7 (d'), 52.3 (q'), 62.5 (t'), 160.8 (d'), 172.5 (s'); exact

mass *m/z* calcd for $C_{13}H_{26}NO_4Si$ (M − Me) 288.16312, found 288.16284; calcd for $C_{13}H_{26}NO_3Si$ (M − $OCH_3$) 272.16818, found 272.16788.

**6-[(t-Butyldimethylsilyl)oxy]-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]norleucine Methyl Ester (82).**



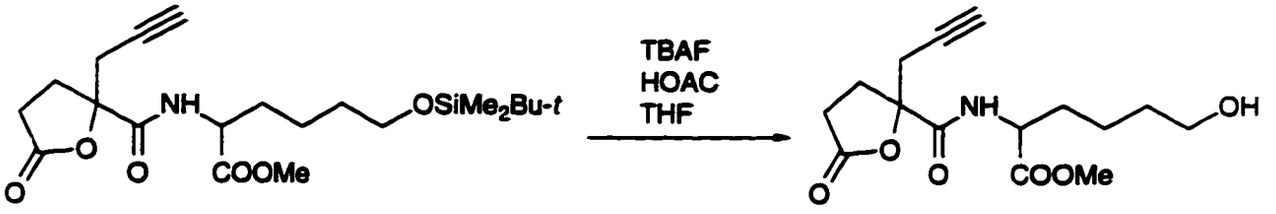

$SOCl_2$ (0.5 mL, excess) was added to a stirred mixture of **71** (82 mg, 0.48 mmol) in dry PhH (5 mL) (protection from moisture by a drying tube filled with Drierite). The mixture was refluxed and Ar was bubbled through the solution to expel HCl. After 1 h at reflux, the solvent was evaporated (protection from moisture). The resulting freshly prepared acid chloride in $CH_2Cl_2$ (2 mL) was added to a solution of amine **80** (138 mg, 0.51 mmol) and pyridine (0.2 mL, excess) in dry $CH_2Cl_2$ (3 mL). The resulting mixture was stirred at room temperature under Ar for 4 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 3:7 EtOAc-hexane, gave two pure isomers **82a** (faster-running on TLC) (131 mg) and **82b** (slower-running on TLC) (30

mg) (total yield 76%).

The pure ($^1$H NMR, 300 MHz) isomer **82a** had: FTIR ($CHCl_3$, cast) 1678, 1756, 1791, 2953, 3311, 3349 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0 (s, 6 H), 0.8 (s, 9 H), 1.3-1.6 (m, 4 H), 1.7-1.8 (m, 1 H), 1.9-2.0 (m, 1 H), 2.1 (t, $J$ = 2.9 Hz, 1 H), 2.5-2.8 (m, 4 H), 2.9 ABX, $J$ = 2.9 1.26 Hz, 2 H), 3.6 (t, $J$ = 5.9 Hz, 2 H), 3.7 (s, 3 H), 4.5-4.6 (m, 1 H), 6.9 (d, $J$ = 8.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ -5.4 (q'), 18.3 (s'), 22. (t'), 25.9 (q'), 28.4 (t'), 28.5 (t'), 29.5 (t'), 31.9 (t'), 32.1 (t'), 52.3 (d'), 52.4 (q'), 62.6 (t'), 72.4 (d'), 77.2 (s'), 85.3 (s'), 170.8 (s'), 171.8 (s'), 174.9 (s'); exact mass *m/z* calcd for $C_{21}H_{35}NO_6Si$ 425.22336, found 425.22400.

The pure ($^1$H NMR, 360 MHz) isomer **82b** had: FTIR ($CHCl_3$, cast) 1678, 1745, 1792, 3312, 3350 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 0.0 (s, 6 H), 0.9 (s, 9 H), 1.4-1.5 (m, 2 H), 1.5-1.6 (m, 2 H), 1.7-1.8 (m, 1 H), 1.9-2.0 (m, 1 H), 2.1 (t, $J$ = 3.2 Hz, 1 H), 2.4-2.5 (m, 1 H), 2.6-2.7 (m, 2 H), 2.7-2.8 (m, 1 H), 2.9 (d, $J$ = 2.8 Hz, 2 H), 3.6 (t, $J$ = 6.8 Hz, 2 H), 3.9 (s, 3 H), 4.5-4.6 (m, 1 H), 6.8 (d, $J$ = 8.3 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ -5.3 (q'), 18.3 (s'), 21.9 (t'), 25.9 (q'), 28.3 (t'), 28.6 (t'), 29.9 (t'), 31.7 (t'), 32.1 (t'), 52.38 (q'), 52.4 (d'), 62.6 (t'), 72.4 (d'), 77.3 (s'), 85.4 (s'), 170.7 (s'), 172.0 (s'), 175.1 (s'); exact mass *m/z* calcd for $C_{20}H_{32}NO_6Si$ (M - $CH_3$) 410.19989, found 410.19955.

**6-Hydroxy-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]norleucine Methyl Ester (84).**



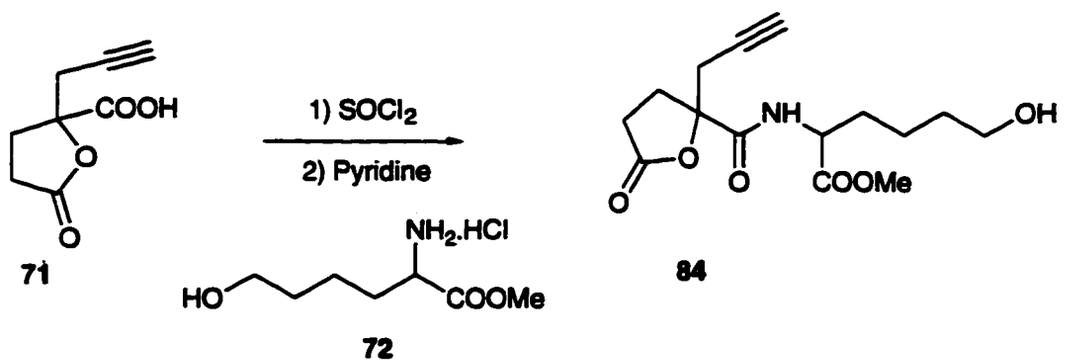

**82** **84**

TBAF (1 M in THF, 1.4 mL, 1.41 mmol) and acetic acid (0.12 mL, 3.41 mmol) were added to a solution of **82a** (chromatographically faster-running isomer of **82** (410 mg, 0.97 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C. The cold bath was removed and stirring was continued for 4 h. The solution was then diluted with EtOAc (40 mL), washed with water (4 x 10 mL) and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 7:3 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) **84a** (279 mg, 93%) as an oil. This material is the same ($^1$H NMR) as the chromatographically slower-running product obtained from the EDCI coupling reaction of the unprotected alcohol (see later).

The above procedure was followed, using TBAF (1 M, 0.9 mL, 0.91 mmol), acetic acid (0.08 mL, 1.39 mmol), **82b** (chromatographically slower-running isomer of **82**, (240 mg, 0.56 mmol). Flash chromatography of the crude product over silica gel (1.5 x 20 cm), using 7:3 EtOAc-hexane, gave **84b**

(149 mg, 85%) as an oil. The material is the same as the chromatographically faster-running product obtained from the EDCI coupling reaction of the unprotected alcohol (see later).

**6-Hydroxy-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]norleucine Methyl Ester (84). (Alternative way to make 84).**

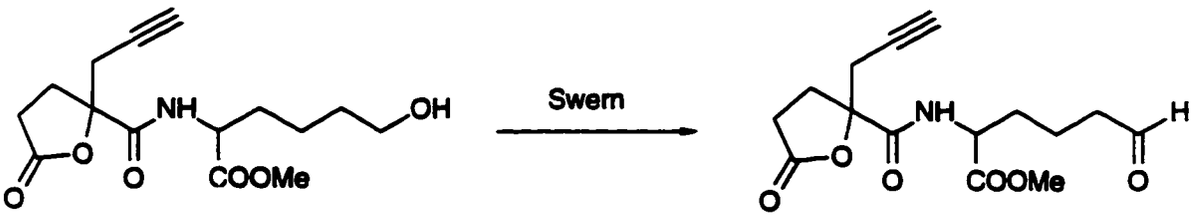



$SOCl_2$ (0.5 mL, 6.91 mmol) was added to a suspension of the acid **71** (173 mg, 1.02 mmol) in dry PhH (5 mL), and the mixture was refluxed with stirring for 2 h (protection from moisture by a drying tube packed with Drierite), cooled and evaporated to dryness, with protection from moisture. The resulting freshly prepared acid chloride in $CH_2Cl_2$ (3 mL) was added to a stirred and cooled (0 °C) mixture of amine salt **72** (257 mg, 1.29 mmol), pyridine (0.6 mL, 7.31 mmol) and $Et_3N$ (0.3 mL, 2.15 mmol) in $CH_2Cl_2$ (5 mL) (Ar atmosphere). Stirring was continued for 2 h and the mixture was quenched with water (30 mL) and extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were washed with water (3 x 10 mL)

and brine (2 x 20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 7:3 EtOAc-hexane, gave **84** as an oil in three fractions, two containing the individual pure isomers, and the third containing both isomers (total weight 123 mg, total yield 39%).

The chromatographically slower-running isomer is identical to the chromatographically slower-running isomer prepared by EDCI coupling of the unprotected alcohol (see later). The chromatographically faster-running isomer is identical to the chromatographically faster-running isomer prepared by EDCI coupling of the unprotected alcohol.

**6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]-carbonyl]norleucine Methyl Ester (70).**



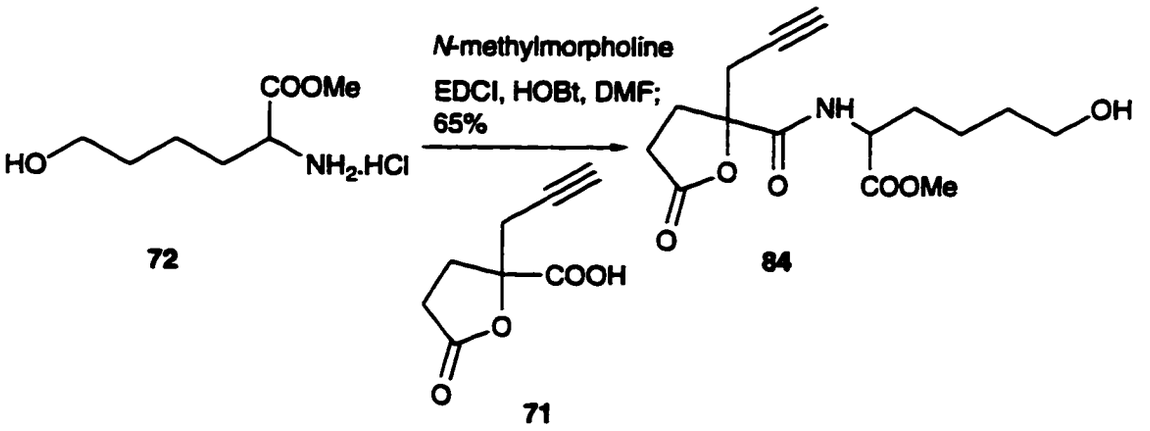

**84** **70**

Freshly distilled DMSO (0.175 mL, 2.51 mmol) was added slowly (Ar atmosphere) to a stirred and cooled (-78 °C) solution of oxalyl chloride (0.14 mL, 1.61 mmol) in dry $CH_2Cl_2$ (2 mL). There was immediate gas evolution. After 0.5 h, **84a** (chromatographically slower-running isomer of **84** (150 mg, 0.48 mmol) in dry $CH_2Cl_2$ (2 mL) was added dropwise. The

mixture was stirred for 1 h at -78 °C, and then $Et_3N$ (0.5 mL, 3.58 mmol) was added, and the cooling bath was removed. The mixture was stirred for another 2 h, quenched with water (20 mL), and extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with water (3 x 10 mL) and brine (2 x 10 mL), and dried ($MgSO_4$). Evaporation of solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **70a** (53 mg, 36%). The material was identical to that prepared by PCC oxidation (see later).

The above procedure was followed, using oxalyl chloride (0.078 mL, 0.89 mmol), DMSO (0.126 mL, 1.71 mmol), **84b** (chromatographically faster-running isomer of **84**, 125 mg, 0.40 mmol) and $Et_3N$ (0.246 mL, 1.76 mmol). Flash chromatography of the crude product over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **70b** (37 mg, 30%). The material was identical to that obtained by PCC oxidation (see later).

**6-Hydroxy-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]norleucine Methyl Ester (84). (Alternative way to make 84).**




The methyl ester hydrochloride salt was prepared from ε-hydroxynorleucine (666 mg, 4.53 mmol) by treatment with saturated methanolic HCl, exactly as described in the literature.[44] Evaporation of the solvent gave the crude ester hydrochloride, which was used directly after being kept overnight under oil pump vacuum. The material was covered with dry DMF (2 mL) and $CH_2Cl_2$ (8 mL), and the mixture was stirred with a glass rod for *ca.* 1 h, by which stage all of the salt had dissolved [use of a magnetic stirring bar was unsuccessful because of the sticky nature of the material]. *N*-Methylmorpholine (4 mL, 36.38 mmol) was then added, and the mixture was stirred (magnetic stirring bar) (Ar atmosphere). After 1 h, the solid lactone acid (760 mg, 4.52 mmol) and 1-hydroxybenzotriazole (608 mg, 4.50 mmol) were tipped into the solution, followed by 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide (872 mg, 4.55 mmol). Stirring at room temperature was continued overnight (Ar atmosphere), and then water (100 mL) was added. The mixture was extracted with $CHCl_3$ (4 x 70 mL), and the combined organic extracts were washed with water (3 x 50 mL) and brine (2 x 70 mL), dried ($MgSO_4$), and evaporated. The crude product was kept overnight under oil pump vacuum to remove traces of *N*-methylmorpholine. Flash chromatography of the material over silica gel (2.5 x 20 cm), using 3:1 EtOAc-hexane, gave **84** as an oil in three fractions, two containing the individual pure isomers, and the third fraction containing both isomers.

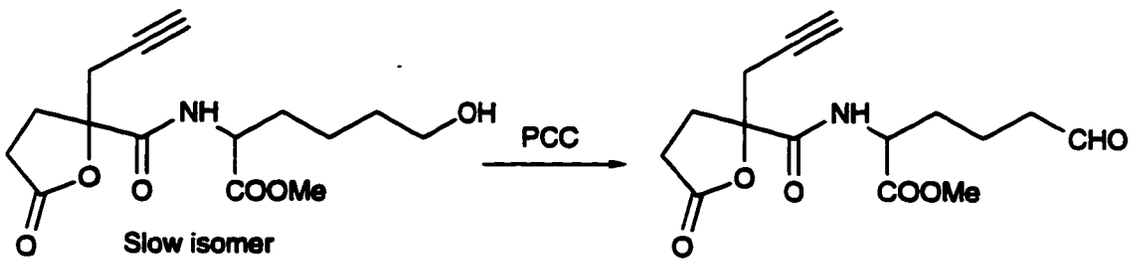
The chromatographically slower-running material (isomer **84a**) (320 mg) had: FTIR ($CHCl_3$ cast) 1672, 1741, 1788, 3286, 3355 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 400 MHz) $\delta$ 1.3-1.42 (m, 2 H), 1.5-1.6 (m, 2 H), 1.7-1.8 (m, 2 H), 1.85-1.95 (m, 1 H), 2.18 (t, $J$ = 2.4 Hz, 1 H), 2.4-2.65 (m, 3 H), 2.7-2.75 (m, 1 H), 2.8-2.83 (ABX, $J$ = 2.8, 0.8 Hz, 2 H) 3.6 (t, $J$ = 6.4, 2 H), 3.75 (s, 3 H), 4.45-4.5 (m, 1 H), 6.95 (d, $J$ = 8.0 Hz, 1 H); $^{13}C$ ($CDCl_3$, 100.6 MHz) $\delta$ 21.8 (t'), 28.4 (t'), 28.4 (t'), 29.5 (t'), 31.5 (t'), 31.6 (t'), 52.2 (q'), 52.5 (d'), 62.1 (t'), 72.4 (s'), 77.2 (d'), 85.4 (s'), 170.9 (s'), 171.8 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_{15}H_{21}NO_6$ 311.13690, found 311.13648.

The chromatographically faster-running material (isomer **84b**) (250 mg) had: FTIR ($CHCl_3$ cast) 1674, 1742, 1790, 3286, 3341 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 400 MHz) $\delta$ 1.4-1.5 (m, 2 H), 1.5-1.6 (m, 3 H), 1.7-1.75 (m, 1 H), 1.9-1.95 (m, 1 H), 2.16 (t,

$J$ = 2.4 Hz, 1 H), 2.35-2.45 (m, 1 H), 2.50-2.65 (m, 2 H), 2.65-2.75 (m, 1 H), 2.75-2.90 (ABX, $J_{AB}$ = 17.6, $J_{AX}$ = 2.5, $J_{BX}$ = 2.5 Hz, 2 H), 3.60-3.70 (dd, $J$ = 10.9, 5.4 Hz, 2 H), 3.70 (s, 3 H), 4.45-4.50 (m, 1 H), 6.9-7.00 (d, $J$ = 7.6 Hz, 1 H); $^{13}C$ ($CDCl_3$, 100.6 MHz) δ 21.9 (t'), 28.3 (t'), 28.6 (t'), 30.0 (t'), 31.5 (t'), 31.8 (t'), 52.4 (q'), 52.5 (d'), 62.3 (t'), 72.4 (s'), 85.5 (s'), 170.8 (s'), 172.0 (s'), 175.1 (s') (two signals overlap); exact mass $m/z$ calcd for $C_{15}H_{21}NO_6$ 311.133690, found 311.13723.

The mixed fraction (both isomers) weighed 343 mg. The total yield amounted to 65% in all.

**Oxidation of slower-running isomer 84a to 6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-norleucine Methyl Ester (70a).**

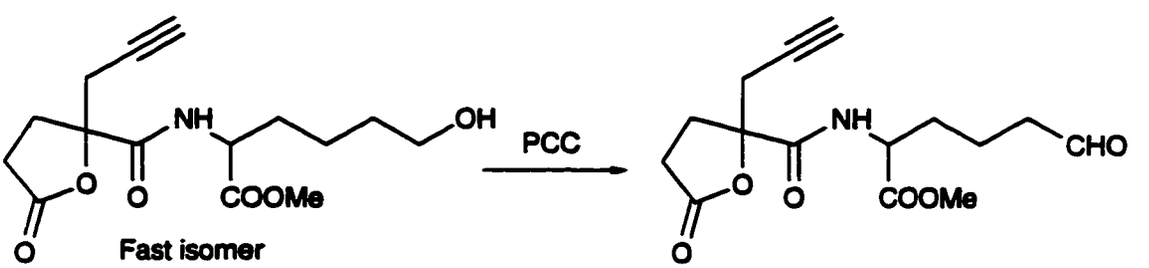



**84a** **70a**

PCC (1.20 g, 5.45 mmol) was added to a stirred mixture of the chromatographically slower-running alcohol **84a** (300 mg, 0.96 mmol) and crushed 4Å molecular sieves (1.20 g) in dry $CH_2Cl_2$ (10 mL). Stirring was continued for 1.5 h (Ar atmosphere), and the mixture was then filtered. The solids

were washed with a little $CH_2Cl_2$, and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using 1:1 EtOAc-hexane, gave aldehyde **70a** as a pure ($^1H$ NMR, 300 MHz), colorless oil (190 mg, 66%): FTIR ($CHCl_3$ cast) 1676, 1724, 1741, 1789, 2732, 3281, 3353 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 300 MHz) δ 1.6-1.85 (m, 3 H), 1.85-1.95 (m, 1 H), 2.2 (t, *J* = 2.9 Hz, 1 H), 2.4-2.5 (m, 3 H), 2.5-2.8 (m, 3 H), 2.85 (ABX, 2 H) 3.75 (s, 3 H), 4.45-4.55 (m, 1 H), 6.9-7.0 (br, 1 H), 9.7 (t, *J* = 1.2 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 75.5 Hz) 17.7 (t'), 28.4 (t'), 28.6 (t'), 29.7 (t'), 31.4 (t'), 42.9 (t'), 52.0 (q'), 52.6 (d'), 72.1 (d'), 77.2 (s') 85.3 (s'), 171.0 (s'), 171.4 (s'), 175.1 (s'), 201.2 (d'); exact mass *m/z* calcd for $C_{15}H_{19}NO_6$ 309.12125, found 309.12152.

**Oxidation of faster-running isomer 84b to 6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-norleucine Methyl Ester (70b).**



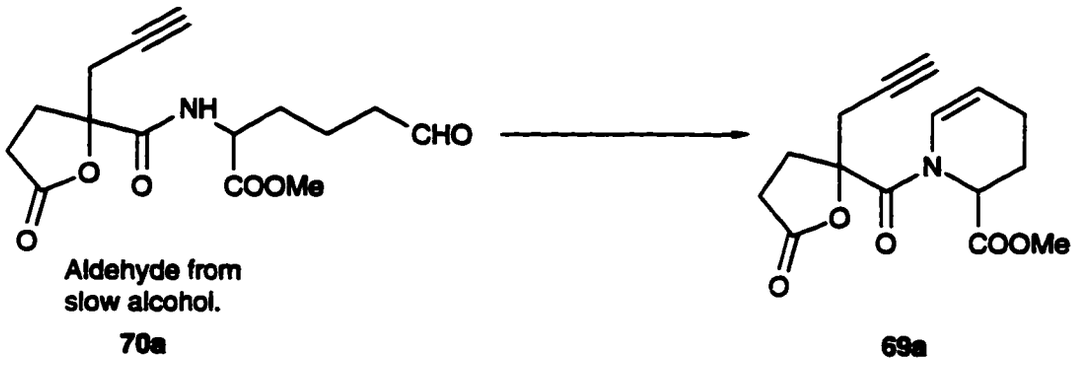

**84b** **70b**

The above procedure was followed, using PCC (880 mg, 4.01 mmol), the chromatographically faster-running alcohol **84b** (200 mg, 0.64 mmol), crushed 4Å molecular sieves (880 mg)

and dry $CH_2Cl_2$ (10 mL). Flash chromatography of the crude product over silica gel (2 x 22 cm), using 1:1 EtOAc-hexane, gave aldehyde **70b** as a pure ($^1H$ NMR, 300 MHz), colorless oil (173 mg, 87%): FTIR ($CHCl_3$ cast) 1676, 1723, 1741, 1789, 2731, 3283, 3357 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 300 MHz) $\delta$ 1.65-1.8 (m, 3 H), 1.85-1.90 (m, 1 H), 2.15 (t, $J$ = 2.7 Hz, 1 H), 2.3-2.4 (m, 1 H), 2.45-2.75 (m, 5 H), 2.80-2.95 (ABX, $J_{AB}$ = 17.4, $J_{AX}$ = 2.7, $J_{BX}$ = 2.7 Hz, 2 H), 3.75 (s, 3 H), 4.5-4.6 (m, 1 H), 6.9-7.0 (br, 1 H), 9.75 (t, $J$ = 1.2 Hz, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 50.3 Hz) $\delta$ 18.0 (t'), 28.1 (t'), 28.6 (t'), 30.1 (t'), 30.9 (t'), 42.9 (t'), 52.0 (q'), 52.4 (d'), 72.0 (d'), 77.7 (s'), 85.5 (s'), 170.6 (s'), 171.7 (s'), 175.1 (s'), 201.7 (d'); exact mass *m/z* calcd for $C_{15}H_{19}NO_6$ 309.12125, found 309.12229; calcd. for $C_{14}H_{18}O_5N$ (M - CHO) 280.11850, found 280.11862.

Note that the two aldehydes (from the two alcohols) have the same $R_f$.

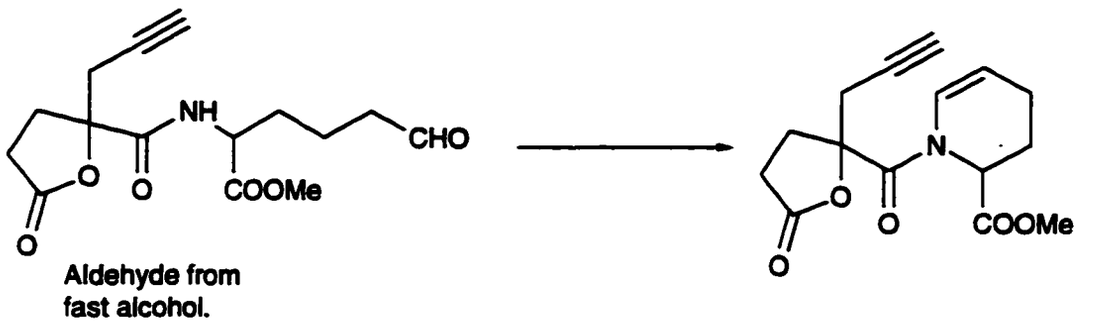
**Methyl 1,2,3,4-Tetrahydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-2-pyridinecarboxylate (69a).**



For this reaction the $CF_3COOH$ must be freshly distilled from $P_2O_5$, but can be stored for 1 week in a tightly stoppered flask kept in a small desiccator containing Drierite. TFA (0.40 mL, 5.19 mmol) was added to a stirred mixture of aldehyde **70a** (150 mg, 0.49 mmol) from the chromatographically slower-running alcohol and crushed 4Å molecular sieves (150 mg) in dry $CH_2Cl_2$ (5 mL) (Ar atmosphere). Stirring at room temperature was continued for 3-4 h, the course of the reaction being closely followed by TLC (silica, 3:7 EtOAc-hexane). As soon as the reaction was complete, the mixture was filtered, and the solids were washed with a little $CH_2Cl_2$. Evaporation of the combined filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) **69a** (122 mg, 82%) as a colorless oil. At room temperature the material consisted of a mixture of two rotamers (variable temperature $^1H$ NMR): FTIR ($CHCl_3$, cast) 1643, 1743, 1794, 3270 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 300 MHz) δ 1.9-2.17 (m, 3 H), 2.18-2.25 (m, 1 H) 2.25-2.60 (m, 3 H), 2.60-2.85 (m, 2 H), 2.90-3.05 (m, 2 H), 3.75 (s, 3 H), 5.05-5.50 (br, 2 H), 7.10-7.20 (br, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 100.6 MHz) (mixture of rotamers) δ 19.7 (t'), 19.2 (t'), 23.7 (t'), 24.3 (t'), 27.8 (t'), 28.2 (t'), 28.8 (t'), 30.3 (t'), 30.7 (t'), 33.1 (t'), 52.7 (d'), 53.0 (d'), 54.1 (q'), 56.5 (q'), 72.5 (d'), 72.9 (d'), 77.1 (s'), 77.8 (s'), 86.7 (s'), 87.6 (s'), 108.6 (d'), 110.8 (d'), 124.5 (d'), 125.2 (d'), 167.8 (s'), 168.1 (s'), 170.8 (s'), 171.6 (s'), 174.9 (s'), 175.4 (s'); exact mass *m/z* calcd for

$C_{15}H_{17}NO_5$ 291.11069, found 291.11123.

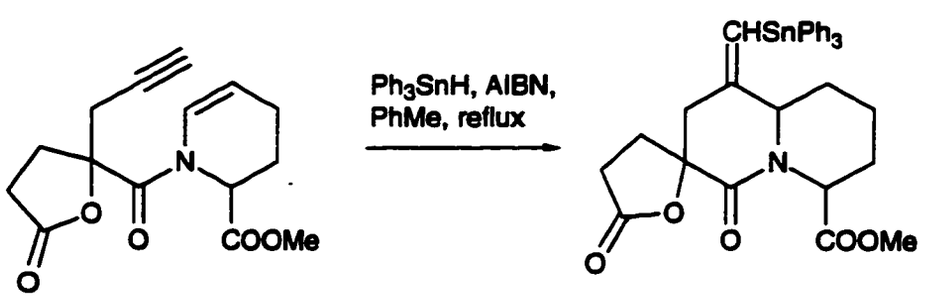
**Methyl 1,2,3,4-Tetrahydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-2-pyridinecarboxylate (69b).**




The above procedure was followed, using TFA (0.50 mL, 6.49 mmol), the chromatographically faster-running alcohol **70b** (222 mg, 0.72 mmol), crushed 4Å molecular sieves (222 mg) and dry $CH_2Cl_2$ (5 mL). Stirring at room temperature was continued for 3-4 h, the course of the reaction being closely followed by TLC (silica, 3:7 EtOAc-hexane). Flash chromatography of the crude product over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) **69b** (120 mg, 65% after correction for recovered starting material) as a colorless oil, and recovered starting material (31 mg, 14%). An increase in reaction time gave a lower yield. At room temperature the product is a single isomer [sharp signals in the $^1$H MHz NMR spectrum (300 MHz)]: FTIR ($CHCl_3$ cast) 1643, 1667, 1743, 1793, 3268 $cm^{-1}$; $^1$H NMR

($CD_2Cl_2$, 300 MHz) δ 1.85-2.05 (m, 3 H) 2.15 (t, *J* = 2.7 Hz, 1 H), 2.30-2.40 (m, 2 H), 2.50-2.75 (m, 2 H), 2.85-2.95 (ABX, 2 H), 2.98-3.05 (m, 1 H), 3.75 (s, 3 H), 5.00-5.10 (br, 1 H), 5.12-5.22 (br, 1 H), 7.1 (d, *J* = 8.7 Hz, 1 H); $^{13}C$ NMR ($CD_2Cl_2$, 100.6 MHz) δ 19.3 (t'), 23.9 (t'), 28.2 (t'), 29.0 (t'), 30.8 (t'), 52.8 (d'), 54.1 (q'), 72.9 (d'), 77.2 (s'), 86.7 (s'), 109.2 (d'), 124.9 (d'), 167.2 (s'), 170.9 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_{15}H_{17}NO_5$ 291.11069, found 291.11014.

**Methyl Octahydro-4',5-dioxo-1'-[(triphenylstannyl)-methylene]-spiro[furan-2(3*H*),3'(4*H*')-[2*H*]quinolizine]-6'-carboxylate (85a).**



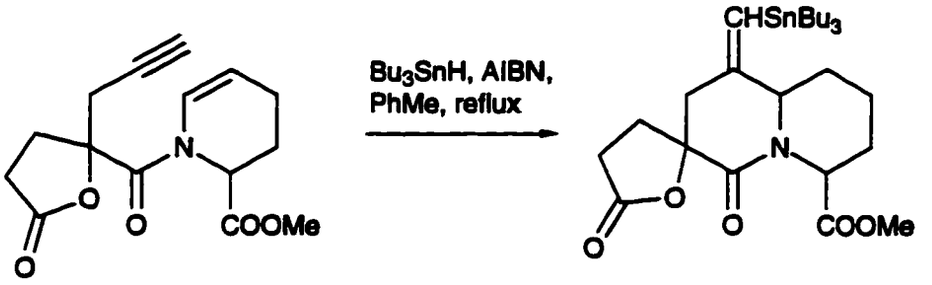

**69a** **85a**

A solution of AIBN (7 mg, 0.04 mmol) and $Ph_3SnH$ (148 mg, 0.42 mmol) in PhMe (1 mL) was injected over 2 min into a stirred and refluxing solution of acetylene **69a** (derived from the chromatographically slower-running alcohol) (46 mg, 0.16 mmol) in PhMe (2 mL) (Ar atmosphere). Refluxing was continued for 4 h, and the mixture was then cooled to room temperature and evaporated. Flash chromatography of the

residue over silica gel (1 x 20 cm), using 3:7 EtOAc-hexane, gave **85a** (72 mg) as a white powder contaminated with triphenyltin residues ($^1$H NMR). The crude material was directly subjected to protodestannylation.

Note that with $Bu_3SnH$, slow addition led to recovery of considerable starting material; hence, the stannane was added quickly this time. Fast addition of $Bu_3SnH$ also led to another product, which was not identified.

**Methyl Octahydro-4',5-dioxo-1'-[(triphenylstannyl)-methylene]-spiro[furan-2(3*H*),3'(4*H*')-[2*H*]quinolizine]-6'-carboxylate (85b).**




**69b** **85b**

A solution of AIBN (10 mg, 0.05 mmol) and $Bu_3SnH$ (210 mg, 0.72 mmol) in PhMe (2 mL) was injected over 2 min into a stirred and refluxing solution of acetylene **69b** (derived from the chromatographically faster-running alcohol) (100 mg, 0.34 mmol) in PhMe (2 mL) (Ar atmosphere). Refluxing was continued for 2 h, and the mixture was then cooled to room temperature and evaporated. Flash chromatography of the

residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave **85b** (170 mg) as a white powder contaminated with tributyltin residues ($^1$H NMR). The crude material was directly subjected to protodestannylation.

**Methyl Octahydro-1'-methylene-4',5-dioxospiro[furan-2(3*H*),3'(4'*H*')-[2*H*]quinolizine]-6'-carboxylate (30a).**


TFA (0.5 mL, 6.51 mmol) was added to a stirred solution of vinyl stannane **85a** (derived from the slower-running alcohol) (72 mg) in THF (2 mL). Stirring was continued overnight at room temperature and then at 60 °C for 2 h. The solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave pure **30a** (29 mg, 62% over two steps) as a pure ($^1$H NMR, 360 MHz), white powder: FTIR ($CHCl_3$ cast) 1655, 1741, 1785 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) δ 1.7-1.8 (m, 3 H), 1.9-2.2 (m, 4 H), 2.4-2.5 (m, 2 H), 2.7-3 (m, 3 H), 3.75 (s, 3 H), 4.10-4.15 (br. 1 H), 4.3 (t, $J$ = 5.7 Hz, 1 H), 5.05 (d, $J$ = 7.9 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 18.2 (t'), 24.2 (t'), 27.6 (t'), 28.5 (t'), 32.4 (t'), 41.6

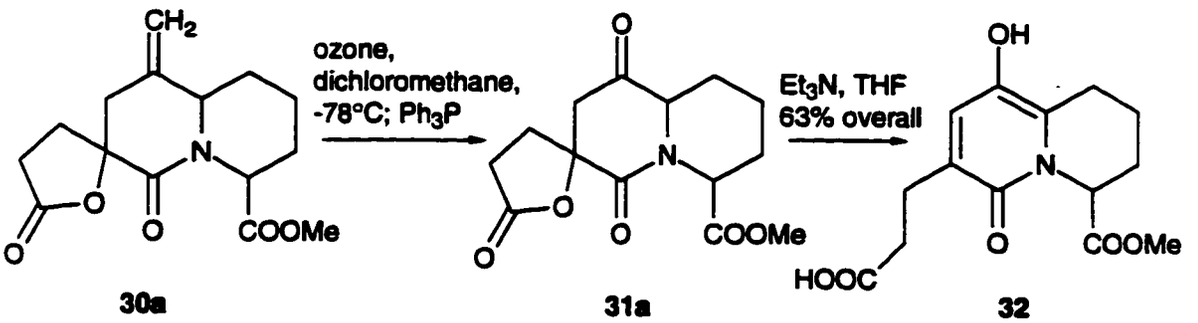
(t'), 52.2 (d'), 56.2 (d'), 57.0 (q'), 81.8 (s'), 113.8 (t'), 138.5 (s'), 169.6 (s'), 171.6 (s'), 176.4 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_5$ 293.12631, found 293.12580.

**Methyl Octahydro-1'-methylene-4',5-dioxospiro[furan-2(3*H*),3'(4'*H*')-[2*H*]quinolizine]-6'-carboxylate (30b).**


TFA (3 drops) was added to a stirred solution of vinyl stannane **85b** (derived from the faster-running alcohol) (170 mg) in THF (5 mL). Stirring was continued at room temperature for 5 h, and the solution was then evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:1 EtOAc-hexane, gave **30b** (86 mg, 89% over two steps) as a pure ($^1$H NMR, 300 MHz), white powder: FTIR ($CHCl_3$ cast) 1659, 1723.35, 1772.74 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.4-1.5 (m, 2 H), 1.55-1.65 (m, 1 H), 1.75-1.85 (m, 1 H), 1.9-2.0 (m, 2 H), 2.25-2.35 (m, 2 H), 2.45-2.55 (m, 1 H), 2.65 (d, *J* = 13.5, 1 H), 2.75-2.85 (m, 1 H), 2.95 (d, *J* = 13.5, 1 H), 3.75 (s, 3 H), 4.10 (d, *J* = 10.2 Hz, 1 H), 5.15 (s, 2 H), 5.35 (d, *J* = 5.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) δ 20.6 (t'), 26.2 (t'), 28.4 (t'), 30.3 (t'), 33.0 (t'),

41.4 (t'), 52.4 (d'), 52.5 (d'), 57.7 (q') 81.9 (s'), 113.9 (t'), 138.4 (s'), 169.6 (s'), 170.9 (s'), 176.3 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_5$ 293.12631, found 293.12936.

**1,3,4,6-Tetrahydro-9-hydroxy-4-(methoxycarbonyl)-6-oxo-2*H*-quinolizine-7-propanoic acid (32) from 30a.**



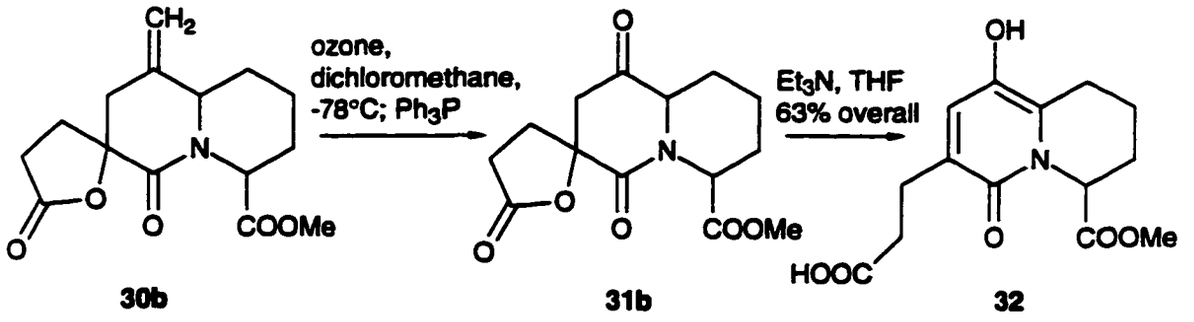

Ozonized oxygen was passed into a stirred and cooled (-78 °C) solution of olefin **30a** (derived from the slower-running alcohol) (30 mg, 0.10 mmol) in $CH_2Cl_2$ (4 mL) contained in a three-necked flask equipped with a reflux condenser (not connected to a water supply) and closed by a drying tube packed with Drierite, an inlet tube (for ozone), and a glass stopper. When the solution became pale blue, the ozonization was stopped, and the excess of ozone was removed with a stream of oxygen. $Ph_3P$ (55 mg, 0.21 mmol) was tipped into the solution, the cooling bath was removed, and stirring was continued for 1.5 h.

The solvent was evaporated and $Et_3N$ (0.10 mL, 0.72 mmol) in dry THF (3 mL) was added. The mixture was stirred at 60 °C for 2 h, cooled to room temperature, diluted with EtOAc

(10 mL), and extracted with water (4 x 5 mL). The combined aqueous extracts were washed with $CHCl_3$ (4 x 5 mL). Evaporation of the aqueous phase gave a solid residue.

A column packed with Amberlite IR-120 ion-exchange resin (20-50Å mesh, 1 x 10 cm) was washed with water until the eluent was colorless. The column was then washed successively with 2 N aqueous NaOH (4 bed volumes), water (until the eluent was neutral to pH paper), 2 N HCl (4 bed volumes), and finally with water (until the eluent was neutral to pH paper). The above solid residue was dissolved in water (*ca.* 0.5 mL) and the solution was passed down the column, using water. The eluent was monitored by TLC [silica, 2:4:4 AcOH-hexane-EtOAc-water (1 drop water to 10 mL of the organic phase), visualization under uv light]. Evaporation of the combined uv-active fractions (water pump, rotary evaporator, bath temperature *below* 60 °C) gave ester **32** (19 mg, 63%) as a pure ($^1H$ NMR, 400 MHz), yellow foam: FTIR (microscope) 1654, 1717, 1740, 2800-3400 (br) $cm^{-1}$; $^1H$ NMR ($D_2O$, 400 MHz) δ 1.58-1.60 (m, 1 H), 1.80-1.88 (m, 1 H), 2.10-2.20 (m, 1 H), 2.25-2.35 (m, 1 H), 2.6-2.70 (m, 2 H), 2.7-2.8 (m, 3 H), 1.90-1.95 (m, 1 H), 3.75 (s, 3 H), 5.10-5.15 (dd, $J$ = 6.8, 4.4 Hz, 1 H), 7.35 (s, 1 H); $^{13}C$ NMR ($D_2O$, 100.6 MHz) δ 16.2 (t'), 23.8 (t'), 26.1 (t'), 26.5 (t'), 33.4 (t'), 54.3 (d'), 57.7 (q'), 126.9 (s'), 132.9 (s'), 133.7 (d'), 137.8 (s'), 161.9 (s'), 175.0 (s'), 178.6 (s'); exact mass *m/z* calcd for $C_{14}H_{17}NO_6$ 295.10559, found 295.10566.

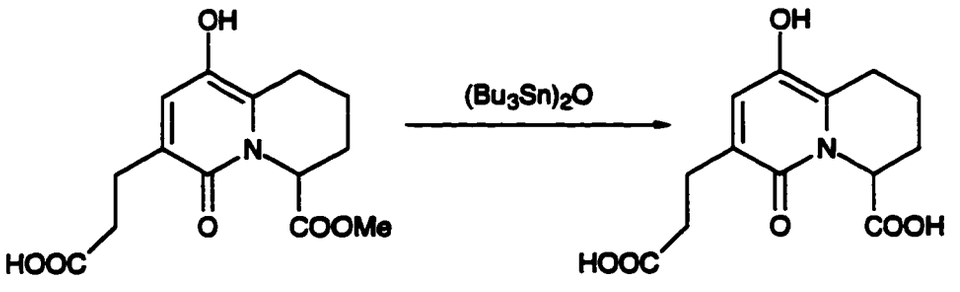
**1,3,4,6-Tetrahydro-9-hydroxy-4-(methoxycarbonyl)-6-oxo-2*H*-quinolizine-7-propanoic acid (32) from 30b.**




**30b** **31b** **32**

The above procedure was followed exactly, using exocyclic olefin **30b** (derived from the faster-running alcohol) (58 mg, 0.20 mmol) in $CH_2Cl_2$ (5 mL), $Ph_3P$ (107 mg, 0.41 mmol), and $Et_3N$ (0.20 mL, 1.43 mmol) in THF (3 mL). Ester **32** (37 mg, 63%) was obtained as a pure ($^1H$ NMR, 400 MHz), yellow foam, spectroscopically identical to material obtained in the previous experiment.

**4-Carboxy-1,3,4,6-tetrahydro-9-hydroxy-6-oxo-2*H*-quinolizine-7-propanoic acid (2).**

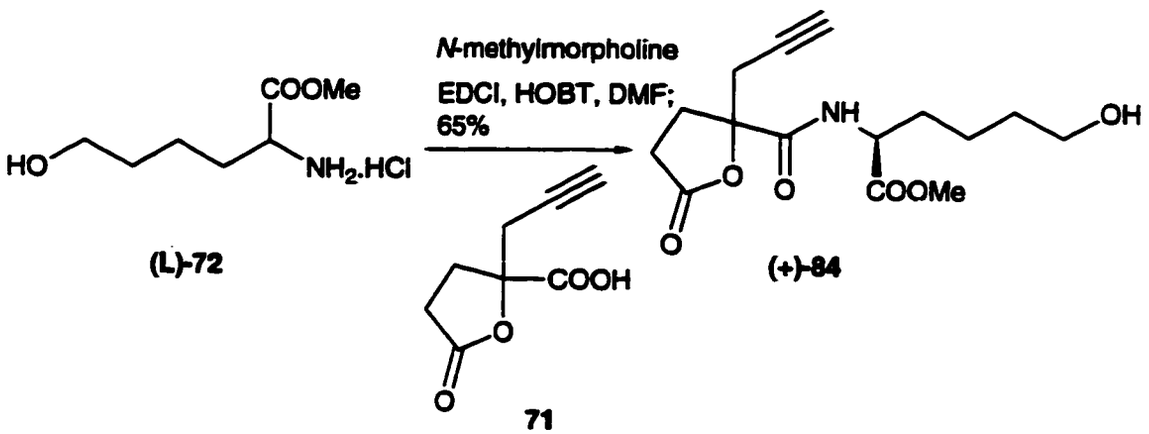



**32** **2**

$(Bu_3Sn)_2O$ (0.5 mL, 0.98 mmol) was added to a solution of

methyl ester **32** (91 mg, 0.31 mmol) in dry PhH (2 mL), and the mixture was refluxed for 3 days (Ar atmosphere) [TLC control, silica, 2:4:4 AcOH-hexane-EtOAc-water (1 drop water to 10 mL of the organic phase)]. The deep red solution was cooled to room temperature and diluted with hexane (10 mL). The resulting solution was extracted with 1% AcOH-water (4 x 5 mL), and the combined aqueous extracts were washed with $CHCl_3$ (4 x 10 mL). Evaporation of the aqueous extracts (rotary evaporator, water pump, *below* 60 °C) and flash chromatography of the residue over C-18 reverse phase silica gel (60 mesh, 10% C-18 capped with TMS, 1 x 20 cm), using 9:1 water-MeCN, gave the crude product. This was dissolved in the minimum amount of water at room temperature. The solution was stored overnight in a refrigerator to obtain pure ($^1$H NMR, 400 MHz) (±)-A58365B[16] (**2**) (60 mg, 67%) as a yellow crystalline solid: mp 209-213 °C; FTIR (microscope) 1651, 1709, 2600-3200 (br) $cm^{-1}$; UV (MeOH) $\lambda_{max}$: 340, 238 nm; $^1$H NMR ($D_2O$, 300 MHz) δ 1.65-1.70 (m, 1 H), 1.85-1.90 (m, 1 H), 2.15-2.25 (m, 1 H), 2.3-2.35 (m, 1 H), 2.65-2.85 (m, 5 H), 2.95-3.00 (m, 1 H), 5.10-5.15 (dd, $J$ = 6.4, 3.6 Hz, 1 H), 7.35 (s, 1 H); $^{13}$C NMR ($D_2O$, 100.6 MHz) δ 16.1 (t'), 23.7 (t'), 26.1 (t'), 26.5 (t'), 33.4 (t'), 57.5 (d'), 126.8 (s'), 132.7 (s'), 133.5 (d'), 137.6 (s'), 161.8 (s'), 176.2 (s'), 178.6 (s'); Exact mass *m/z* calcd for $C_{13}H_{15}NO_6$ 281.08994, found 281.08743.

**(+)-6-Hydroxy-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]norleucine Methyl Ester [(+)-84].**




The methyl ester hydrochloride salt was prepared from (L)-ε-hydroxynorleucine (603 mg, 3.05 mmol) by treatment with saturated methanolic HCl, exactly as described in the literature.[44] Evaporation of the solvent gave the crude ester hydrochloride, which was used directly after being kept overnight under oil pump vacuum. The material was covered with dry DMF (4 mL) and $CH_2Cl_2$ (15 mL), and the mixture was stirred with a glass rod for *ca.* 1 h, by which stage all of the salt had dissolved [use of a magnetic stirring bar was unsuccessful because of the sticky nature of the material]. *N*-Methylmorpholine (4 mL, 36.38 mmol) was then added, and the mixture was stirred (magnetic stirring bar) (Ar atmosphere). After 1 h, the solid lactone acid (640 mg, 3.81 mmol) and 1-hydroxybenzotriazole (717 mg, 4.68 mmol) were tipped into the solution, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (805 mg, 4.11 mmol). Stirring at room

temperature was continued overnight (Ar atmosphere), and then water (100 mL) was added. The mixture was extracted with $CHCl_3$ (4 x 70 mL), and the combined organic extracts were washed with water (3 x 50 mL) and brine (2 x 70 mL), dried ($MgSO_4$), and evaporated. The crude product was kept overnight under oil pump vacuum to remove traces of *N*-methylmorpholine. Flash chromatography of the material over silica gel (2.5 x 20 cm), using 3:1 EtOAc-hexane, gave (+)-**84** as an oil in three fractions, two containing the individual pure isomers, and the third fraction containing both isomers.

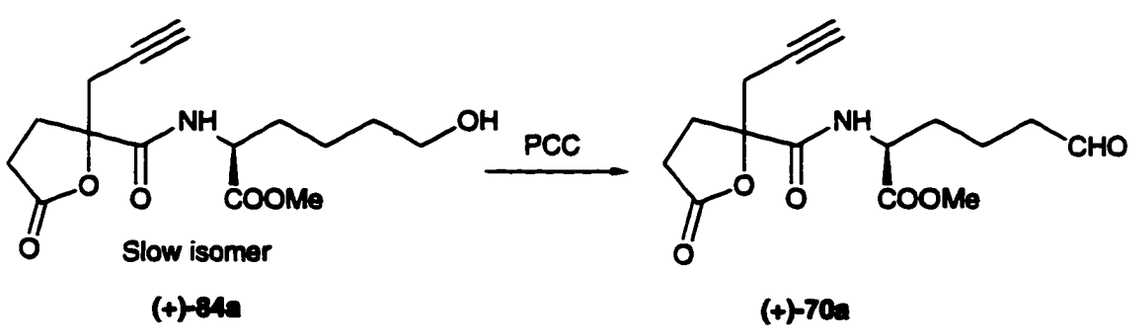
The chromatographically slower-running material [isomer (+)-**84a**] (303 mg) had: $[\alpha]_D^{21}$ = +3.57 ° (c 1.485 $CHCl_3$); FTIR ($CHCl_3$ cast) 1672, 1741, 1788, 3286, 3355 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) δ 1.35-1.42 (m, 2 H), 1.5-1.6 (m, 2 H), 1.7-1.85 (m, 2 H), 1.85-1.95 (m, 1 H), 2.18 (t, *J* = 2.9 Hz, 1 H), 2.4-2.65 (m, 3 H), 2.7-2.75 (m, 1 H), 2.8 (d, *J* = 2.52 Hz, 2 H) 3.65 (t, *J* = 6.12, 2 H), 3.78 (s, 3 H), 4.5-4.6 (m, 1 H), 7.0 (d, *J* = 7.9 Hz, 1 H); $^{13}C$ ($CDCl_3$, 100.6 MHz) δ 21.8 (t'), 28.4 (t'), 29.5 (t'), 31.5 (t'), 31.6 (t'), 52.2 (q'), 52.5 (d'), 62.1 (t'), 72.4 (s'), 77.2 (d'), 85.4 (s'), 170.9 (s'), 171.8 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_{15}H_{22}NO_6$ ($M^+$ + 1) 312.14471, found 312.14228; Calcd for $C_{13}H_{18}NO_4$ ($M^+$ - COOMe) 252.12358, found 252.12339.

The chromatographically faster-running material [isomer (+)-**84b**] (160 mg) had: $[\alpha]_D^{21}$ = +9.43 ° (c 1.1126 $CHCl_3$); FTIR ($CHCl_3$ cast) 1674, 1742, 1790, 3286, 3341 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) δ 1.4-1.5 (m, 2 H), 1.5-1.6 (m, 3 H), 1.7-

1.75 (m, 1 H), 1.9-1.95 (m, 1 H), 2.15 (t, $J$ = 2.88 Hz, 1 H), 2.35-2.45 (m, 1 H), 2.50-2.65 (m, 2 H), 2.65-2.75 (m, 1 H), 2.8-2.85 (ABX, 2 H), 3.65 (t, $J$ = 6.12, 2 H), 3.80 (s, 3 H), 4.45-4.50 (m, 1 H), 6.9-7.00 (d, $J$ = 7.6 Hz, 1 H); $^{13}C$ ($CDCl_3$, 100.6 MHz) δ 21.9 (t'), 28.3 (t'), 28.6 (t'), 30.0 (t'), 31.5 (t'), 31.8 (t'), 52.4 (q'), 52.5 (d'), 62.3 (t'), 77.4 (s'), 85.5 (s'), 170.8 (s'), 172.0 (s'), 175.1 (s'); exact mass *m/z* calcd for $C_{15}H_{21}NO_6$ 311.13690, found 311.13712.

The mixed fraction (both isomers) weighed 551 mg. The total yield amounted to 83% in all.

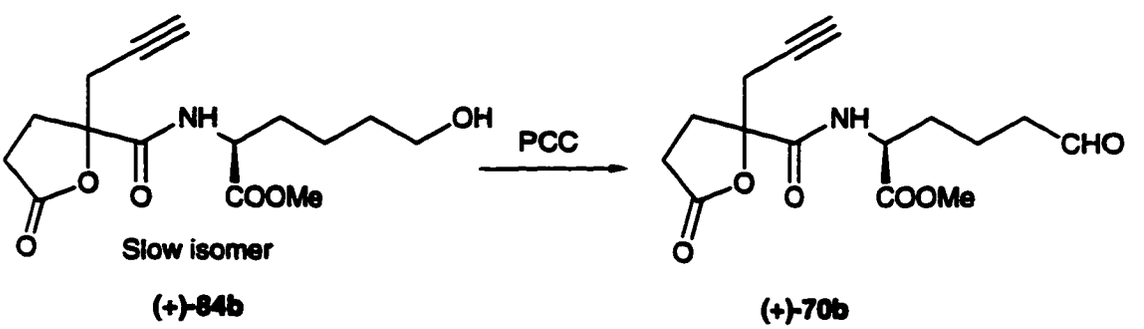
**Oxidation of slower-running isomer (+)-84a to (+)-6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]-carbonyl]-norleucine Methyl Ester [(+)-70a].**




PCC (310 mg g, 1.41 mmol) was added to a stirred mixture of the chromatographically slower-running alcohol (+)-**84a** (110 mg, 0.35 mmol) and crushed 4Å molecular sieves (500 mg) in dry $CH_2Cl_2$ (10 mL). Stirring was continued for 1.5 h (Ar atmosphere), and the mixture was then filtered. The solids were washed with a little $CH_2Cl_2$, and the combined filtrates

were evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using 1:1 EtOAc-hexane, gave aldehyde (+)-**70a** as a pure ($^1$H NMR, 300 MHz), colorless oil (78 mg, 76%): $[\alpha]_D^{21}$ = +6.22 ° (c 0.724, $CHCl_3$); FTIR ($CHCl_3$ cast) 1676, 1724, 1741, 1789, 3281, 3353 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) δ 1.6-1.85 (m, 3 H), 1.85-1.95 (m, 1 H), 2.15 (t, *J* = 2.63 Hz, 1 H), 2.4-2.5 (m, 3 H), 2.5-2.8 (m, 3 H), 2.85 (ABX, 2 H) 3.75 (s, 3 H), 4.45-4.55 (m, 1 H), 6.9-7.0 (br, 1 H), 9.7 (t, *J* = 1.08 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 100.6 Hz) 17.7 (t'), 28.4 (t'), 28.6 (t'), 29.7 (t'), 31.4 (t'), 42.9 (t'), 52.0 (q'), 52.6 (d'), 72.1 (d'), 77.2 (s') 85.3 (s'), 171.0 (s'), 171.4 (s'), 175.1 (s'), 201.2 (d'); exact mass *m/z* calcd for $C_{15}H_{18}NO_6$ ($M^+$ - 1) 308.11340, found 308.11295.

**Oxidation of faster-running isomer (+)-84b to (+)-6-Oxo-*N*-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]-carbonyl]-norleucine Methyl Ester [(+)70b].**

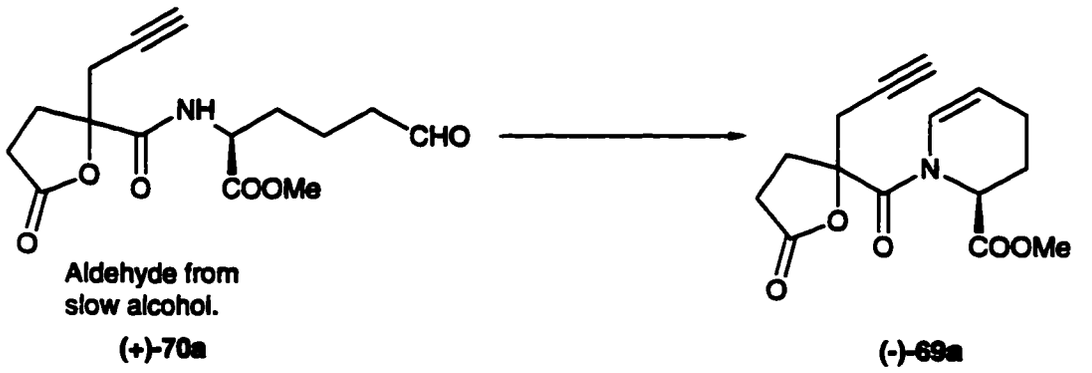



The above procedure was followed, using PCC (468 mg, 2.12 mmol), the chromatographically faster-running alcohol (+)-**84b** (468 mg, 2.12 mmol), crushed 4Å molecular sieves (480

mg) and dry $CH_2Cl_2$ (10 mL). Flash chromatography of the crude product over silica gel (2 x 22 cm), using 1:1 EtOAc-hexane, gave aldehyde (+)-**70b** as a pure ($^1H$ NMR, 300 MHz), colorless oil (140 mg, 64%): $[\alpha]_D^{21}$ = +11.5 ° (c 1.139, $CHCl_3$); FTIR ($CHCl_3$ cast) 1676, 1723, 1741, 1789, 2731, 3283, 3357 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.65-1.8 (m, 3 H), 1.85-1.90 (m, 1 H), 2.15 (t, *J* = 2.52 Hz, 1 H), 2.3-2.4 (m, 1 H), 2.45-2.75 (m, 5 H), 2.80-2.95 (ABX, 2 H), 3.75 (s, 3 H), 4.5-4.6 (m, 1 H), 6.9-7.0 (br, 1 H), 9.75 (t, *J* = 1.08 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 100.6 Hz) δ 18.0 (t'), 28.1 (t'), 28.6 (t'), 30.1 (t'), 30.9 (t'), 42.9 (t'), 52.0 (q'), 52.4 (d'), 72.0 (d'), 77.7 (s'), 85.5 (s'), 170.6 (s'), 171.7 (s'), 175.1 (s'), 201.7 (d'); exact mass *m/z* calcd for $C_{15}H_{19}NO_6$ 309.12125, found 309.12268; calcd. for $C_{14}H_{18N}O_5$ (M - CHO) 280.11850, found 280.11707.

Note that the two aldehydes (from the two alcohols) have the same $R_f$.

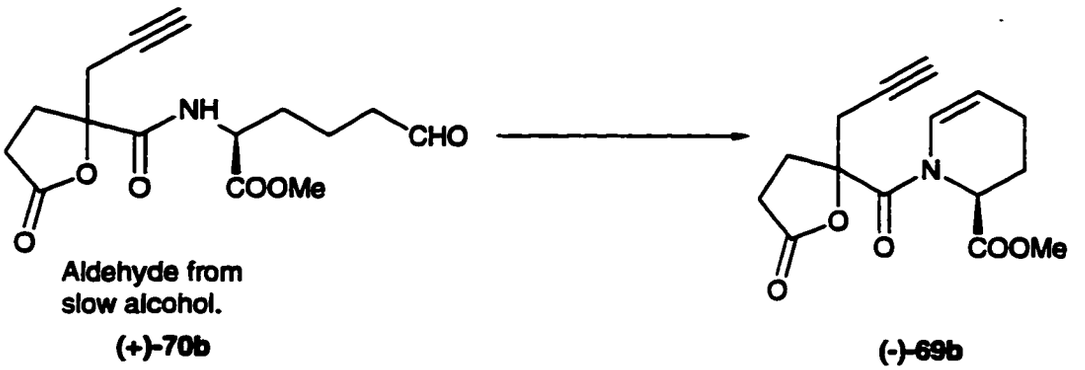
**(-)-Methyl 1,2,3,4-Tetrahydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-2-pyridinecarboxylate [(-)-69a].**



For this reaction the $CF_3COOH$ must be freshly distilled from $P_2O_5$, but can be stored for 1 week in a tightly stoppered flask kept in a small desiccator containing Drierite. TFA (0.40 mL, 5.19 mmol) was added to a stirred mixture of aldehyde (+)-**70a** (315 mg, 1.02 mmol) from the chromatographically slower-running alcohol and crushed 4Å molecular sieves (300 mg) in dry $CH_2Cl_2$ (5 mL) (Ar atmosphere). Stirring at room temperature was continued for 3-4 h, the course of the reaction being closely followed by TLC (silica, 3:7 EtOAc-hexane). As soon as the reaction was completed, the mixture was filtered, and the solids were washed with a little $CH_2Cl_2$. Evaporation of the combined filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1H$ NMR, 300 MHz) (-)-**69a** (151 mg, 96% after correction for recovered starting material 150 mg)) as a colorless oil. At room temperature the material consisted of a mixture of two rotamers (variable temperature $^1H$ NMR): $[\alpha]_D^{21}$ = -62.7° (c 1.01, $CHCl_3$); FTIR ($CHCl_3$, cast) 1643, 1743, 1794, 3270 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) δ 1.9-2.17 (m, 3 H), 2.18 (t, $J$ = 2.7 Hz 1 H), 2.25-2.60 (m, 3 H), 2.60-2.85 (m, 2 H), 2.90-3.05 (m, 2 H), 3.75 (d, 3 H), 5.05-5.50 (br, 2 H), 7.10-7.20 (br, 1 H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) (mixture of rotamers) δ 18.7 (t'), 18.8 (t'), 23.2 (t'), 23.9 (t'), 27.4 (t'), 27.8 (t'), 28.4 (t'), 30.3 (t'), 30.7 (t'), 32.8 (t'), 52.5 (d'), 52.8 (d'), 53.7 (q'), 56.1 (q'), 72.4 (d'), 72.9 (d'), 77.1 (s'), 77.8 (s'), 86.4 (s'), 87.4 (s'), 108.5 (d'), 110.6 (d'),

124.3 (d'), 124.9 (d'), 167.5 (s'), 167.8 (s'), 170.5 (s'), 171.3 (s'), 174.6 (s'), 175.2 (s'); exact mass *m/z* calcd for $C_{15}H_{17}NO_5$ 291.11069, found 291.11042.

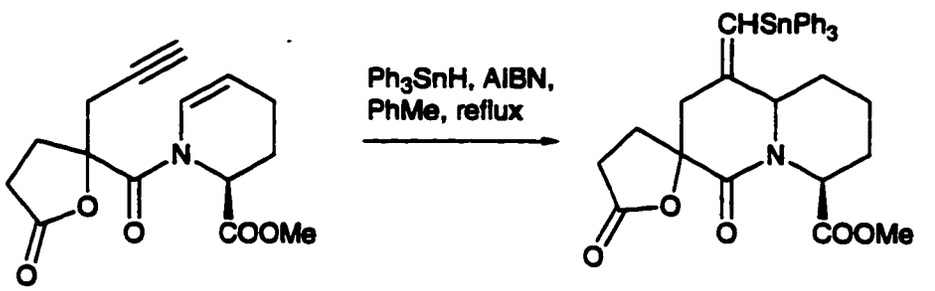
**(-)-Methyl 1,2,3,4-Tetrahydro-1-[[tetrahydro-5-oxo-2-(2-propynyl)-2-furanyl]carbonyl]-2-pyridinecarboxylate [(-)69b].**




The above procedure was followed, using TFA (0.50 mL, 6.49 mmol), the chromatographically faster-running alcohol (+)-**70b** (470 mg, 1.52 mmol), crushed 4Å molecular sieves (422 mg) and dry $CH_2Cl_2$ (5 mL). Stirring at room temperature was continued for 3-4 h, the course of the reaction being closely followed by TLC (silica, 3:7 EtOAc-hexane). Flash chromatography of the crude product over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave pure ($^1$H NMR, 300 MHz) (-)-**69b** (159 mg, 73% after correction for recovered starting material 240 mg) as a colorless oil. An increase in reaction time gave a lower yield. At room temperature the product is a single isomer [sharp signals in the $^1$H MHz NMR spectrum

(300 MHz): $[\alpha]_D^{21}$ = -114.9 ° (c 0.684, $CHCl_3$); FTIR ($CHCl_3$ cast) 1643, 1667, 1743, 1793, 3268 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) δ 1.85-2.05 (m, 3 H) 2.15 (t, *J* = 2.54 Hz, 1 H), 2.30-2.40 (m, 2 H), 2.50-2.75 (m, 2 H), 2.85-2.95 (ABX, 2 H), 2.98-3.05 (m, 1 H), 3.75 (s, 3 H), 5.00-5.10 (br, 1 H), 5.12-5.22 (br, 1 H), 7.05-7.12 (d, *J* = 8.7 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 19.3 (t'), 23.9 (t'), 28.2 (t'), 29.0 (t'), 30.8 (t'), 52.8 (d'), 54.1 (q'), 72.9 (d'), 77.2 (s'), 86.7 (s'), 109.2 (d'), 124.9 (d'), 167.2 (s'), 170.9 (s'), 175.3 (s'); exact mass *m/z* calcd for $C_{15}H_{17}NO_5$ 291.11069, found 291.11049.

**(-)-Methyl Octahydro-4',5-dioxo-1'-[(triphenylstannyl)methylene]-spiro[furan-2(3*H*),3'(4*H*')-[2*H*]quinolizine]-6'-carboxylate [(-)-85a].**

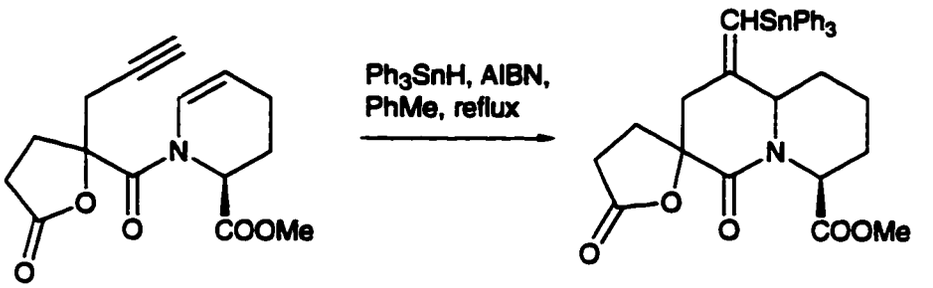



**(-)-69a** **(-)-85a**

A solution of AIBN (14 mg, 0.08 mmol) and $Ph_3SnH$ (363 mg, 1.03 mmol) in PhMe (1 mL) was injected over 2 min into a stirred and refluxing solution of acetylene (-)-**69a** (derived from the chromatographically slower-running alcohol) (127 mg, 0.44 mmol) in PhMe (6 mL) (Ar atmosphere). Refluxing was

continued for 4 h, and the mixture was then cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 3:7 EtOAc-hexane, gave (-)-**85a** (228 mg) as a white powder contaminated with triphenyltin residues ($^1$H NMR). The crude material was directly subjected to protodestannylation.

**(-)-Methyl Octahydro-4',5-dioxo-1'-[(triphenylstannyl)methylene]-spiro[furan-2(3*H*),3'(4*H*')-[2*H*]quinolizine]-6'-carboxylate [(-)-85b].**




A solution of AIBN (10 mg, 0.05 mmol) and $Bu_3SnH$ (367 mg, 1.26 mmol) in PhMe (2 mL) was injected over 2 min into a stirred and refluxing solution of acetylene (-)-**69b** (derived from the chromatographically faster-running alcohol) (150 mg, 0.58 mmol) in PhMe (2 mL) (Ar atmosphere). Refluxing was continued for 2 h, and the mixture was then cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 3:7 EtOAc-hexane, gave (-)-**85b** (220 mg) as a white powder contaminated with tributyltin residues ($^1$H NMR). The crude material was

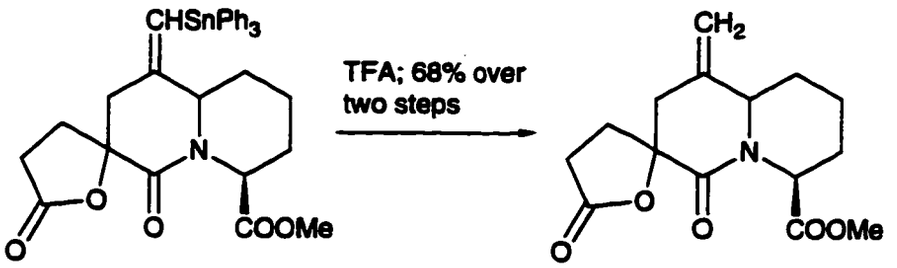
directly subjected to protodestannylation.

**(-)-Methyl Octahydro-1'-methylene-4',5-dioxospiro-[furan-2(3*H*),3'(4'*H*')-[2*H*]quinolizine]-6'-carboxylate [(-)30a].**


TFA (0.5 mL, 6.51 mmol) was added to a stirred solution of vinyl stannane (-)-**85a** (derived from the slower-running alcohol) (228 mg) in THF (2 mL). Stirring was continued overnight at room temperature and then at 60 °C for 2 h. The solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave pure (-)-**30a** (85 mg, 65% over two steps) as a pure ($^1$H NMR, 360 MHz), white powder: $[\alpha]_D^{21}$ = -21.58 ° (c 0.811, $CHCl_3$); FTIR ($CHCl_3$ cast) 1655, 1741, 1785 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.7-1.8 (m, 3 H), 1.9-2.2 (m, 4 H), 2.4-2.5 (m, 2 H), 2.7-3 (m, 3 H), 3.75 (s, 3 H), 4.10-4.15 (br. 1 H), 4.3 (t, $J$ = 5.7 Hz, 1 H), 5.05-5.10 (d, $J$ = 7.9 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 18.2 (t'), 24.2 (t'), 27.6 (t'), 28.5 (t'), 32.4 (t'), 41.6 (t'), 52.2 (d'), 56.2 (d'), 57.0 (q'), 81.8 (s'), 113.8 (t'), 138.5

(s'), 169.6 (s'), 171.6 (s'), 176.4 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_5$ 293.12631, found 293.12662.

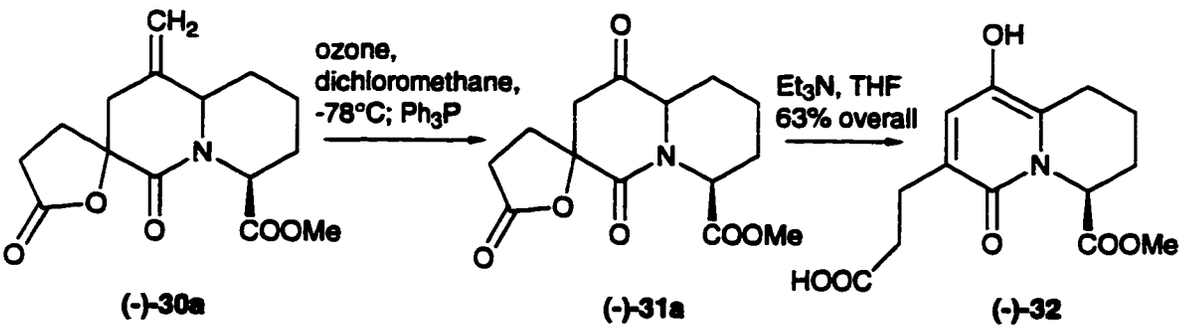
**(-)-Methyl Octahydro-1'-methylene-4',5-dioxospiro-[furan-2(3*H*),3'(4'*H*')-[2*H*]quinolizine]-6'-carboxylate [(-)-30b].**




TFA (3 drops) was added to a stirred solution of vinyl stannane (-)-**85b** (derived from the faster-running alcohol) (220 mg) in THF (5 mL). Stirring was continued at room temperature for 5 h, and the solution was then evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:1 EtOAc-hexane, gave (-)-**30b** (97 mg, 68% over two steps) as a pure ($^1$H NMR, 300 MHz), white powder: $[\alpha]_D^{21}$ = -101.86 ° (c 0.91, $CHCl_3$); FTIR ($CHCl_3$ cast) 1659, 1723.35, 1772.74 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.4-1.5 (m, 2 H), 1.55-1.65 (m, 1 H), 1.75-1.85 (m, 1 H), 1.9-2.0 (m, 2 H), 2.25-2.35 (m, 2 H), 2.45-2.55 (m, 1 H), 2.6 (d, *J* = 13.5, 1 H), 2.75-2.85 (m, 1 H), 2.95 (d, *J* = 13.5 Hz, 1 H), 3.75 (s, 3 H), 4.1 (d, *J* = 10.2 Hz, 1 H), 5.1 (s, 2 H), 5.35 (d, *J* = 5.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 20.6 (t'), 26.2

(t'), 28.4 (t'), 30.3 (t'), 33.0 (t'), 41.4 (t'), 52.4 (d'), 52.5 (d'), 57.7 (q') 81.9 (s'), 113.9 (t'), 138.4 (s'), 169.6 (s'), 170.9 (s'), 176.3 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_5$ 293.12631, found 293.12611.

**(-)-1,3,4,6-Tetrahydro-9-hydroxy-4-(methoxycarbonyl)-6-oxo-2*H*-quinolizine-7-propanoic acid [(-)-32] from [(-)-30a].**




Ozonized oxygen was passed into a stirred and cooled (-78 °C) solution of olefin (-)-**30a** (derived from the slower-running alcohol) (170 mg, 0.58 mmol) in $CH_2Cl_2$ (4 mL) contained in a three-necked flask equipped with a reflux condenser (not connected to a water supply) and closed by a drying tube packed with Drierite, an inlet tube (for ozone), and a glass stopper. When the solution became pale blue, the ozonization was stopped, and the excess of ozone was removed with a stream of oxygen. $Ph_3P$ (250 mg, 0.95 mmol) was tipped into the solution, the cooling bath was removed, and stirring was continued for 1.5 h.

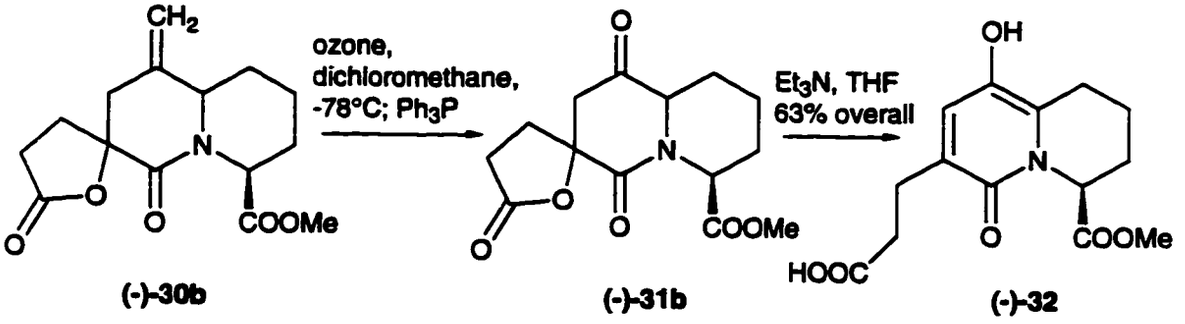
The solvent was evaporated and $Et_3N$ (0.10 mL, 0.72 mmol)

in dry THF (3 mL) was added. The mixture was stirred at 60 °C for 2 h, cooled to room temperature, diluted with EtOAc (10 mL), and extracted with water (4 x 5 mL). The combined aqueous extracts were washed with $CHCl_3$ (4 x 5 mL). Evaporation of the aqueous phase gave a solid residue.

A column packed with Amberlite IR-120 ion-exchange resin (20-50Å mesh, 1 x 10 cm) was washed with water until the eluent was colorless. The column was then washed successively with 2 N aqueous NaOH (4 bed volumes), water (until the eluent was neutral to pH paper), 2 N HCl (4 bed volumes), and finally with water (until the eluent was neutral to pH paper). The above solid residue was dissolved in water (*ca.* 0.5 mL) and the solution was passed down the column, using water. The eluent was monitored by TLC [silica, 2:4:4 AcOH-hexane-EtOAc-water (1 drop water to 10 mL of the organic phase), visualization under uv light]. Evaporation of the combined uv-active fractions (water pump, rotary evaporator, bath temperature *below* 60 °C) gave ester (-)-**32** (110 mg, 63%) as a pure ($^1$H NMR, 400 MHz), yellow foam: $[\alpha]_D^{21}$ = -132 ° (c 1.073, $H_2O$); FTIR (microscope) 1654, 1717, 1740, 2800-3400 (br) $cm^{-1}$; $^1$H NMR ($D_2O$, 360 MHz) δ 1.58-1.60 (m, 1 H), 1.80-1.88 (m, 1 H), 2.10-2.20 (m, 1 H), 2.25-2.35 (m, 1 H), 2.6-2.70 (m, 2 H), 2.7-2.8 (m, 3 H), 1.90-1.95 (m, 1 H), 3.75 (s, 3 H), 5.10-5.15 (dd, *J* = 6.8, 4.4 Hz, 1 H), 7.35(s, 1 H); $^{13}$C NMR ($D_2O$, 100.6 MHz) δ 16.2 (t'), 23.8 (t'), 26.1 (t'), 26.5 (t'), 33.4 (t'), 54.3 (d'), 57.7 (q'), 126.9 (s'), 132.9 (s'), 133.7 (d'), 137.8 (s'), 161.9 (s'),

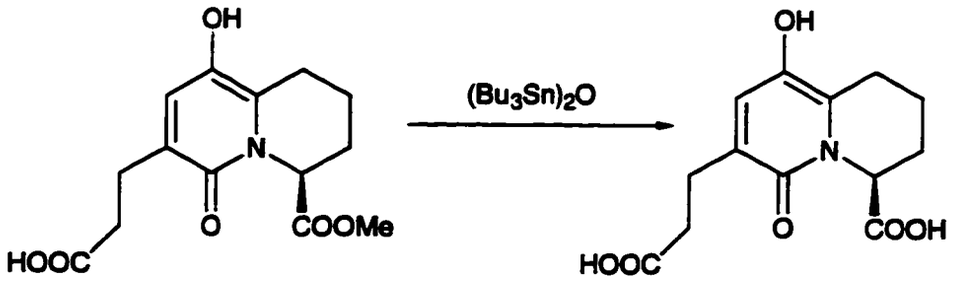
175.0 (s'), 178.6 (s'); exact mass *m/z* calcd for $C_{14}H_{17}NO_6$ 295.10559, found 295.10599.

**(-)-1,3,4,6-Tetrahydro-9-hydroxy-4-(methoxycarbonyl)-6-oxo-2*H*-quinolizine-7-propanoic acid [(-)-32] from [(-)30b].**




The above procedure was followed exactly, using exocyclic olefin (-)**30b** (derived from the faster-running alcohol) (58 mg, 0.20 mmol) in $CH_2Cl_2$ (5 mL), $Ph_3P$ (107 mg, 0.41 mmol), and $Et_3N$ (0.20 mL, 1.43 mmol) in THF (3 mL). Ester **32** (37 mg, 63%) was obtained as a pure ($^1H$ NMR, 400 MHz), yellow foam, spectroscopically identical to material obtained in the previous experiment.

**(-)-4-Carboxy-1,3,4,6-tetrahydro-9-hydroxy-6-oxo-2*H*-quinolizine-7-propanoic acid (-)-A58365B.**




(-)-32 (-) A58365B 2

$(Bu_3Sn)_2O$ (0.5 mL, 0.98 mmol) was added to a solution of methyl ester **32** (42 mg, 0.14 mmol) in dry PhH (2 mL), and the mixture was refluxed for 3 days (Ar atmosphere) [TLC control, silica, 2:4:4 AcOH-hexane-EtOAc-water (1 drop water to 10 mL of the organic phase)]. The deep red solution was cooled to room temperature and diluted with hexane (10 mL). The resulting solution was extracted with 1% AcOH-water (4 x 5 mL), and the combined aqueous extracts were washed with $CHCl_3$ (4 x 10 mL). Evaporation of the aqueous extracts (rotary evaporator, water pump, *below* 60 °C) and flash chromatography of the residue over C-18 reverse phase silica gel (60 mesh, 10% C-18 capped with TMS, 1 x 20 cm), using 9:1 water-MeCN, gave the crude product. This was dissolved in the minimum amount of water at room temperature. The solution was stored overnight in a refrigerator to obtain pure ($^1H$ NMR, 400 MHz) (-)-A58365B (**2**) (27 mg, 70%) as a yellow crystalline solid: mp 209-213 °C; $[\alpha]_D^{21}$ = -114 ° (c 0.16, $H_2O$); literature[11] value: $[\alpha]_D^{25}$ = -141 ° (c 0.16, $H_2O$); FTIR (microscope) 1651,

1709, 2600-3200 (br) $cm^{-1}$; UV (MeOH) $\lambda_{max}$: 340, 238 nm; $^1H$ NMR ($D_2O$, 360 MHz) $\delta$ 1.65-1.70 (m, 1 H), 1.85-1.90 (m, 1 H), 2.15-2.25 (m, 1 H), 2.3-2.35 (m, 1 H), 2.65-2.85 (m, 5 H), 2.95-3.00 (m, 1 H), 5.10-5.15 (dd, $J$ = 6.4, 3.6 Hz, 1 H), 7.35 (s, 1 H); $^{13}C$ NMR ($D_2O$, 75.5 MHz) $\delta$ 16.1 (t'), 23.7 (t'), 26.1 (t'), 26.5 (t'), 33.4 (t'), 57.5 (d'), 126.8 (s'), 132.7 (s'), 133.5 (d'), 137.6 (s'), 161.8 (s'), 176.2 (s'), 178.6 (s'); exact mass *m/z* calcd for $C_{13}H_{15}NO_6$ 281.08984, found 281.08753.

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