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THIOLESTERS IN ORGANIC SYNTHESIS AND THEIR APPLICATION TO THE SYNTHESIS OF (±)-α-COSTAL

by

HLA WYNN

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

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EDMONTON, ALBERTA
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Supervisor

M J Robins

James A. Plambeck

External Examiner

DATE 22nd Oct. 1984

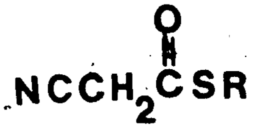
For my parents

ABSTRACT

A facile approach to various β-hydroxypropionitrile and acrylonitrile derivatives has been developed using cyanothiolacetate I ($R=CH_2Ph$ or *t*-[illegible]ked β-hydroxypropionitrile equivalent. Benzyl and *t*-butyl cyanothiolacetates were found to undergo facile dialkylation with a variety of alkyl halides to give dialkylation products of general structure **II**. Monoalkylation was found to be more difficult to control. However, under carefully controlled conditions, products of general structure **III** could be obtained in reasonable yields. *t*-Butyl cyanothiolacetate was found to undergo Knoevenagel-type condensation with a variety of aldehydes and ketones to give α,β-unsaturated cyanothiolacetates **IV**. Treatment of **IV** with 1 mol. equiv. of sodium borohydride in ethanol at 0°C resulted in the selective reduction of the carbon-carbon double bond giving rise to monosubstituted cyanothiolacetates **III** (R=*t*-Bu). This two-step sequence thus provides an effective means for the monoalkylation of the cyanothiolacetate. Selective reduction of compounds **II** and **III** with an excess of sodium borohydride gave rise to β-hydroxypropionitrile derivatives **V** and **VI** respectively. Compounds of type **VI** could also be prepared directly from unsaturated cyanothiolacetates **IV** by treatment with an excess of sodium borohydride (4 mol. equiv.) at room temperature. Further dehydration of monosubstituted β-hydroxypropionitriles **VI**, either directly by the use of dicyclohexylcarbodiimide and copper(I) chloride in refluxing ether or by a two-step sequence involving mesylation and elimination, gave acrylonitrile derivatives **VII**. S-t-Butyl cyanothiolacetate was also found to undergo Michael reaction with a variety of α,β-unsaturated ketones in the presence of sodium hydride and chlorotrimethylsilane to give, after proper work-up, adducts of general structure **VIII** in good yields. Ketalization of **VIII** gave rise to the corresponding ketals **IX** which, on treatment with an excess of sodium borohydride, resulted in the formation of β-hydroxypropionitrile derivatives **X**. Dehydration of **X** resulted in the formation of acrylonitrile derivatives **XI**. These results are detailed in the first part of this thesis.

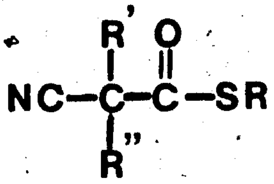
In the second part, the first total synthesis of α-costal (**XII**) is described. A salient feature of the synthesis was the use of S-t-butylcyanothiolacetate to facilitate the introduction of the acrolein unit present in the natural product. The synthesis was initiated with 2-methyl-1,3-cyclohexadione which was converted to ketone

XIII by known procedures with modifications. Treatment of **XIII** with lithium diisopropylamide and phenylselenenyl chloride followed by oxidation gave rise to α,β-unsaturated ketone **XIV**. Epoxidation of **XIV** with hydrogen peroxide and sodium hydroxide afforded keto epoxide **XV** as a single stereoisomer. This compound was subjected to Wharton's reaction with hydrazine hydrate and acetic acid. The alcohol **XVI** thus obtained was oxidized with pyridinium dichromate to give enone **XVII**. Hydrosilation of **XVII** with Wilkinson's catalyst (tris-triphenylphosphine rhodium (I) chloride) and triethylsilane followed by treatment of the resulting silyl enol-ether with tetra-n-butylammonium fluoride resulted in the formation of ketone **XVIII**. Ketone **XVIII** was condensed with S-t-butyl cyanothiolacetate in the presence of 1,4-diazabicyclo[2.2.2]octane as a base and sodium sulfate as a dehydrating agent. Sodium borohydride reduction of the resulting mixture **XIX** gave a diastereomeric mixture of cyano alcohols **XX** which was subjected to dehydration with dicyclohexylcarbodiimide in the presence of copper (I) chloride to give epimeric nitriles **XXI** and **XXII** in 2:1 ratio. On treatment with diisobutylaluminum hydride, the major isomer gave α-costal (**XII**) and the minor isomer gave epi-α-costal (**XXIII**) respectively.



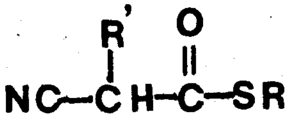
$NCCH_2\overset{O}{\overset{\|}{C}}SR$

I



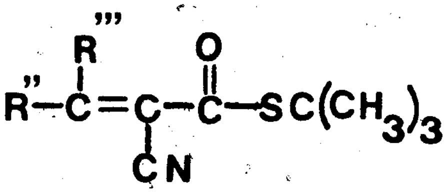
$NC-\underset{R''}{\overset{R'}{C}}-\overset{O}{\overset{\|}{C}}-SR$

II



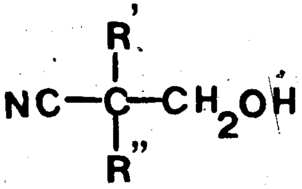
$NC-\overset{R'}{C}H-\overset{O}{\overset{\|}{C}}-SR$

III



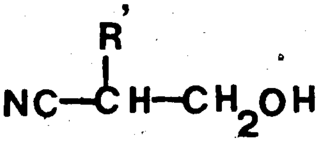
$R''-\overset{R'''}{C}=\underset{CN}{C}-\overset{O}{\overset{\|}{C}}-SC(CH_3)_3$

IV



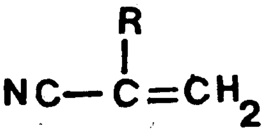
$NC-\underset{R''}{\overset{R'}{C}}-CH_2OH$

V



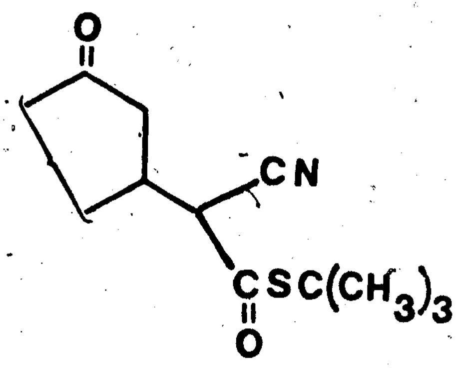
$NC-\overset{R'}{C}H-CH_2OH$

VI



$NC-\overset{R}{C}=CH_2$

VII



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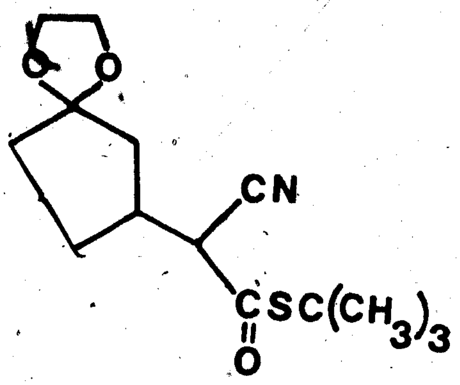

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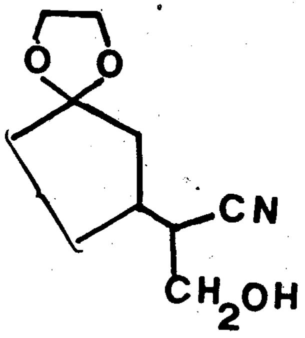
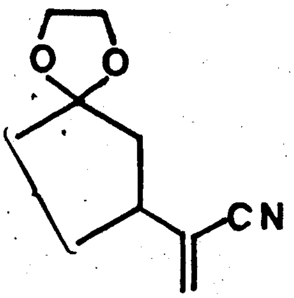


X



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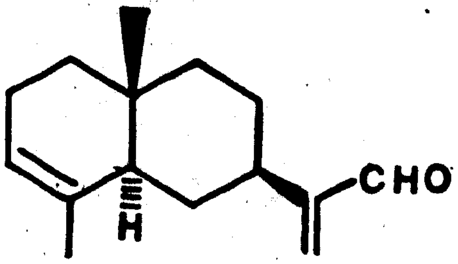

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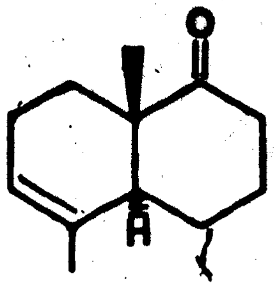

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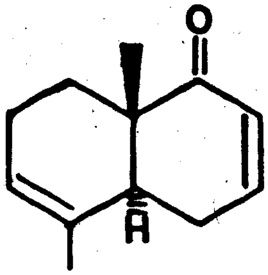

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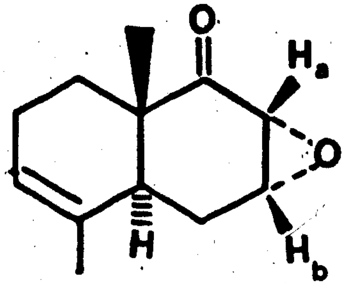

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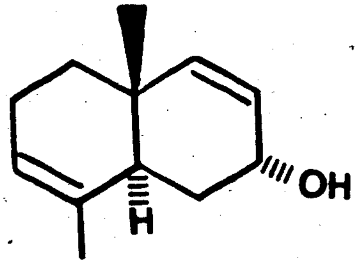

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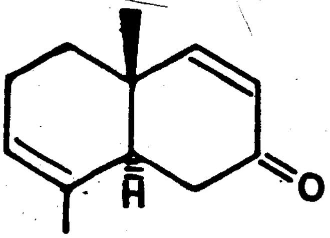

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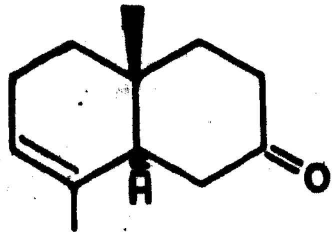

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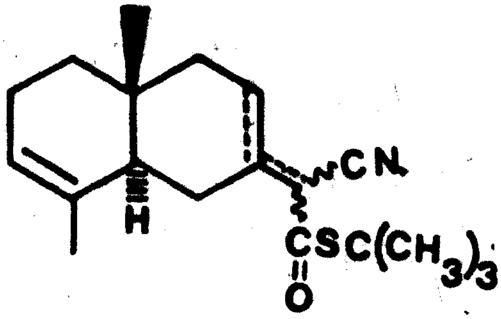

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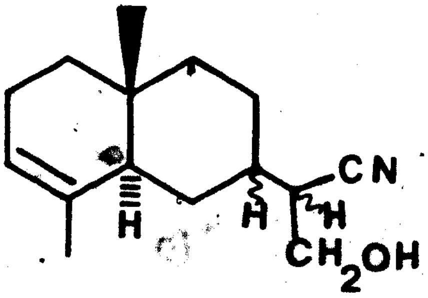
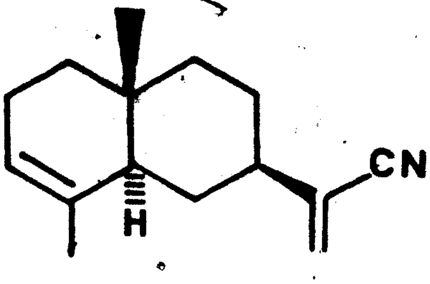


XX



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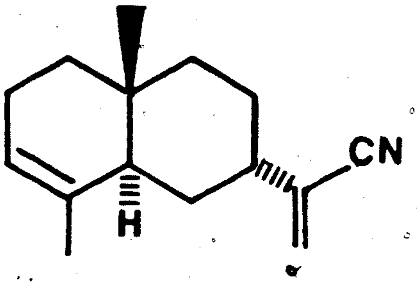

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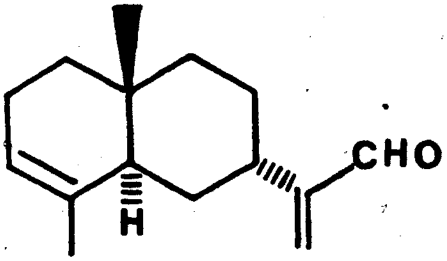

XXIII

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INTRODUCTION

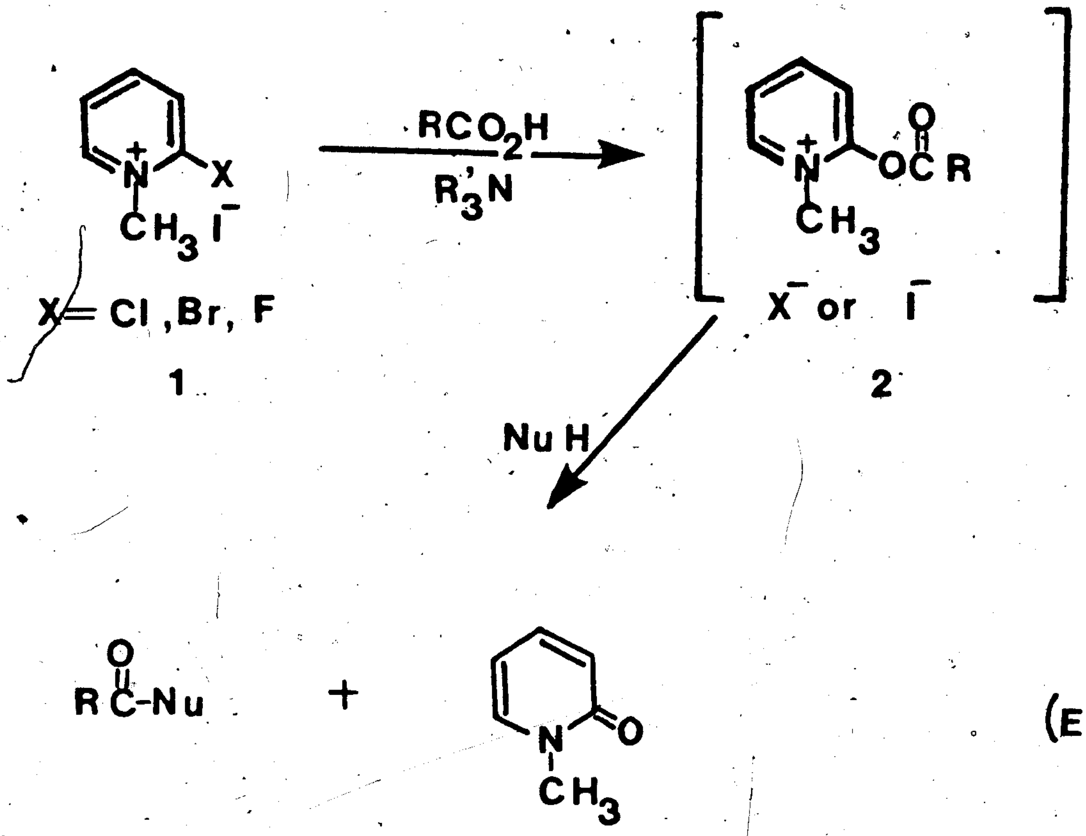
The preparation of a thiolester was first reported by Muhler[1] in 1875 by the reaction between acetyl chloride and ethyl mercaptan to give ethyl thiolacetate. In the following six decades several other preparative methods were recorded,[2] but very little attention had been made with respect to their reactivities and applications. In 1946, their application to the natural steroids was reported by Jeger and coworkers.[3] They showed that by the use of Raney nickel promoted reductive desulfurization of the intermediate thiolester, the transformation of a carboxylic functionality into a primary alcohol group could be achieved. This method was later extended to the preparation of aldehydes and alcohols[4] from carboxylic acids <u>via</u> the corresponding thiolesters. For their studies on steroids, Levin and coworkers[5] prepared a number of steroid thiolesters, either by the reaction of an acid chloride with an excess of mercaptan in pyridine or by treatment of the acid chloride with a suspension of lead mercaptide in ether. Very few reports on the chemistry of thiolesters appeared in the literature until 1960.[6] Since then the interest in thiolesters has grown significantly due to their widespread applications as useful intermediates in organic synthesis.[7] Their extensive synthetic applications have also attracted much attention for the development of new and improved methods for their preparation.

In 1974, Mukaiyama and coworkers[8] illustrated the preparation of thiolesters in high yields by treatment of trimethylsilyl sulfides with carboxylic esters in the presence of aluminum chloride (Eq. 1). The use of onium salts of aza arenes **1** to activate the carboxylic acids was also reported by Mukaiyama[9] (Eq. 2). The intermediate **2** thus formed reacted with nucleophiles (e.g. ROH, RSH, etc.) under practically neutral conditions giving very high yields of the corresponding esters.

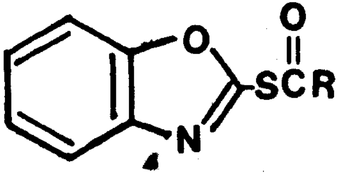
Employing S- and N-acyl derivatives of 2-mercaptobenzoxazole **3a** and **3b**, another method was developed by Ueda and coworkers.[10] They found that reagents **3a** and **3b** were highly reactive acylating agents, presumably due to the pseudoaromatic and electron-withdrawing characters of the benzoxazole ring system.

A new convenient method for the preparation of thiolesters using very mild conditions was reported by Kim and Yang.[11] They treated carboxylic acids with 1-fluoro-2,4,6-trinitrobenzene (**4**) and thiols in the presence of 4,4-dimethylaminopyridine in acetonitrile to induce the

$$\mathrm{R\overset{O}{\overset{\|}{C}}OR' + (CH_3)_3SiSR'' \xrightarrow{AlCl_3} R\overset{O}{\overset{\|}{C}}SR''} \qquad \text{(Eq.1)}$$



(Eq. 2)



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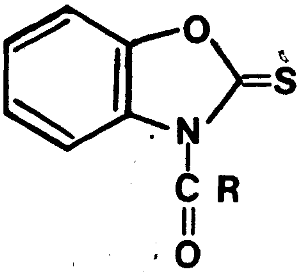
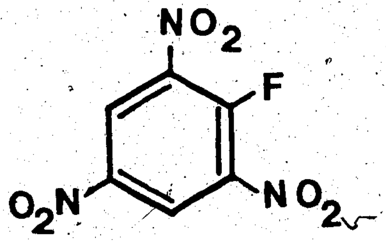


3 b

direct formation of thiolesters in good yields. Carboxylic acid imidazolides **5** or 1,2,4-triazolides **6**, which were readily accessible from carboxylic acids with carbonyl diimidazole and carbonyl 1,2,4-triazole respectively, have been shown to react with alkyl and aryl mercaptans to give thiolesters in excellent yields.[12]

Recently, it has also been shown that a large number of phosphorus-containing reagents such as diphenyl phosphorazidate (**7**),[13] diethyl phosphorocyanidate (**8**),[15] N,N-dimethylphosphoramidic dichloride (**9**),[15] phenylphosphorodichloridate (**10**),[16,17] and N,N-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (**11**)[18] are also useful as activating agents for the direct conversion of carboxylic acids to the corresponding thiolesters. Indirectly, Masamune et al.[19-21] prepared S-t-butyl thiolesters **12** from the corresponding acids by treatment of the intermediate acid chlorides (Eq. 3) or the mixed anhydrides (Eq. 4) with thallous 2-methylpropane-2-thiolate.

In recent years, thiolesters have found extensive use in organic synthesis. Some examples are as follows. In the area of natural product synthesis, it is now well established that the thiolester group plays an important role as an activating group to facilitate the formation of



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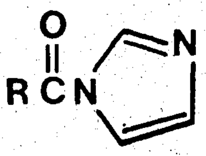

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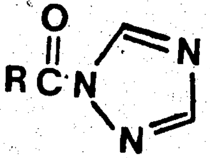

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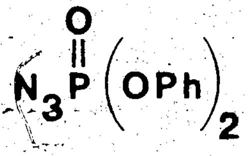
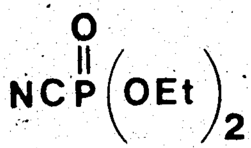
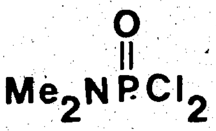

$N_3\overset{O}{\overset{\|}{P}}\left(OPh\right)_2$

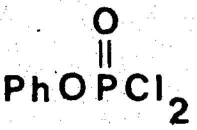
7


$NC\overset{O}{\overset{\|}{P}}\left(OEt\right)_2$

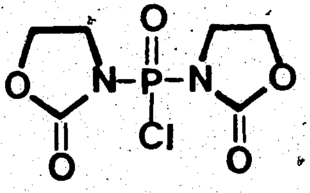
8


$Me_2N\overset{O}{\overset{\|}{P}}Cl_2$

9


$PhO\overset{O}{\overset{\|}{P}}Cl_2$

10



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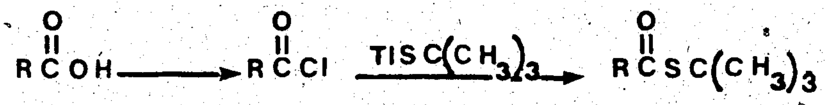
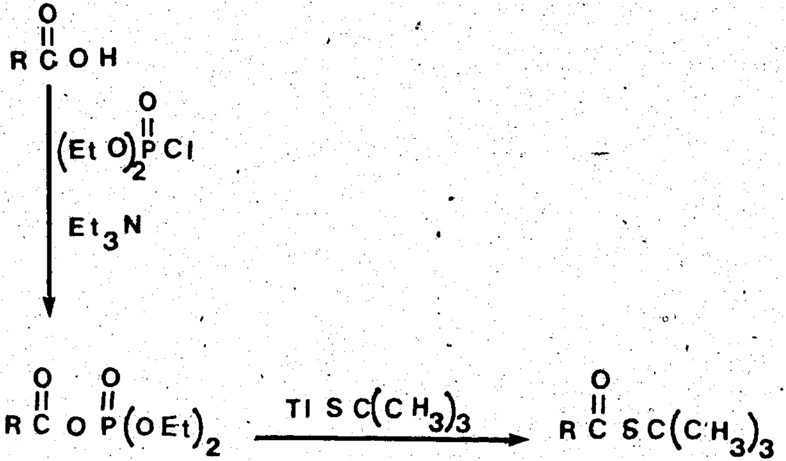


$$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH} \longrightarrow \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl} \xrightarrow{\mathrm{TlSC(CH_3)_3}} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{SC(CH_3)_3} \qquad \text{(Eq. 3)}$$

12



$$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH} \xrightarrow[\mathrm{Et_3N}]{\mathrm{(EtO)_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{Cl}} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{(OEt)_2} \xrightarrow{\mathrm{TlSC(CH_3)_3}} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{SC(CH_3)_3} \qquad \text{(Eq. 4)}$$

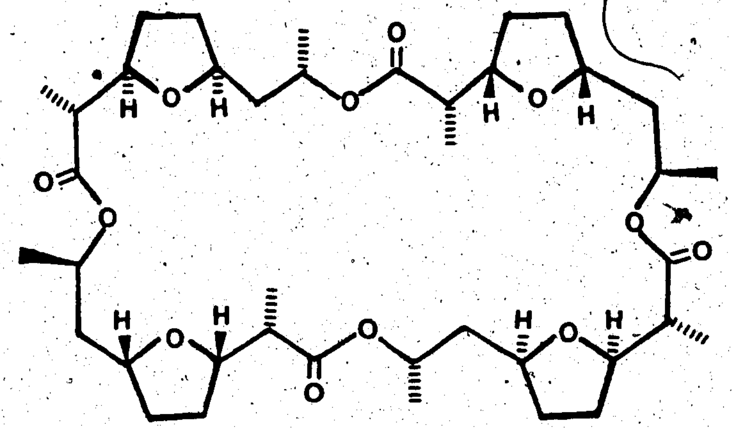
12

medium and large lactone rings[22-26] which has been a major problem in this field for many years. Successful applications of thiolesters have led to the synthesis of many biologically important macrolide lactones, such as nonactin **13**,[27] recifeiolide **14**,[28] and methymycin **15**.[20]

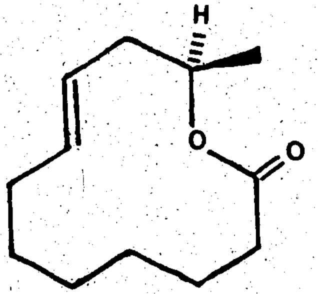
Examples in other areas of organic synthesis include the Dieckmann condensation of dithiol diesters (e.g. **16**→**17**)[29] which was shown to proceed under much milder conditions than those required for the oxygen analogues. Interestingly, unlike simple thiolesters which give rise to alcohols or aldehydes upon reduction with Raney nickel (*vide supra*), β-keto thiolesters were found to undergo complete dealkylthiolcarbonylation (e.g. **17**→**18**)[30,31] when subjected ~~to~~ Raney nickel treatment.

Based on this interesting observation Liu and coworkers demonstrated the feasibility of using S,S'-diethyl dithiomalonate (**19**) as an ethanol carbanion equivalent in alkylation[30] and Michael reactions[32] as illustrated in Schemes I and II respectively.

One interesting feature of the thiolester group is its susceptibility to reduction with sodium borohydride to the alcohol level. This was first observed by Fujita *et al.*,[33] on the highly activated thiolesters such as compound **20**. It was shown later by Liu and coworkers that



13



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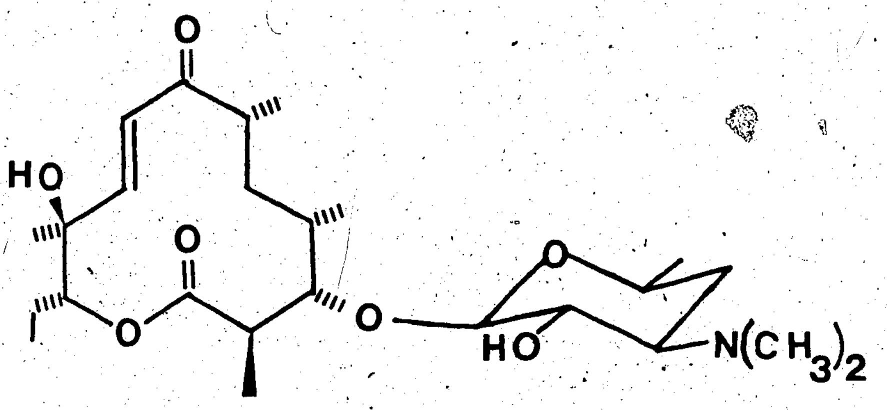

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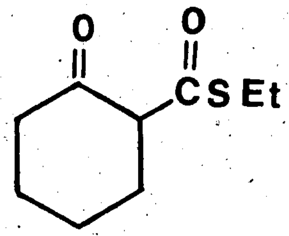
16



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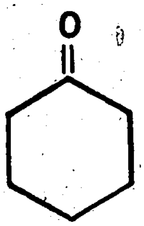

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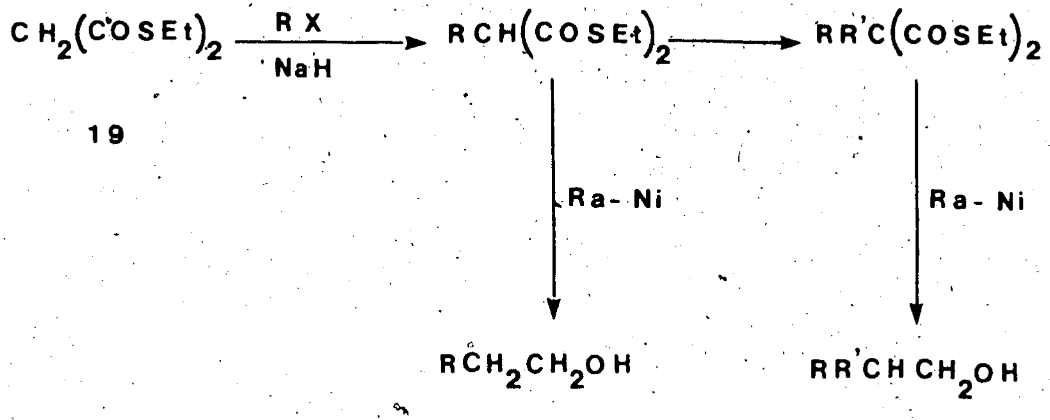
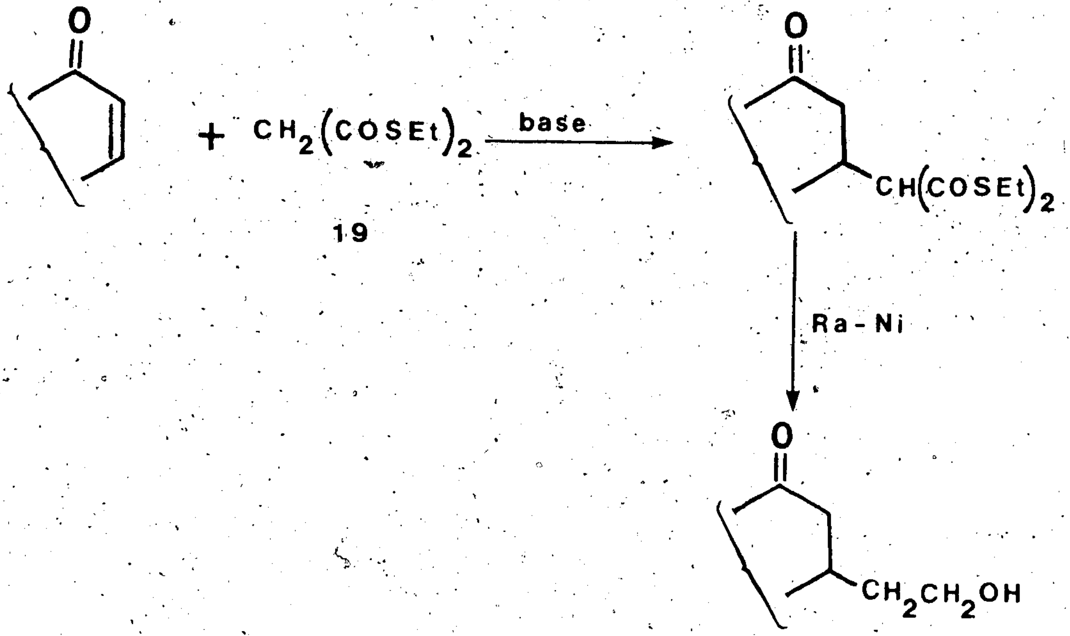
Scheme I



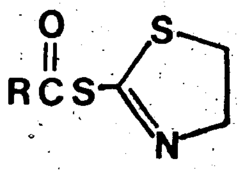
Scheme II



ordinary thiolesters could also be reduced in the same way.[34] They further showed that the thiolester group could be selectively reduced in the presence of other commonly encountered acid derivatives such as amide, ester, and nitrile.[34]

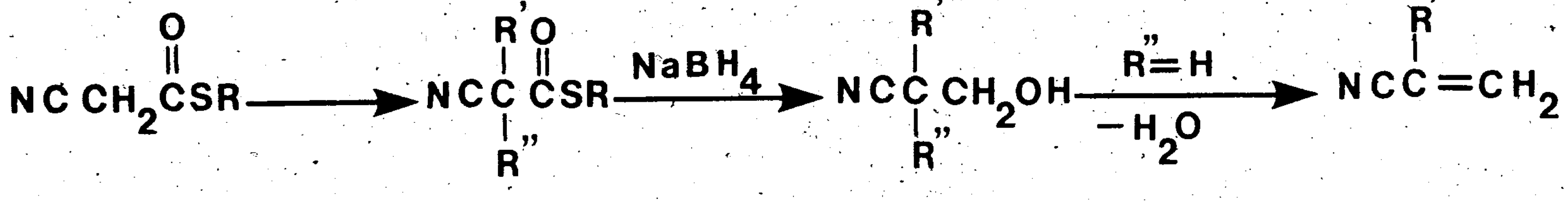
The ease of reduction of thiolester group with sodium borohydride suggests a number of interesting possibilities for its use as a latent hydroxymethyl unit in synthesis, especially, when such a unit with or without protection can not be directly involved in a desired transformation. The first part of this thesis describes a general approach to the synthesis of β-hydroxypropionitriles and acrylonitriles using cyanothiolester **21** as a starting material. As illustrated in Scheme III, the synthetic approach is greatly facilitated due to the ability of the thiolester group present in the starting material to serve both as an activating group for the carbon-carbon bond formation and a convenient source of hydroxymethyl moiety.

In the second part of the thesis an application of this method to the total synthesis of a sesquiterpenoid is demonstrated.



20

Scheme III

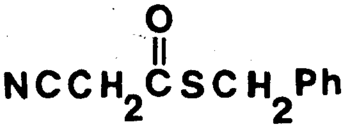


21

RESULTS AND DISCUSSION

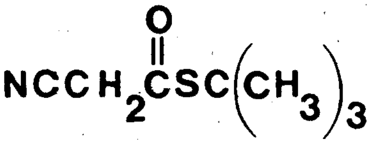
Three cyanothiolacetates **22**, **23**, and **24** were used for the present studies. These compounds were readily prepared from cyanoacetic acid and the corresponding thiols, viz. α-toluenethiol, 2-methyl-2-propanethiol, and ethanethiol according to the procedure by Liu and Sabesan,[16] using phenyl phosphorodichloridate as an activating agent.

Yields were reproducible in the range of 60-63%. S-Benzyl cyanothiolacetate (**22**) was initially used but exploration on this compound was very brief due to its instability. This unfavorable instability was due to self disproportionation into dibenzyl disulfide during the purification by column chromatography, as well as during the reaction especially at elevated temperatures. On the other hand, thiolester **23** was shown to be stable and could be stored at room temperature for prolonged periods of time. This thiolester, which was used extensively throughout this work, was purified first by distillation under reduced pressure at 100°C/2.0 torr rather than direct purification by silica gel chromatography as



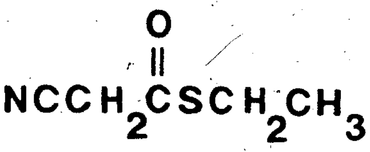
$$\mathrm{NCCH_2\overset{O}{\overset{\|}{C}}SCH_2Ph}$$

22



$$\mathrm{NCCH_2\overset{O}{\overset{\|}{C}}SC\left(CH_3\right)_3}$$

23



$$\mathrm{NCCH_2\overset{O}{\overset{\|}{C}}SCH_2CH_3}$$

24

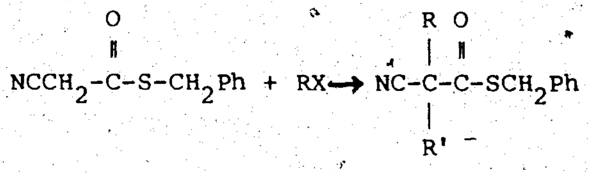
reported.[16] The distillate was further purified by column chromatography on silica gel using 40% petroleum ether in benzene as an eluent. Thiolester **24**, b.p. 100°C/4.0 torr, was purified in a similar manner.

As illustrated in Scheme III the feasibility of the general synthetic approach to β-hydroxypropionitrile and acrylonitrile derivatives depends on the ability of the cyanothiolacetates to undergo reactions with various elecrophiles, such as alkyl halides in alkylations and α,β-unsaturated carbonyl compounds in Michael reactions. Cyanothiolacetates in which the methylene unit is flanked by two electron-withdrawing groups are expected to be strongly acidic. Their acidities, which remain to be determined, should be comparable to that of the O-analogue, ethylcyanoacetate, which has a pka value of 9.[35] Indeed, cyanothiolacetates could be easily deprotonated with a variety of bases. The carbanion thus generated was found to undergo reactions with a variety of electrophilic reagents, albeit in certain cases, carefully controlled conditions were necessary. Three major types of reactions have been successfully investigated including alkylation, Michael reaction, and Knoevenagel-type condensation[36] with carbonyl compounds. These reactions are individually discussed in detail in the following sections. Also discussed are transformations of various reaction products to β-hydroxypropionitriles and acrylonitriles, where appropriate in accordance with Scheme III.

1. Alkylation Reactions of Cyanothiolacetates

Table I summarizes the results of alkylation reactions of S-benzyl cyanothiolacetate (**22**) with several alkylating agents. All the reactions were carried out in 1,2-dimethoxyethane (DME) at room temperature using sodium hydride as a base. Dialkylation with reactive alkyl halides was found to be rather promising under these conditions. For example, when thiolester **22** was treated with *ca* two equivalents each of benzyl bromide and sodium hydride, an 89% yield of dibenzyl derivative **25** was obtained (Entry 1). The ^1H nmr spectrum showed a singlet at δ4.00 for the two benzylic protons of the thiolester group. Interestingly, the remaining benzylic protons appeared as two doublets at δ3.00 and δ3.35 with a coupling constant of 14 Hz each. A complex signal centered at δ7.22 integrating for a total of fifteen protons was readily attributed to the aromatic protons. The ir spectrum showed a strong absorption at 1659 cm^{-1} due to thiolester carbonyl stretching. The mass spectrum

Table I. Alkylation reactions of S-benzyl cyanothiolacetate[a]



$$NCCH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}CH_2Ph + RX \longrightarrow NC\text{-}\underset{R'}{\underset{|}{\overset{R}{\overset{|}{C}}}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}SCH_2Ph$$

Entry	Alkylating agent (equiv.)	Base (equiv.)	Time (h)	Product(s)		% Yield[d]	
				mono	di	mono	di
1.	$PhCH_2Br$ (2.5)	NaH (2.2)	24	-	R = R' = $PhCH_2$- **25**	0	89
2.	$I(CH_2)_5I$ (1.2)	NaH (2.2)	31.5	-	R, R' = $(CH_2)_5$ **26**	0	31
3.	$CH_3(CH_2)_3I$ (1.0)	NaH (1.0)	22	R = $CH_3(CH_2)_3$-; R' = H **27**	R = R' = $CH_3(CH_2)_3$- **28**	23	27[b]
4.	$(CH_3)_2CHI$ (2.0)	NaH (1.5)	50	R = $(CH_3)_2CH$-; R' = H **29**	R = R' = $(CH_3)_2CH$- **30**	23	5[c]

[a] All the reactions were performed in 1,2-dimethoxyethane at room temperature.

[b] The starting material was recovered in 8% yield.

[c] The starting material was recovered in 23% yield.

[d] Yields were based on the amount of starting material used.

displayed a molecular ion peak at 371.1340 corresponding to the formula $C_{24}H_{21}NOS$. Under the similar conditions, cyanothiolacetate **22** was shown to undergo dialkylation with 1,5-diiodopentane to give cyclic compound **26**[*] as the only product in modest yield (Entry 2).

Attempts to achieve monoalkylation were met with rather unfavorable results. The yield was generally low for the desired product, the formation of which was always accompanied by that of the dialkylated compound even under carefully controlled conditions. For example, when _n_-butyl iodide (Entry 3) was used as an alkylating agent, only 23% yield of the desired product **27** was formed along with 27% yield of the dialkylated product **28** despite using one equivalent each of the alkylating agent and the base. The ratio of mono- and dialkylation products was somewhat improved when a bulkier alkylating agent such as diisopropyl iodide (Entry 4) was involved. However the reaction which gave the monoalkylation product **29** in 23% yield and the dialkylation product **30** in 5% yield was extremely slow. Even after 50 h at room temperature with

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[*] All the new compounds gave satisfactory ir, ^1H nmr, and high resolution mass spectra and/or elemental analysis. These data are recorded in the experimental section. Only a selected few are described in this section.

an excess of the reagent, it was incomplete with 23% recovery of the starting material. Attempts were made to enhance the reaction rate by raising the reaction temperature. However, in refluxing DME in the presence of sodium hydride, the starting thiolacetate was shown to decompose rapidly and a substantial amount of dibenzyl disulfide was formed.

Because of this undesired instability exerted by thiolester **22**, a more stable analogue was sought. At the same time, it was felt that a larger thiolester could probably suppress the unfavorable dialkylation. S-*t*-Butyl cyanothiolacetate (**23**) seemed to satisfy these considerations and a new series of experiments on alkylation reactions was carried out with this compound. Results are summarized in Table II.

Treatment of cyanothiolacetate **23** with 2.5 equiv. each of allyl bromide and sodium hydride (Entry 1) in DME at room temperature for 3 h gave a diallyl derivative **31** in 69% yield. This compound was characterized by the following spectral data. The ^1H nmr spectrum showed a sharp singlet at $\delta 1.50$ due to the *t*-butyl group. Two sets of doublet of doublets ($J = 14$, $J' = 8$ Hz each) were observed at $\delta 2.48$ and 2.68 due to four allylic methylene protons. A doublet of doublets at $\delta 5.23$ ($J = 17$, $J' = 2$

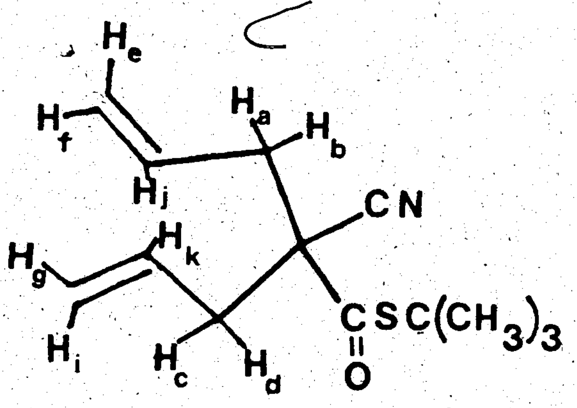

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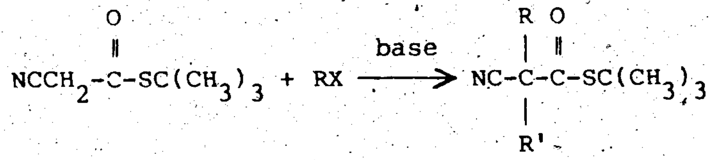
Table II. Alkylation reactions with S-t-butyl cyanothiolacetate

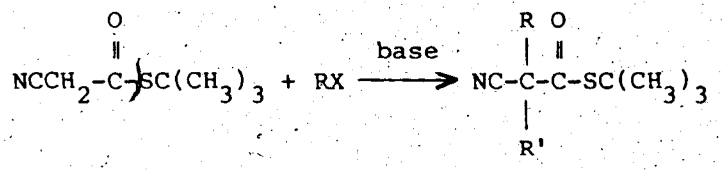


$$NCCH_2\overset{O}{\overset{\|}{C}}SC(CH_3)_3 + RX \xrightarrow{base} NC\underset{R'}{\overset{R}{C}}\overset{O}{\overset{\|}{C}}SC(CH_3)_3$$

Entry	Alkylating agent (equiv.)	Base (equiv.) Solvent	Time (h)	Temp (°C)	Product(s)		% Yield[a]		Recovered thiolester %
					mono	di	mono	di	
1.	$CH_2=CH-CH_2Br$ (2.5)	NaH (2.5) DME	3	r.t.	-	$R=R'=CH_2=CH-CH_2-$ **31**	-	69	
2.	$I(CH_2)_5I$ (1.2)	NaH (2.2) THF	30	r.t.	-	$R,R'=(CH_2)_5$ **32**	-	53	20
3.	$I(CH_2)_5I$ (1.2)	t-BuOLi (2.2) HMPA (2.2) THF	17	r.t.	-	**32**	-	77	
4.	$CH_3(CH_2)_3I$ (1.6)	t-BuOLi (1.6) HMPA (1.7) THF	72	0	$R=CH_3(CH_2)_3-$; $R'=H$ **33**	$R=R'=CH_3(CH_2)_3-$ **34**	20	64	13
5.	$CH_3(CH_2)_3Br$ (1.6)	t-BuOLi (1.6) HMPA (1.7) THF	60	0	**33**	**34**	25	20	38

(Continued)

Table II (Continued)

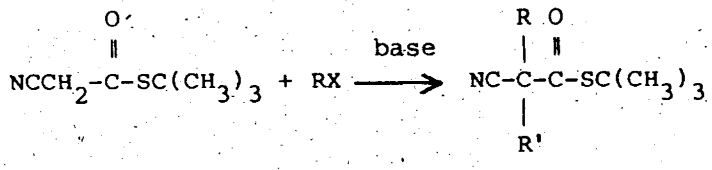


$$NCCH_2-\overset{O}{\overset{\|}{C}}-SC(CH_3)_3 + RX \xrightarrow{base} NC-\underset{R'}{\underset{|}{\overset{R}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-SC(CH_3)_3$$

Entry	Alkylating agent (equiv.)	Base (equiv.) Solve	Time (h)	Temp (°C)	Product(s)		% Yield[a]		Recovered thioester %
					mono	di	mono	di	
6.	$CH_3(CH_2)_3Cl$ (2.6)	t-BuOLi (2.6) HMPA (2.6) THF	32	reflux	**33**	**34**	36	0.6	61
7.	$PhCH_2Br$ (1.1)	t-BuOLi (1.1) HMPA (1.1) THF	96	r.t.	$R=PhCH_2-$; $R'=H$ **35**	$R=R'=PhCH_2-$ **36**	16	51	9
8.	$PhCH_2Br$ (1.7)	LiH (1.7) HMPA (1.7) THF	26	-5	**35**	**36**	17	46	19
9.	$(CH_3)_2CHI$ (2.5)	t-BuOLi (2.5) HMPA (2.5) THF	48	0	$R=(CH_3)_2CH-$; $R'=H$ **37**	$R=R'=(CH_3)_2CH-$ **38**	49	9	30

(Continued)

Table II (Continued)



$$NCCH_2\overset{O}{\overset{\|}{C}}SC(CH_3)_3 + RX \xrightarrow{base} NC\overset{R}{\underset{R'}{C}}\overset{O}{\overset{\|}{C}}SC(CH_3)_3$$

Entry	Alkylating agent (equiv.)	Base (equiv.) Solv.	Time (h)	Temp (°C)	Product(s) mono	Product(s) di	% Yield[a] mono	% Yield[a] di	Recovered thiolester %
10.	$(CH_3)_2CHBr$ (2.5)	t-BuOLi (2.5) HMPA (2.5) THF	15	r.t.	$R=(CH_3)_2CH-$; $R'=H$ **37**	$R=R'=(CH_3)_2CH-$ **38**	52	4	35
11.	$(CH_3)_2CHBr$ (2.5)	"	5	reflux	**37**	**38**	41	6	25
12.	$CH_3(CH_2)_6CH_2Br$ (1.1)	t-BuOLi (1.1) HMPA (1.1) THF	40.5	-5	$R=CH_3(CH_2)_6CH_2-$; $R'=H$ **39**	$R=R'=CH_3(CH_2)_6CH_2-$ **40**	11	2	82
13.	$CH_3(CH_2)_6CH_2Br$ (1.2)	LiH (1.2) HMPA (1.2) THF	48	-5	**39**	**40**	27	2	51

[a] Yields were based on the amount of starting material used.

Hz) was assignable for vinylic protons H_e and H_i, whereas a doublet of doublets of doublets at δ5.24 (J = 11, J' = 2, J" = 1 Hz) was assignable for vinylic protons H_f and H_g. A doublet of doublets of triplets at δ5.80 (J = 16, J' = 11, J" = 7 Hz) was assigned to vinylic protons H_j and H_k. The ir spectrum showed a characteristic band at 1675 cm^{-1} for the thiolester group, a weak band at 2240 cm^{-1} for the nitrile group, and another weak band at 3080 cm^{-1} indicative of an olefinic stretching. The mass spectrum did not give the molecular ion peak but showed a M^+-56 ion peak at 181.0559 corresponding to the loss of a C_4H_8 unit. However, elemental analysis results confirmed the molecular formula to be $C_{13}H_{19}NOS$. Ring formation could be easily carried out as well. For instance, the reaction with 1,5-diiodopentane led to the exclusive formation of cyclic product **32**. The reaction was found to proceed better when lithium t-butoxide was used as a base (Entry 3) instead of sodium hydride (Entry 2).

As in the previous cases with the benzyl derivative, dialkylation was inevitable, when various attempts were made to carry out monoalkylation on cyanothiolacetate **23** even under carefully controlled conditions. Thus, when n-butyl iodide (Entry 4) was used as an alkylating agent in the presence of lithium t-butoxide (1.6 equiv.) and hexamethylphosphoramide (1.7 equiv.) in tetrahydrofuran (THF) at 0°C for 72 h, only a 20% yield of the desired product **33** was formed along with a 64% yield of dialkylated compound **34**, and the starting thioester was recovered in 13%. It was assumed that, due to the long reaction period the initially formed monoalkylated compound underwent further alkylation at a reasonably fast rate to give the dialkylated compound. Furthermore, since _n_-butyl iodide is a reactive alkylating agent, the reaction was difficult to control even at low temperature. Based on this consideration, the less reactive bromo- and chloro- analogues were used (Entries 5 and 6). As expected, both of them reacted at a slower rate than 1-iodobutane and suppressed the formation of the dialkylated compound to a large extent, particularly in the case of 1-chlorobutane. This reaction, in fact, did not occur at room temperature but at elevated temperature it proceeded to give almost exclusively the monoalkylation product **33** (Entry 6). Unfortunately the yield of 36%, which could not be further improved, was rather unsatisfactory.

More satisfactory results were obtained with isopropyl iodide (Entry 9) and even better with the corresponding bromide (Entry 10). The rates of these reactions carried out at room temperature were found to be slow but could be enhanced by the use of a rather large excess (2.5 equiv.) of the alkylating agent, which did not seem to effect the ratio of monoalkylated product **37** to dialkylated product **38**. Attempts to further accelerate the reaction, by raising the temperature, resulted in the formation of the desired product in somewhat poorer yield (Entry 11).

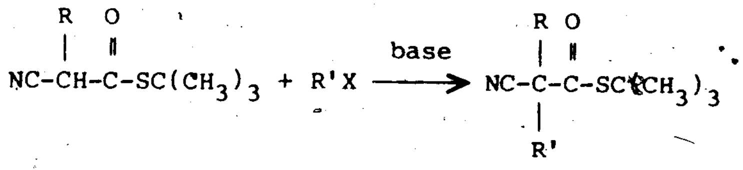
With benzyl bromide, a rather reactive alkylating agent, the attempted monoalkylation was unsuccessful. Under various conditions (e.g. Entries 7 and 8) the dialkylated compound **36** was always formed in substantial amount while the desired compound **35** was produced in minor quantity. The ^1H nmr spectrum of compound **36**, which was obtained in crystalline form, m.p. 92-95°C, showed a characteristic singlet at $\delta 1.34$ for the t-butyl protons and two doublets ($J = 14$ Hz each), one at $\delta 3.00$ and the other at $\delta 3.37$, each attributing for two benzylic protons (one from each benzyl group). A singlet at $\delta 7.32$ for ten protons was due to aromatic protons. A strong absorption at 1670 cm^{-1} due to thiolester carbonyl and a weak band at 2240 cm^{-1} for nitrile stretching were observed in the ir spectrum. The mass spectrum displayed a molecular ion peak at 337.1502 which was consistent with the formula

$C_{21}H_{23}NOS$. Compound **35** showed a singlet at δ1.48 for t-butyl protons. Two doublets at δ3.20 (J = 8 Hz) and 3.23 (J = 6 Hz) integrating for one proton each were due to the benzylic protons. A doublet of doublets at δ3.70 was attributable for the methine proton, with coupling constants of 8 Hz and 6 Hz. Aromatic protons appeared as a multiplet at δ7.31. The ir spectrum showed a strong band at 1685 cm^{-1} for thiolester carbonyl and a weak band at 2250 cm^{-1} for nitrile moiety. The mass spectrum gave a molecular ion peak at 247.1026 which confirmed the formula $C_{14}H_{17}NOS$.

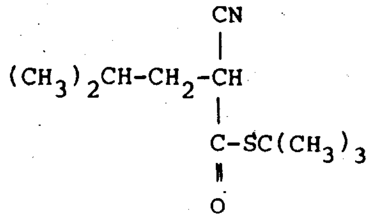
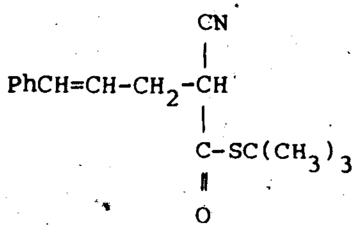
Monoalkylation with n-octylbromide was also studied (Entries 12 and 13). The reactions were carried out at -5°C. At this temperature, the formation of dialkylation product **40** was successfully suppressed. However the reaction, which required about two days in order to achieve 50% conversion, was too slow to be synthetically useful.

Further alkylations on several monoalkylated compounds were also studied to give the dialkylated thiolesters with non-identical substituents. The substrates **41** and **43** used for these studies were prepared by a different route which will be discussed in the next section. Results of these studies are summarized in Table III.

Table III. Dialkylation of cyanothiolacetate **23** with non-identical substituents[a]

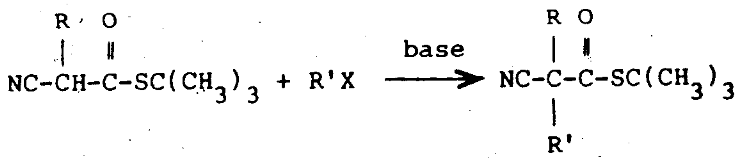


$$NC\text{-}\overset{R}{\overset{|}{C}}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}SC(CH_3)_3 + R'X \xrightarrow{\text{base}} NC\text{-}\underset{R'}{\overset{R}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}SC(CH_3)_3$$

Entry	Substrate	Alkylating agent (equiv.)	Base (equiv.)	Time (h)	Product (% Yield)[b]
1.	 $(CH_3)_2CH\text{-}CH_2\text{-}\underset{\underset{O}{\overset{\|}{C}}\text{-}SC(CH_3)_3}{\overset{CN}{CH}}$ **41**	$PhCH_2Br$ (1.0)	NaH (1.0)	9.5	R=$(CH_3)_2CH\text{-}CH_2$-; R'=$PhCH_2$- **42** (85)
2.	 $PhCH{=}CH\text{-}CH_2\text{-}\underset{\underset{O}{\overset{\|}{C}}\text{-}SC(CH_3)_3}{\overset{CN}{CH}}$ **43**	CH_3CH_2I (1.0)	NaH (1.0)	22	R=Ph-CH=$CHCH_2$-; R'=Et **44** (66)

(Continued)

Table III. (Continued)



$$\mathrm{NC{-}\underset{}{\overset{R}{C}}H{-}\overset{O}{\overset{\|}{C}}{-}SC(CH_3)_3} + \mathrm{R'X} \xrightarrow{\text{base}} \mathrm{NC{-}\underset{R'}{\overset{R}{C}}{-}\overset{O}{\overset{\|}{C}}{-}SC(CH_3)_3}$$

Entry	Substrate	Alkylating agent (equiv.)	Base (equiv.)	Time (h)	Product (% Yield)[b]
3.	**43**	CH_2=CH-CH_2Br (1.2)	NaH (1.1)	16	R=PhCH=CH-CH_2-; R'=CH_2=CH-CH_2- **45** (54)

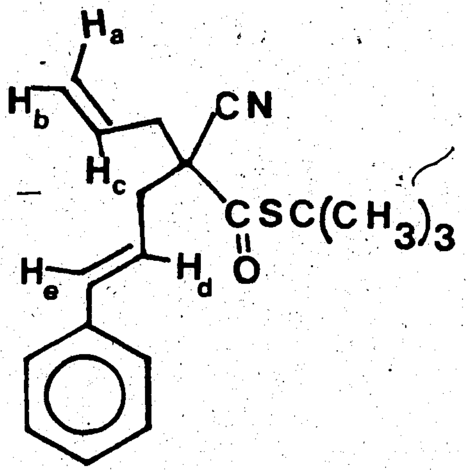
[a] All the reactions were carried out in DME at room temperat[illegible]

[b] Yields were based on the amount of starting material used.

The second alkylation, in accordance with expectation, occurred readily. All the alkylation reactions were carried out in DME at room temperature with sodium hydride as a base. When compound **41** was subjected to alkylation with benzyl bromide under these conditions (Entry 1), compound **42** was obtained in 85% yield. The ^{1}H nmr spectrum displayed the following signals. Two doublets, one at $\delta 0.94$ and the other at $\delta 1.03$, each integrating for three protons and with a coupling constant of 6 Hz, were due to the methyl groups. A signal for the *t*-butyl group appeared as a singlet at $\delta 1.40$. Two magnetically non-equivalent benzylic methylene protons appeared as a pair of doublets at $\delta 2.92$ and $\delta 3.20$ having the same coupling constant of 14 Hz. A multiplet at $\delta 7.30$ for five protons was due to the benzene moiety. In the ir spectrum, absorption bands were observed at 1580, 1620 and 3010-3100 cm^{-1} due to the benzene ring. Thiolester group appeared at 1690 cm^{-1} and nitrile at 2260 cm^{-1}. A molecular ion peak at 303.1651 in the mass spectrum confirmed the required formula of $C_{18}H_{25}NOS$.

Under the similar conditions, alkylation of compound **43** with ethyl iodide resulted in the formation of the ethyl derivative in 66% yield (Entry 2). When the alkylation was carried out using allyl bromide as the alkylating agent, a 54% yield of product **45** was obtained (Entry 3). The ^1H nmr of this compound gave a singlet at δ1.44 for the t-butyl group and a complex signal at δ2.50 to 3.00 for a total of four protons was due to the allylic protons. A doublet of doublets at δ5.24 with coupling constants of 16 and 2 Hz was due to the terminal vinylic proton H_a. Another doublet of doublets (J = 10, J' = 2 Hz) at δ5.26 corresponded to the terminal vinylic proton H_b. A triplet of doublets of doublets with coupling constants of 16, 10, and 7 Hz at δ5.82 was evident for the vinylic proton H_c. Vinylic proton H_d appeared as a triplet of doublets at δ6.16, with coupling constants of 7 and 16 Hz, while vinylic proton H_e appeared at δ6.55 as a broad doublet (J = 16 Hz). Aromatic protons were found at δ7.32 as a multiplet. The ir spectrum contained absorption bands at 1605 cm^{-1} due to carbon-carbon double bond stretch, 1670 cm^{-1} due to thiolester carbonyl, and 2240 cm^{-1} due to nitrile. The mass spectrum displayed a molecular ion peak at 313.1495 confirming the required formula of $C_{19}H_2$ [illegible].

The preceding results indicated that dialkylation allowing the incorporation of two identical substituents could be readily effected using both thiolesters **22** and **23**. For the introduction of two non-identical



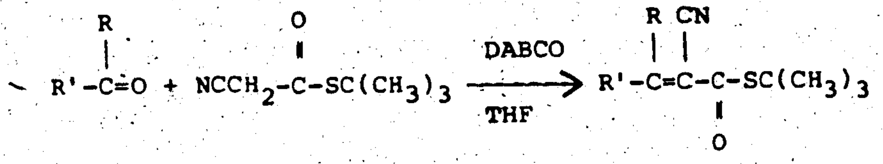
45

substituents, the second alkylation process was found to be equally facile. On the contrary, results obtained for the monoalkylation of thiolesters **22** and **23** were rather disappointing due to the competing dialkylation process. Of the two cyanothiolesters, the t-butyl derivative **23** was found to give consistently better results because of its stability. No single set of conditions could be used to effectively introduce a single alkyl group. Depending upon the nature of the alkylating agents, suitable adjustment of reaction conditions was necessary. In general, however, a combination of lithium t-butoxide as a base and HMPA/THF as a solvent system seemed to give better yields of the products.

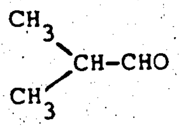
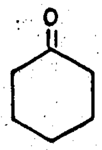
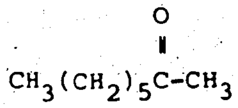
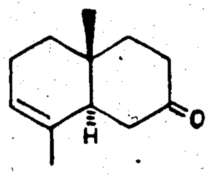
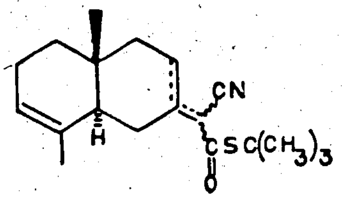
2. Reactions of Cyanothiolacetate 23 with Carbonyl Compounds and Selective Reduction of the Condensation Products.

Cyanothiolacetate **23** was found to undergo condensation readily with a variety of aldehydes and ketones giving Knoevenagel-type reaction products. The results of these condensation reactions are to be found in Table IV. The generality of the reaction was apparent in that both ketones and aldehydes can be used to give products in synthetically useful yields. In general, the

Table IV. Condensation of S-*t*-butyl cyanothiolacetate (**23**) with ketones and aldehydes[a]



$$R'-\overset{R}{\overset{|}{C}}=O + NCCH_2-\overset{O}{\overset{\|}{C}}-SC(CH_3)_3 \xrightarrow[THF]{DABCO} R'-\overset{R}{\overset{|}{C}}=\overset{CN}{\overset{|}{C}}-\underset{O}{\underset{\|}{C}}-SC(CH_3)_3$$

Entry	Ketones and Aldehydes	Time (h)	Temp. (°C)	Product	% Yield[f]
1.	PhCH=CH-CHO	13	r.t.	R=H; R'=PhCH=CH- **46**[b]	94[c]
2.	 $(CH_3)_2CH-CHO$	5	r.t.	R=H; R'=$(CH_3)_2CH-$ **47**[b]	66
3.		20	r.t.	R,R'=$-(CH_2)_5-$ **48**	87
4.	 $CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}-CH_3$	25	r.t.	R=$CH_3(CH_2)_5-$; R'=CH_3- **49**[d]	57
5.	 **50**	15	reflux	 **51**[b]	21[c]
6.	**50**	48	r.t.[e]	**51**	71[c]

(Continued)

Table IV. (Continued)

[a] Unless otherwise specified all reactions were carried out in THF using 1.5 equiv. each of 1,4-diazabicyclo[2.2.2]octane (DABCO) and carbonyl compounds.

[b] Obtained as a mixture of stereoisomers.

[c] These reactions were run with 1.5 equiv. each of DABCO and the thiolester.

[d] According to ^{1}H nmr only one isomer was obtained. Its regiochemistry remains to be determined.

[e] This reaction was carried out using 1.5 equiv. each of DABCO and thiolester in the presence of 3 equiv. of anhydrous sodium sulfate.

[f] Yields were obtained on the basis of the amount of starting material used.

reactions could be effected at room temperature using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base and THF as a solvent. When trans-cinnamaldehyde (Entry 1) was treated with thiolester **23** under these conditions, condensation took place readily to give a 94% yield of product **46** which was obtained as a mixture of two inseparable regioisomers in a ratio of 1:2. The ^1H nmr spectrum displayed two singlets, one at δ1.46 and the other at δ1.56 for the t-butyl group of the minor and major isomers respectively. Aromatic protons for the major isomer appeared at a normal region of δ7.30, while for the minor isomer, the signal shifted downfield to δ7.42. The vinylic protons experienced considerable downfield shifts due to extended conjugation. Because of the mixture nature of the substrate, these signals were rather complex. The ir spectrum showed absorption bands at 1558, 1576, and 1604 cm^{-1} due to carbon-carbon double bonds and aromatic ring. Furthermore, diagnostic bands at 1662 and 2211 cm^{-1} respectively for thiolester group and nitrile were also observed. A molecular ion peak at 271.1031 in the mass spectrum further supported the structure of **46**.

Under similar conditions, condensation of cyanothiolacetate **23** with isobutyraldehyde (Entry 2), cyclohexanone (Entry 3), 2-octanone (Entry 4) gave rise to the expected products **47**, **48**, and **49** in good yields. The only exceptional case which did not give satisfactory results under these conditions was the condensation with ketone **50**. At room temperature only a small amount of product **51** (8% yield) was formed after three days. Even in refluxing THF, only 21% yield of the desired product was obtained (Entry 5). However, when the reaction was run in the presence of anhydrous sodium sulfate at room temperature for 48 h, the yield was remarkably improved to 71% (Entry 6). The improvement was apparently due to the fact that the reaction was reversible and the removal of water facilitated the formation of the desired product.

The facile condensation of thiolester **23** with various ketones and aldehydes provided an opportunity to effect the monoalkylation in an indirect manner, if selective reduction of the carbon-carbon double bond of the product could be achieved. There are ample examples in the literature for the selective reduction, by chemical means,* of a double bond in conjugation with one or more electron-withdrawing groups.[37-41] It was found that

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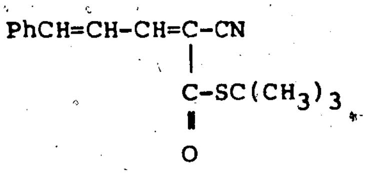
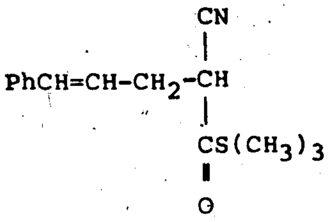
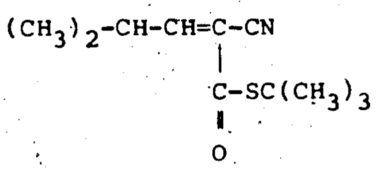
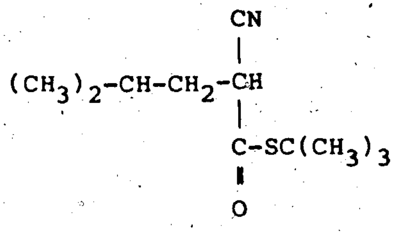
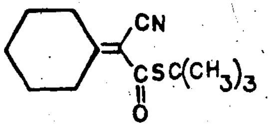
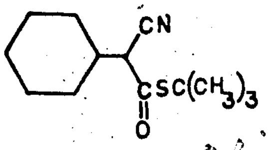
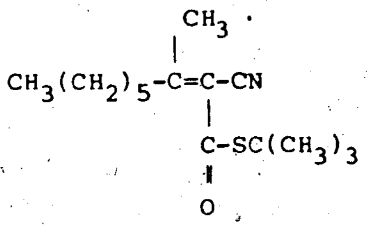
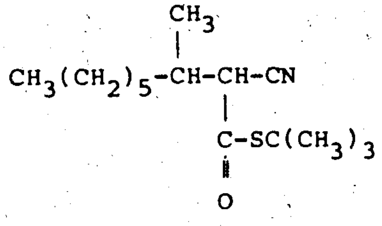
*Catalytic hydrogenation of the carbon-carbon double bond in our case is apparently inadequate due to the presence of the sulfur element which is known as a poison to the catalyst.

selective reduction of the α,β-unsaturated cyanothiolacetates could also be easily carried out. As shown in Table V unsaturated cyanothiolacetate **46** underwent 1,4-reduction on exposure to 1 mol.equiv. of sodium borohydride in ethanol for 2.5 h at room temperature to give the corresponding saturated compound **43** in 83% yield (Entry 1). This procedure for selective reduction is apparently general. Three additional compounds **41**, **52**, and **53** (Entries 2-4) were readily prepared at 0°C (45 min) in comparable yields.

In conclusion cyanothiolacetate **23** was shown to undergo facile Knoevenagel-type condensation with a variety of aldehydes and ketones under mild conditions. It was further shown that carbon-carbon double bond of the condensation product could be selectively reduced with sodium borohydride. This selective reduction provided an indirect method to effect the overall monoalkylation of the cyanothiolacetate in high yields. Despite its two-step sequence, the reactions were operationally simple without any accompanying dialkylation as was encountered in the previous direct alkylation methods.

Table V. Selective reduction of the α,β-unsaturated cyanothiolacetates to saturated cyanothiolacetates

Entry	α,β-Unsaturated cyanothiolacetate	Time[a] (h)	Product	% Yield[c]
1.	 $PhCH{=}CH{-}CH{=}C(CN){-}C({=}O){-}SC(CH_3)_3$ **46**	2.5	 $PhCH{=}CH{-}CH_2{-}CH(CN){-}C({=}O)S(CH_3)_3$ **43**	83
2.	 $(CH_3)_2{-}CH{-}CH{=}C(CN){-}C({=}O){-}SC(CH_3)_3$ **47**	0.75[b]	 $(CH_3)_2{-}CH{-}CH_2{-}CH(CN){-}C({=}O){-}SC(CH_3)_3$ **41**	91
3.	 **48**	0.75[b]	 **52**	97
4.	 $CH_3(CH_2)_5{-}C(CH_3){=}C(CN){-}C({=}O){-}SC(CH_3)_3$ **49**	0.75[b]	 $CH_3(CH_2)_5{-}CH(CH_3){-}CH(CN){-}C({=}O){-}SC(CH_3)_3$ **53**	74

[a] Unless otherwise stated these reactions were performed in ethanol using 1 mole equiv. of sodium borohydride at 0°C to room temperature.

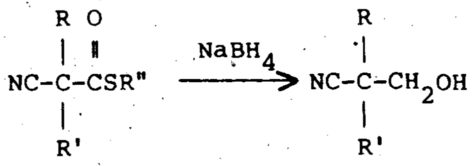
[b] This reaction was carried out at 0°C.

[c] Yields were obtained on the basis of the amount of starting material used.

3. Conversion of Alkylation and Condensation Products to β-Hydroxypropionitrile and Acrylonitrile Derivatives

The next stage of our studies was to explore the feasibility of converting the alkylation and Knoevenagel-type condensation products, derived from cyanothiolacetates, to β-hydroxypropionitrile derivatives and, where applicable, further to acrylonitrile derivatives. This requires a selective reduction of the thiolester group in the presence of a cyano group. As shown in Table VI, the selective reduction of the alkylation products was readily achieved at room temperature by the use of an excess of sodium borohydride (ca. 2 to 4 mol.equiv.) as a reducing agent. Initially, isopropyl alcohol was used as the solvent in order to prevent the possible transesterification reaction between the solvent and the reactant. This solvent was found to be adequate and a number of compounds were reduced smoothly to give the desired products. For example, when cyanothiolacetate **25** (Entry 1) was treated with 4.8 mol. equiv. of sodium borohydride in isopropyl alcohol for 24 h at room temperature, a 96% yield of crystalline alcohol **54**, m.p. 100-102°C, was obtained. A molecular ion peak at 251.1313 in the mass spectrum confirmed the required molecular formula $C_{17}H_{17}NO$. The ^1H nmr spectrum showed a broad

Table VI. Selective reduction of alkylation products to β-hydroxypropionitriles



$$NC\text{-}\underset{R'}{\overset{R}{C}}\text{-}\overset{O}{C}SR'' \xrightarrow{NaBH_4} NC\text{-}\underset{R'}{\overset{R}{C}}\text{-}CH_2OH$$

Entry	Substrate	Time^a (h)	Product	% Yield
1.	R=R'=R"=$PhCH_2$- **25**	24^b	R=R'=$PhCH_2$- **54**	96
2.	R=$CH_3(CH_2)_3$-; R'=H; R"=$PhCH_2$- **27**	25	R=$CH_3(CH_2)_3$-; R'=H **55**	90
3.	R=$CH_3(CH_2)_3$-; R'=H; R"=-$C(CH_3)_3$ **33**	25	**55**	98
4.	R=R'=$CH_3(CH_2)_3$-; R"=$PhCH_2$- **28**	11^b	R=R'=$CH_3(CH_2)_3$- **56**	64
5.	R=R'=$CH_3(CH_2)_3$-; R'=-$C(CH_3)_3$ **34**	19	**56**	90

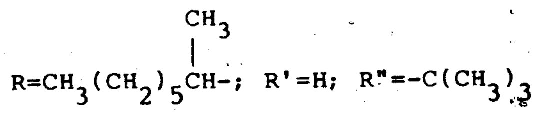
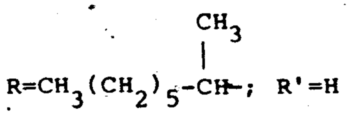
(Continued)

Table VI. (Continued)

Entry	Substrate	Time[a] (h)	Product	% Yield
6.	$R=R'=CH_2=CH\text{-}CH_2\text{-};\ R''=\text{-}C(CH_3)_3$ **31**	11	$R=R'=CH_2=CH\text{-}CH_2\text{-}$ **57**	80
7.	$R,R'=\text{-}(CH_2)_5\text{-};\ R''=\text{-}C(CH_3)_3$ **32**	18	$R,R'=\text{-}(CH_2)_5\text{-}$ **58**	94
8.	$R=PhCH_2\text{-};\ R'=H;\ R''=\text{-}C(CH_3)_3$ **35**	24	$R=PhCH_2\text{-};\ R'=H$ **59**	90
9.	$R=(CH_3)_2CH\text{-};\ R'=H;\ R''=\text{-}C(CH_3)_3$ **37**	15	$R=(CH_3)_2CH\text{-};\ R'=H$ **60**	91
10.	$R=CH_3(CH_2)_7\text{-};\ R'=H;\ R''=\text{-}C(CH_3)_3$ **39**	1[c]	$R=CH_3(CH_2)_6CH_2\text{-};\ R'=H$ **61**	99

(Continued)

Table VI. (Continued)

Entry	Substrate	Time[a] (h)	Product	% Yield
11.	$R=(CH_3)_2CHCH_2-$; $R'=PhCH_2-$; $R''=-C(CH_3)_3$ **42**	13	$R=(CH_3)_2CHCH_2-$; $R'=PhCH_2-$ **62**	90
12.	$R=CH_3CH_2-$; $R'=PhCH=CHCH_2-$; $R''=-C(CH_3)_3$ **44**	19	$R=CH_3CH_2-$; $R'=PhCH=CHCH_2-$ **63**	92
13.	$R=CH_2=CHCH_2-$; $R'=PhCH=CHCH_2-$; $R''=-C(CH_3)_3$ **45**	10	$R=PhCH=CHCH_2-$; $R'=CH_2=CHCH_2-$ **64**	85
14.	 $R=CH_3(CH_2)_5\overset{\overset{CH_3}{\mid}}{C}H-$; $R'=H$; $R''=-C(CH_3)_3$ **53**	1	 $R=CH_3(CH_2)_5-\overset{\overset{CH_3}{\mid}}{C}H-$; $R'=H$ **65**	92

[a] Unless otherwise specified, all reactions were performed in absolute ethanol at ambient temperature using 4 mol.equiv. of sodium borohydride.

[b] Performed in isopropyl alcohol.

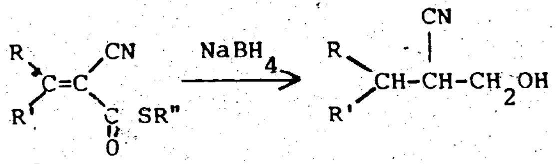
[c] These reactions were run at 0°C.

singlet at δ2.95 due to four benzylic protons, a singlet at δ3.53 due to the methylene unit bearing the hydroxyl group, and a multiplet at δ7.33 due to the aromatic protons. In the ir spectrum, the presence of a hydroxyl group was evident from the broad absorption band at 3490-3500 cm^{-1} and a strong absorption at 1050 cm^{-1}. A weak band at 2220 cm^{-1} for the cyano group was also observed. Similarly, reduction of thiolester **28** gave rise to alcohol **56** (Entry 4) in 64% yield.

It was later found that ethanol could also serve as an adequate solvent for reduction. Not in a single case were traces of transesterification product (i.e. -COSR → -COOEt) detected. Consequently, ethanol was consistently used as a preferred solvent. By the use of this solvent, alcohol **55** was readily prepared either from S-benzyl thiolester **27** (Entry 2) or from S-t-butyl thiolester **33** (Entry 3) in excellent yield. The ^1H nmr spectrum of **55** showed a triplet at δ0.94 with coupling constant of 6 Hz due to the methyl group, a broad singlet at δ2.13 due to the hydroxyl group, and a broad triplet at δ2.75 with coupling constant of 6 Hz due to the methine proton adjacent to the cyano group. In the ir spectrum, a broad band at 3400-3500 cm^{-1} for the hydroxyl group and a weak band at 2250 cm^{-1} for the cyano group were observed. The mass spectrum did not show a molecular ion peak but a peak at 97.0892 due to the loss of a CH$_2$O unit. Preparation of cyano alcohols **56-65** (Entries 5-14) was show[illegible]e equally facile using ethanol as a solvent and without exception high yields of the desired products were obtained.

In the previous section, it has been shown that the carbon-carbon double bond of the Knoevenagel-type condensation products could be selectively reduced with sodium borohydride under controlled condition. When an excess of sodium borohydride (ca. 4 mol. equiv.) was used, further reduction of the thiolester group occurred as expected, thus allowing the direct conversion of a condensation product to the corresponding β-hydroxypropionitrile. For example, treatment of unsaturated cyanothiolester **49** with 4 mol. equiv. of sodium borohydride in ethanol at 0°C for 50 min resulted in the concomitant reduction of both the carbon-carbon double bond and the thiolester group to give β-hydroxypropionitrile **65** in 95% yield (Entry 1, Table VII). This compound showed in the ^{1}H nmr spectrum a broad triplet at δ0.90 with a coupling constant of 6 Hz for the terminal methyl group. The branched methyl group appeared as a doublet (J = 8 Hz) at δ1.07, whereas a hydroxyl proton was

Table VII. Reduction of Knoevenagel-type condensation products with sodium borohydride to β-hydroxypropionitriles.



Entry	Substrate	Time[a] (min)	Product	% Yield
1.	$R=CH_3(CH_2)_5-$; $R'=CH_3-$; $R''=-C(CH_3)_3$ **49**	50	$R=CH_3(CH_2)_5-$; $R'=CH_3-$ **65**	95
2.	$R=PhCH=CH-$; $R'=H$; $R''=-C(CH_3)_3$ **46**	55	$R=PhCH=CH-$; $R'=H$ **66**	78
3.	$R=(CH_3)_2CH-$; $R'=H$; $R''=-C(CH_3)_3$ **47**	15	$R=(CH_3)_2CH-$; $R'=H$ **67**	84
4.	$R,R'=-(CH_2)_5-$; $R''=-C(CH_3)_3$ **48**	30	$R,R'=-(CH_2)_5-$ **68**	98

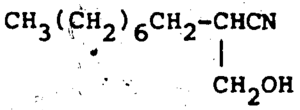
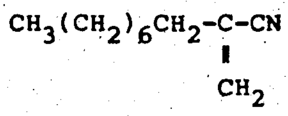
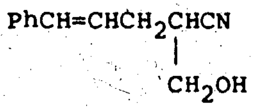
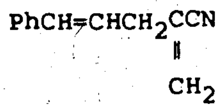
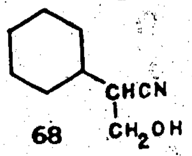
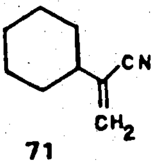
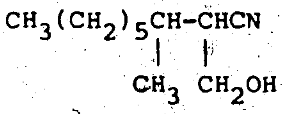
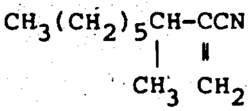
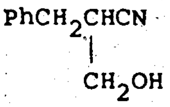
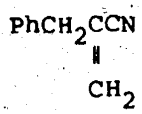
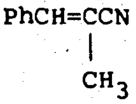
[a] All reactions were performed in absolute ethanol at 0°C using 4 mol.equiv. of sodium borohydride.

observed at δ2.04 as a broad singlet which disappeared upon D_2O exchange. In the ir spectrum, the absence of any carbonyl absorption and the presence of a broad hydroxyl absorption band centered at 3450 cm^{-1} and a weak nitrile absorption at 2240 cm^{-1} were in agreement with the assigned structure.

The direct reduction of the condensation product to the corresponding saturated alcohol was found to be general. Three additional examples (**46**→**66**, **47**→**67**, and **48**→**68**) are also to be found in Table VII.

Two methods were successfully explored for the dehydration of β-hydroxypropionitrile with a single substituent at the α-carbon. Results are compiled in Table VIII. Indirectly, the dehydration could be carried out by mesylation followed by elimination. Thus, mesylation of n-octyl derivative **61** (Entry 1) with methanesulfonyl chloride and triethylamine in chloroform, at room temperature for 6 h followed by elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene for 4 h gave a 94% yield of acrylonitrile derivative **69**. In agreement with the expected structure, compound **69** showed the following spectral data. In the ^1H nmr spectrum, two triplets, one at δ0.90 with a coupling constant of 6 Hz and the other (broad) at δ2.25 with a

Table VIII. Dehydration of β-hydroxypropionitriles

Entry	Alcohol	Reagent[a] (equiv.)	Acrylonitrile	% Yield
1.	 $\mathrm{CH_3(CH_2)_6CH_2{-}CH(CH_2OH)CN}$ **61**	(i) MsCl[b] (3.0) Et$_3$N (5.0) (ii) DBU; C_6H_6[c]	 $\mathrm{CH_3(CH_2)_6CH_2{-}C({=}CH_2){-}CN}$ **69**	94
2.	**61**	DCC (1.5)	**69**	85
3.	 $\mathrm{PhCH{=}CHCH_2CH(CH_2OH)CN}$ **66**	DCC (1.5)	 $\mathrm{PhCH{=}CHCH_2C({=}CH_2)CN}$ **70**	69
4.	 **68**	DCC (1.5)	 **71**	80
5.	 $\mathrm{CH_3(CH_2)_5CH(CH_3){-}CH(CH_2OH)CN}$ **65**	DCC (1.5)	 $\mathrm{CH_3(CH_2)_5CH(CH_3){-}C({=}CH_2)CN}$ **72**	70
6.	 $\mathrm{PhCH_2CH(CH_2OH)CN}$ **59**	DCC (1.5)	 $\mathrm{PhCH_2C({=}CH_2)CN}$ **73**	52
7.	**59**	(i) MsCl[b] (3.0) Et$_3$N (5.0) (ii) DBU; C_6H_6[c]	**73** +  $\mathrm{PhCH{=}C(CH_3)CN}$ **74**	51

[a] Unless otherwise specified all reactions were performed in refluxing ether in the presence of a trace amount of copper(I) chloride.

[b] Chloroform was used as a solvent.

[c] At refluxing benzene.

coupling constant of 7 Hz, were attributed to the methyl group and the vinylic methylene group respectively. A doublet of doublets at δ5.65 (J = J' = 1 Hz) and a doublet at δ5.80 (J = 1 Hz), integrating to one proton each, were attributed to the vinylic protons. The ir spectrum exhibited an olefinic absorption at 1630 cm^{-1} and a nitrile absorption band which shifted to a lower frequency of 2130 cm^{-1} due to conjugation. The mass spectrum gave a molecular ion peak of 165.1477 corresponding to the formula $C_{11}H_{19}N$.

The dehydration could also be directly effected by the use of dicyclohexyl carbodiimide (DCC) as a dehydrating agent. The reaction occurred readily in refluxing ether in the presence of a trace amount of copper (I) chloride.[42] This procedure was found to be general and several acrylonitriles (**69-73**) were readily prepared from the corresponding β-hydroxypropionitriles (Entries 2-6) in good yields.

Other than operational simplicity, the direct method proved to be superior to the two-step sequence previously discussed in cases in which the products are sensitive to heat and/or basic conditions. For instance, dehydration of compound **59** with DCC (Entry 6) gave cleanly a single product **73** which showed, in the ^1H nmr spectrum, a broad singlet at δ3.56 for the benzylic protons and a narrowly split triplet (J = 1 Hz) at δ5.69 and a singlet at δ5.91 for the vinylic protons. On the other hand, dehydration of compound **59** by the two-step sequence, i.e. mesylation followed by elimination, gave a mixture of two isomeric products **73** and **74** in a ratio of approximately 1:5. The ^{1}H nmr spectrum of the latter compound showed a one-proton singlet at δ7.20 due to the vinylic proton and a three-proton singlet at δ2.15 due to the vinylic methyl group. The formation of this compound was apparently due to the isomerization of the double bond of the expected product **73** which occurred by the prolonged heating with base during the elimination step.

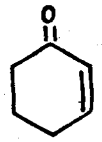
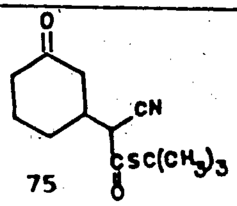
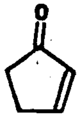
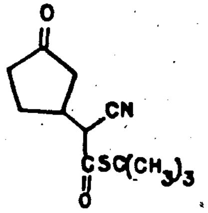
In summary, experimental results showed that various alkylation products and Knoevenagel-type condensation products derived from cyanothiolacetates **21** could be selectively reduced to give β-hydroxypropionitrile derivatives. Monosubstituted β-hydroxypropionitriles could further be dehydrated to give acrylonitrile derivatives.

4. Michael Reactions of Cyanothiolacetates

In the previous sections we have described the base-induced alkylations and condensations of cyanothiolacetates. In this section, the Michael addition of the carbanions derived from these substrates to various α,β-unsaturated ketones is discussed. Our initial attempts to induce the addition were based on the work done by Liu and Oppong,[32] in which they had extensively studied the Michael reactions of S,S'-diethyl dithiomalonate **19**. Their studies showed that the best conditions for **19** to undergo Michael reaction were by the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in 1,2-dimethoxyethane (DME) as a solvent. Similar conditions were initially used for the present studies. Table IX summarizes the results obtained using thiolester **23** as a Michael donor.

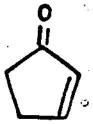
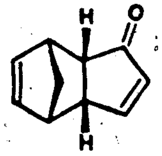
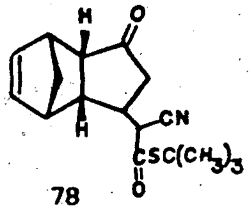
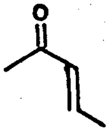
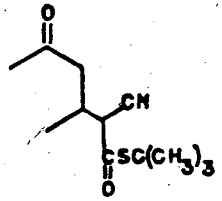
When 2-cyclohexen-1-one (Entry 1) was treated with 1.2 equiv. of thiolester **23** at room temperature for 36 h, the Michael adduct **75** was isolated in 61% yield as a mixture of two diastereomers in equal quantity. The ^1H nmr spectrum of the mixture showed a large singlet at δ1.50, characteristic of the t-butyl group. Two doublets of equal intensity, one at δ3.45 with a coupling constant of 6 Hz and the other at δ3.50 with a coupling constant of

Table IX. Michael reactions of thiolester **23** using DABCO as a base[a]

Entry	Enone (equiv.)	Equiv. of Thiolester	Equiv. of DABCO	Time (h)	Temp.	Product[b]	% Yield[e]
1.	 (1.0)	1.2	1.2	36	r.t.	 **75**	61
2.	" (1.0)	1.2	1.2[c]	35	reflux	**75**	48
3.	" (2.5)	1.0	1.0	36	r.t.	**75**	54
4.	" (1.5)	1.0	0.5	192	r.t.	**75**	52
5.	" (2.0)	1.0	0.3	168	r.t.	**75**	58
6.	 (1.0)	1.2	1.2	6	r.t.	 **76**	36

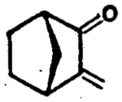
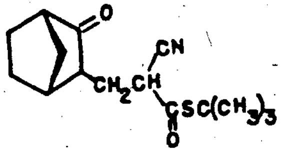
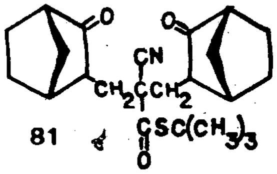
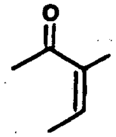
(Continued)

Table IX. (Continued)

Entry	Enone (equiv.)		Equiv. of Thiolester	Equiv. of DABCO	Time (h)	Temp.	Product[b]	% Yield[e]
7.		(1.0)	1.0	1.0	23	r.t.	76	46
8.	 77	(1.0)	1.5	1.2	25	r.t.	 78	78
9.	77	(1.0)	1.5	1.2[d]	24	r.t.	78	80
10.		(2.5)	1.0	1.0	48	r.t.	 79	37
11.	"	(1.0)	1.2	1.2[d]	20	r.t.	79	17

(Continued)

Table IX. (Continued)

Entry	Enone (equiv.)	Equiv. of Thiolester	Equiv. of DABCO	Time (h)	Temp.	Product[b]	% Yield[e]
12.	 (1.0)	1.5	1.2	46	r.t.	 80	11
						 81	14
13.	 (1.5)	1.0	1.2	144	r.t.	no reaction	--

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[a] Unless otherwise stated these reactions were performed in 1,2-dimethoxyethane (DME).

[b] All these products were obtained as diastereomeric mixtures.

[c] This reaction was carried out in ether.

[d] These reactions were carried out in THF.

[e] Yields were obtained on the basis of the amount of starting material used.

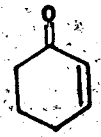
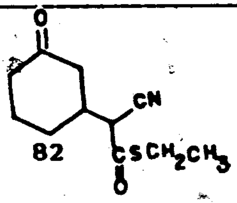
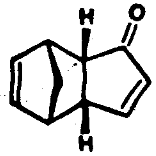
4 Hz, observed for the methine proton adjacent to the cyano group indicated clearly the presence of two diastereomers. The ir spectrum gave two strong absorption bands, one at 1677 cm^{-1} for the thiolester carbonyl and the other at 1715 cm^{-1} for the ketone carbonyl. A weak band at 2240 cm^{-1}, characteristic of nitrile group was also displayed. The molecular ion peak at 253.1137 in the mass spectrum was in accord with the required formula $C_{13}H_{19}NO_2S$. Attempts to improve the yield of adduct **75** by modifying the reaction conditions such as temperature and solvent (Entry 2), reaction time (Entries 4 and 5), and ratios of both reagents and reactants (Entries 3-5) were unsuccessful. In no case, could improvement on yield be achieved.

Several other α,β-unsaturated ketones were also examined including 2-cyclopenten-1-one, tricyclic ketone **77**, 3-penten-2-one, 3-methylene-2-norbornanone, and 3-methyl-3-penten-2-one. The experimental results showed that the conditions under investigation were applicable only to certain cases. For instance, the Michael reaction with enone **77** proceeded rather well to give a 78% yield of adduct **78** when DME was used as a solvent (Entry 8). When THF was used, a slightly improved yield of 80% was obtained (Entry 9). However, for the majority of the enones examined, the conditions applied, with or without modification, were found to be rather unsatisfactory. Yields of adducts were generally low, ranging from 0-46%. As well, occasionally, bis-addition was observed as in the case of 3-methylene-2-norbornanone (Entry 12).

In search of adequate conditions for the Michael reaction, we have examined a series of tertiary amine bases including 4-dimethylaminopyridine (DMAP), Hunig's base (ethyldiisopropylamine), N,N-dimethylaniline, pyridine, and imidazole. Three enones, 2-cyclohexen-1-one, tricyclic ketone **77**, and 3-methylene-2-norbornanone were used as Michael acceptors. Other than S-*t*-butyl cyanothiolacetate (**23**), the corresponding ethyl derivative **24** was also used as a Michael donor for the present studies. Results are summarized in Table X.

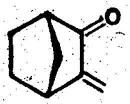
The reaction of S-ethyl cyanothiolacetate (**24**) with 2-cyclohexen-1-one was used to evaluate the suitability of the various amine bases. As can be seen in Entries 5 and 6, N,N-dimethylaniline and pyridine were totally ineffective and resulted only in the recovery of the starting material. Of the four other bases examined (Entries 1-4), none was found to be particularly effective. In all cases, product **82** was obtained in poor yields. However, DMAP (Entry 1) and DABCO (Entry 2)

Table X. Michael reactions using different tertiary amine bases[a]

Entry	Enone (equiv.)		Thiolester (equiv.)	Base (equiv.)	Time (h)	Product	% Yield[c]
1.		(1.0)	24 (1.5)	DMAP (1.5)	19	 82	26
2.	"	(1.0)	24 (1.2)	DABCO (1.2)	48	82	23
3.	"	(1.0)	24 (1.2)	Hunig's base (1.2)	44	82	19
4.	"	(1.0)	24 (1.5)	Imidazole (1.5)	52	82	16
5.	"	(1.0)	24 (1.5)	N,N'-Dimethylaniline (1.2)	52	NR[b]	-
6.	"	(1.0)	24 (1.2)	Pyridine (1.2)	38	NR[b]	-
7.	 77	(1.0)	23 (1.5)	DMAP (1.2)	26	78	74
8.	77	(1.0)	23 (1.5)	DABCO (1.2)	25	78	78

(Continued)

Table X. (Continued)

Entry	Enone (equiv.)		Thiolester (equiv.)	Base (equiv.)	Time (h)	Product	% Yield[c]
9.		(1.0)	23 (1.5)	DMAP (1.2)	24	80	14
10.	"	(1.0)	23 (1.5)	DABCO (1.2)	46	80	11

[a] All these reactions were performed in DME as a solvent and at room temperature.

[b] No reaction.

[c] Yields were based on the amount of starting material used.

appeared to be somewhat superior. As a result, further studies were centered on these two bases. It was also noted that the yield (61%) of Michael adduct **75** derived from S-t-butyl cyanothiolacetate (**23**) (Table IX, Entry 1) was considerably better than the yield of 23% obtained for adduct **82** derived from S-ethyl cyanothiolacetate (**24**) (Table X, Entry 2). These results indicated that the former thiolester **23** was a better Michael donor. Hence, in the later studies this thiolester was used exclusively.

DMAP was also effective to induce the addition of thiolester **23** to tricyclic enone **77** (Entry 7). The yield (74%) was found to be comparable to that obtained with DABCO as a base (Entry 8). Unfortunately, the addition of thiolester **23** to 3-methylene-2-norbornanone could not be improved by the use of this base (Entry 9). Low yield (14%) of adduct **80** was again obtained as in the case using DABCO as a base (Entry 10).

Based on these results, it could be concluded that the use of a tertiary amine base for the induction ~~of~~ the Michael addition reactions was not generally effective and alternative methods were needed.

Generally, in Michael reactions in which the donor can also serve as a good leaving group, the rate limiting step in which the new carbon-carbon bond is formed is reversible. The position of the equilibrium depends, to a large extent, on the stability of the intermediate enolate ion.[35] In principle, the equilibrium could be shifted to the side of the product formation by trapping the intermediate enolate ion with an adequate electrophile. As shown in Scheme IV, one such electrophile could be chlorotrimethylsilane which is expected to react with the enolate ion rapidly to give a stable silyl enol-ether which could then be converted to the desired ketone. Based on this principle a general method for the Michael reaction was developed. Initially, the Michael reaction of thiolester **23** and 2-cyclohexen-1-one was examined in DME at room temperature in the presence of imidazole and chlorotrimethylsilane. The results were promising but not highly satisfactory. After a number of trials and modifications, it was found that the best results were obtained by the use of sodium hydride as a base, chlorotrimethylsilane as a trapping agent, and benzene as a solvent. By the use of this combination, a number of reactions were successfully explored. Results are compiled in Table XI.

In a typical experiment, thiolester **23** (1 equiv.) was treated with 1.2 equiv. of 2-cyclohexen-1-one, 0.9 equiv. of chlorotrimethylsilane and 1.5 equiv.. of sodium

Scheme IV

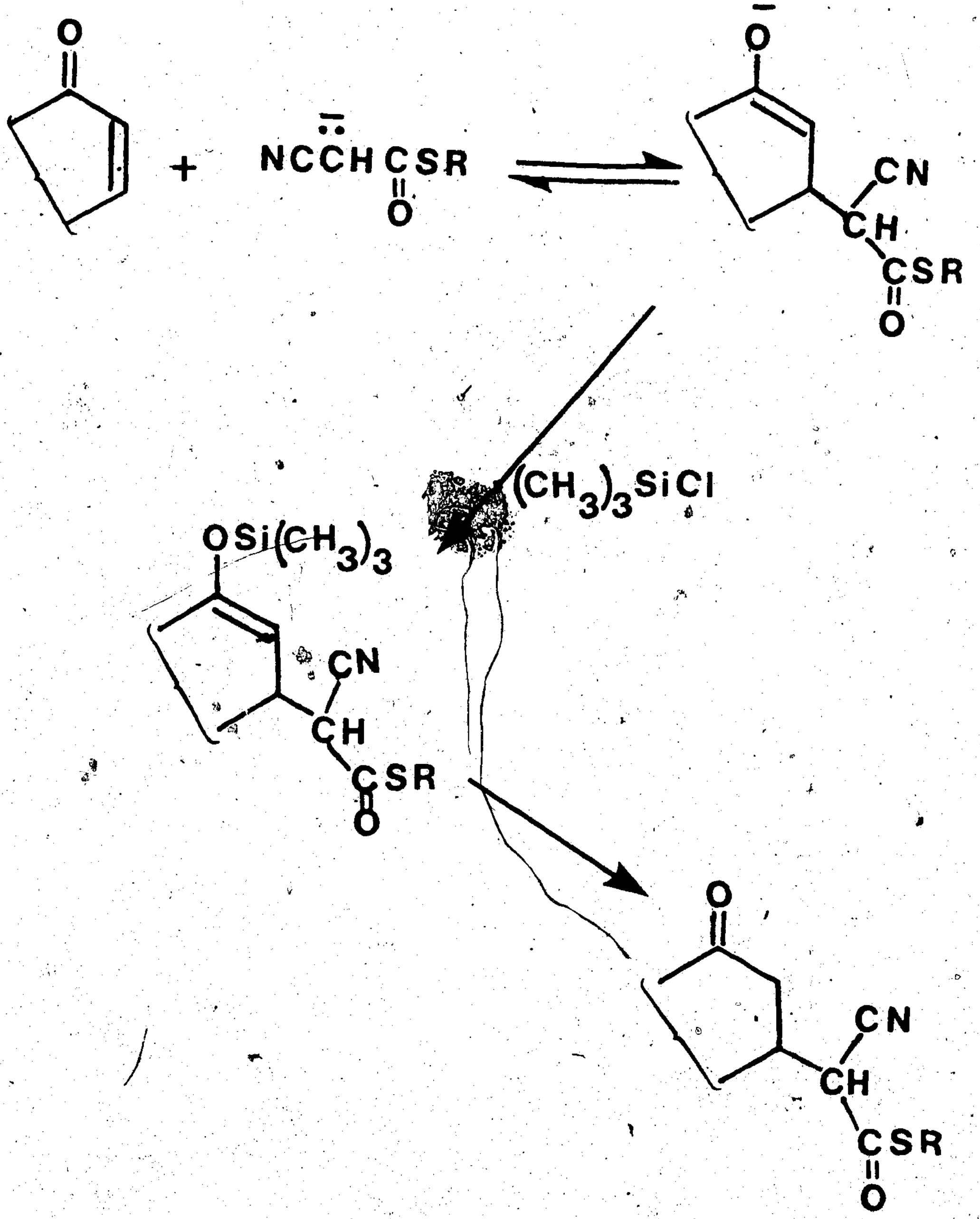
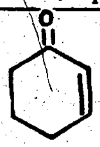
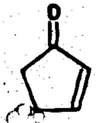
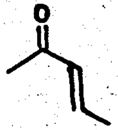
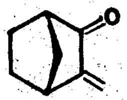
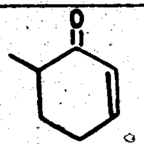
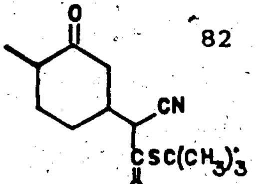
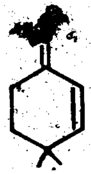
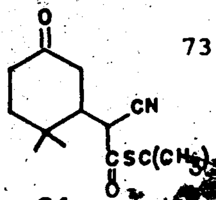
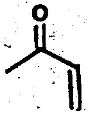
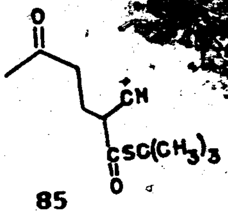

O
+
NCCHCSR
O
O
CN
CH
CSR
O
$(CH_3)_3SiCl$
$OSi(CH_3)_3$
CN
CH
CSR
O
O
CN
CH
CSR
O

Table XI. Michael reactions of thiolester 23 using sodium hydride[a] in the presence[b] or absence of chlorotrimethylsilane

			With Chlorotrimethylsilane					Without Chlorotrimethylsilane			
Entry	Enone (equiv)		Equiv. of thiolester	Time (h)	Temp. (°C)	Product	% Yiel[illegible]	Time (h)	Temp. (°C)	Product	% Yield[e]
1.		(1.2)	1.0	17	r.t.	75	86	22	r.t.	75	90
2.		(1.0)	1.2	3	10	76	100	3.5	15	76	93
3.	"	(1.2)	1.0	2	10	76	64				
4.	77	(1.0)	1.2	23	r.t.	78	84	25	r.t.	78	49
5.		(1.0)	1.2	8	7	79	62	24	-20^c	79	58
6.	"	(1.2)	1.0	27	-20^c	79	68				
7.		(1.0)	1.2	2	7	80	63	3	7	80	71

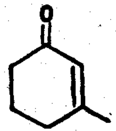
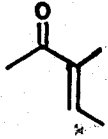
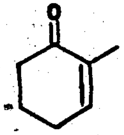
(Continued)

Table XI. (Continued)

			With Chlorotrimethylsilane				Without Chlorotrimethylsilane			
Entry	Enone (equiv)	Equiv. of thiolester	Time (h)	Temp. (°C)	Product	% Yield	Time (h)	Temp. (°C)	Product	% Yield[e]
8.	 (1.2)	1.0	16	r.t.	 **83**	82	14	r.t.	**83**	49
9.	 (1.2)	1.0	22	r.t.	 **84**	73	25	r.t.	**84**	46
10.	 (1.0)	1.2	3	10	 **85**					

(Continued)

Table XI. (Continued)

		With Chlorotrimethylsilane					Without Chlorotrimethylsilane			
Entry	Enone (equiv)	Equiv. of thiolester	Time (h)	Temp. (°C)	Product	% Yield	Time (h)	Temp. (°C)	Product	% Yield[e]
11.	 (1.0)	1.2	48	r.t.	NR[d]	–				
12.	 (1.0)	1.2	22	r.t.	NR[d]	–				
13.	 (1.2)	1.0	2	reflux	NR[d]					

[a] The amount of sodium hydride used was 1.5 equiv, based on the thiolester 23.

[b] The amount of chlorotrimethylsilane used was 0.9 equiv. based on the thiolester 23.

[c] Toluene was used as a solvent.

[d] No reaction.

[e] Yields were based on the amount of starting material used.

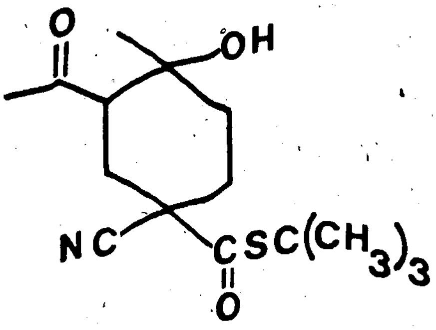
hydride at room temperature for 17 h. An 86% yield of adduct **75** was isolated after standard aqueous work-up and purification. In this case and two other cases (Entries 7 and 10) the normal work-up was found to be sufficient to generate the ketone carbonyl from the corresponding enol-ether. In most cases (Entries 2-6, 8 and 9) however, ~~the~~ silyl enol-ether moiety was shown to be rather stable and a brief treatment of the crude product with potassium fluoride in methanol was necessary to s[illegible]re the desired product.

During the studies, it was also noted that it was important to keep the amount of the trapping agent slightly less than that of the thiolester. In a number of experiments when an excess of chlorotrimethylsilane was used, the yield of the product was substantially lower.

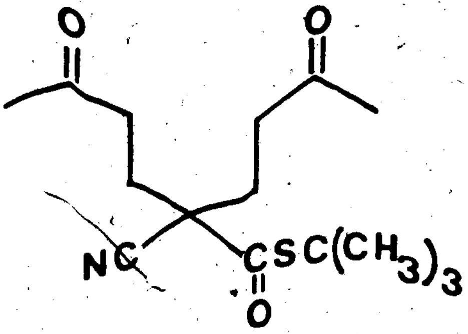
Of the results shown in the Table, two cases are particularly noteworthy. Whereas all the products possessing two or more chiral centers were obtained as mixtures of diastereomers, adduct **84** was produced, surprisingly, as a single stereoisomer in crystalline form (m.p. 74-77°C). The ^{1}H nmr spectrum showed only two singlets, one at δ1.14 and the other at δ1.22 for the *gem*-dimethyl group, a large singlet at δ1.52 for the *t*-butyl group, and a single doublet at δ3.74 with a coupling constant of 2 Hz for the methine proton adjacent to the cyano group. Furthermore, the ^{13}C nmr spectrum displayed only a single set of signals.

Another noteworthy case is the addition of thiolester **23** to methyl vinyl ketone (Entry 10), a highly reactive Michael acceptor. The best yield obtained for the adduct **85** was 48% when the reaction was carried out in benzene at 10°C for 3 h. The low yield was partly due to the formation of a by-product which was characterized as a diastereomeric mixture of compound **86**. This compound was apparently formed *via* bis-addition product **87** involving an intramolecular aldol process. In order to suppress the formation of this bis-product as well as to improve the yield of adduct **85**, the reaction was performed in toluene at low temperatures (-40°C and -60°C). Contrary to our expectation, the yields obtained for the desired product were lower and an increasing amount of compound **86** to the extent of 34% yield was obtained.

The reactions of the thiolester **23** with β,β-disubstituted enones such as 3-methyl-2-cyclohexen-1-one (Entry 11) and α,β-disubstituted enones such as 3-methyl-3-penten-2-one and 2-methyl-2-cyclohexen-1-one were also examined using the described conditions. In all of these cases, no detectable amount of adduct was produced. These



86



87

two types of enones are known to be poor Michael acceptors which do not usually undergo addition reaction with Michael donors of low nucleophilicity, such as malonic acid derivatives.[43] Our case was no exception.

Table XI also summarizes the results of several Michael reactions carried out using sodium hydride as the sole reagent in the absence of chlorotrimethylsilane. These experiments were performed in order to determine whether chlorotrimethylsilane indeed played a role in assisting the Michael reaction. An examination of the results reveals that, although in several cases (Entries 1, 2, 5 and 7) the yields of adducts were comparabl[illegible], other cases (Entries 4, 8 and 9) the adducts were obtained in substantially better yields when chlorotrimethylsilane was present.

Standard conditions for Michael reaction of analogous donors such as dialkyl malonate often involve the combination of a base, such as hydroxide and alkoxide, and a protic solvent, such as water and alcohol.[44,45] These conditions are expected to be inadequate for the thiolester under investigation, since the thiolester is labile toward these strongly nucleophilic reagents. Experimentally, this was proven to be true. When the addition of cyanothiolester **23** to 4,4-dimethyl-2-

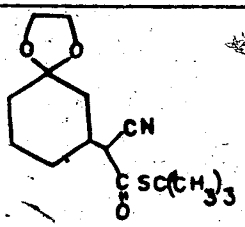
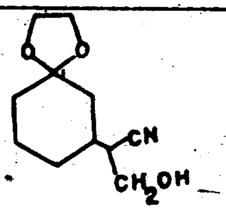
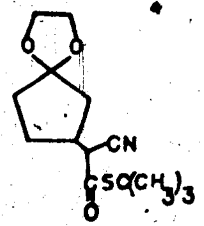
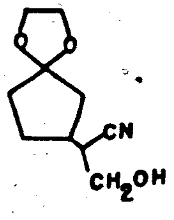
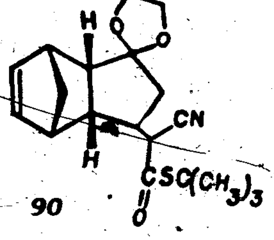
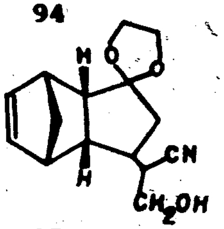
cyclohexen-1-one was attempted in ethanol with potassium hydroxide at room temperature, adduct 84 was obtained in a poor yield of 19%.

5. Conversion of Michael Adducts to β-Hydroxypropionitrile and Acrylonitrile Derivatives

Having developed a general method for the addition of thiolester 23 to conjugated enones, we turned our attention to the possible conversion of the adducts to β-hydroxypropionitriles and acrylonitriles. Since the ketone carbonyl is more reactive towards sodium borohydride than the thiolester carbonyl, its protection was necessary prior to the selective reduction of the latter functional group. In all the cases examined, the protection was readily achieved in the form of a ketal using standard ketalization conditions. Thus, treatment of adduct 75 with ethylene glycol in refluxing benzene in the presence of p-toluenesulfonic acid with continuous removal of water gave the ketal 88 in virtually quantitative yield. Subsequent reduction of ketal 88 with sodium borohydride in ethanol at 0°C gave rise to the desired alcohol 93 in 90% yield over two steps (Table XII, Entry 1). The ^1H nmr spectrum of alcohol 93 showed a triplet of doublets at δ2.72 with coupling constants of 11 and 6 Hz corresponding to the methine proton adjacent to the nitrile group. A doublet with coupling constant of 6 Hz at δ3.82 was due to the methylene group bearing the hydroxy unit. The ir spectrum revealed a strong absorption band centered at 3450 cm^{-1} due to hydroxyl group and a weak absorption band at 2240 cm^{-1} due to nitrile group. A molecular ion peak at 211.1209 in the mass spectrum confirmed the required formula $C_{11}H_{17}NO_3$. Under similar conditions four additional Michael adducts were ketalized and reduced to give the desired ketal alcohols in good overall yields. Particulars of these experiments are summarized in Table XII, Entries 2-5.

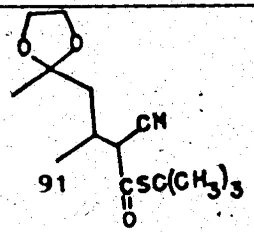
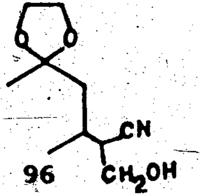
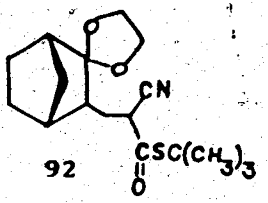
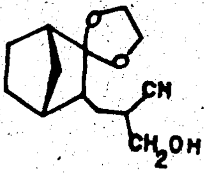
The conversion of ketal alcohols to the corresponding acrylonitriles was equally straightforward. Both methods described previously in Section 3 were found to be also applicable. Direct dehydration of ketal alcohol **93** with DCC in refluxing ether in the presence of a trace amount of copper (I) chloride proceeded smoothly to give a 79% yield of acrylonitrile derivative **98** (Table XIII, Entry 1). Similarly, compound **100** was prepared from the corresponding alcohol **94** in 65% yield (Entry 2). Similar ^1H nmr spectra were observed for both compounds **98** and **100**. Thus, the ^1H nmr spectrum of **98** showed a singlet at [illegible]95 for the ketal protons, a doublet at δ5.70 (J = 2 Hz)

Table XII. Ketalization[a] and reduction[b] of Michael adducts

	Ketalization			Reduction			
Entry	Adduct	Time (h)	Product	Equiv. of $NaBH_4$	Time (h)	Product	% Yield[c]
1	75	7	 88	4	1	 93	90
2.	76	24	 89	4	3.5	 94	100
3.	78	21	 90	5	10	 95	78

(Continued)

Table XII. (Continued)

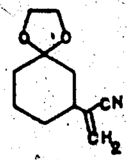
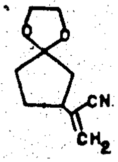
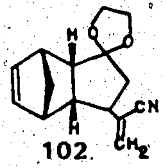
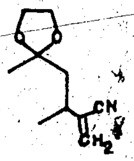
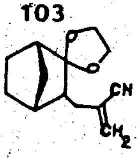
	Ketalization			Reduction			
Entry	Adduct	Time (h)	Product	Equiv. of $NaBH_4$	Time (h)	Product	% Yield[c]
4.	81	22	 91	4	3	 96	79
5.	82	12	 92	2	8	 97	91

[a] These reactions were performed using ethylene glycol (10 equiv.) and p-toluenesulfonic acid (0.1 equiv.) in refluxing benzene.

[b] All the reactions were run at room temperature.

[c] Yields are based on Michael adducts over two steps.

Table XIII. Dehydration of the ketal alcohols

Entry	Ketal alcohol	Method[a]	Time (h)	Product	% Yield
1.	93	A	16	 98	79
2.	94	A	31	 100	65
3.	95	A	48	 102	60
4.	95	B	b	102	58
5.	96	A	24	 103	77
6.	97	A	21	 104	87

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[a] Method A - A direct dehydration using DCC (1.5 equiv.) and a trace amount of copper(I) chloride in refluxing ether.

Method B - A two-step procedure involving mesylation using methane sulfonyl chloride and triethylamine followed by elimination with DBU in refluxing benzene.

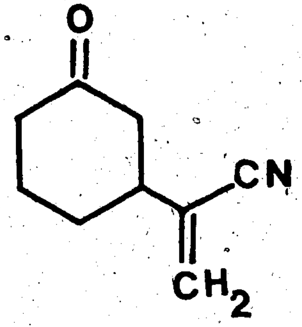
[b] The time for mesylation was 24 h and the time required for elimination was 50 min.

and a broad singlet ($W_{1/2}$ = 2 Hz) at δ5.82 for the two vinylic protons. Compound **100** displayed the following signals: ketal protons appeared at δ3.94 as a singlet and two vinylic protons appeared at δ5.75 and 5.83 as two doublets with coupling constants of 2 Hz each.

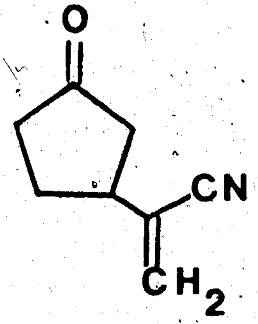
Ketal alcohol **95** was converted by two different methods into acrylonitrile derivative **102**. Direct dehydration with DCC gave a 60% yield of the latter compound (Entry 3). Indirectly, mesylation of **95** with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature followed by treatment of the resulting mesylate with DBU in refluxing benzene gave the same compound in comparable yield (Entry 4). This compound showed a single set of signals in the ^{13}C nmr spectrum indicating the presence of a single stereoisomer. The ^{1}H nmr spectrum exhibited the terminal vinylic protons as two doublets, one at δ5.76 (J = 2 Hz) and the other at δ5.86 ($J_{W_{1/2}}$ = 2 Hz). Two doublet of doublets, one at δ6.10 (J = 6, J' = 4 Hz) and the other at δ6.34 (J = 6, J' = 3 Hz) were attributable for the vinylic protons of the bicyclic ring system. The ir spectrum displayed an olefinic absorption band at 1630 cm^{-1} and a nitrile absorption band at 2220 cm^{-1}. The mass spectrum showed a molecular ion peak at 243.1256, which confirmed the molecular formula $C_{15}H_{17}NO_2$. Table XIII also summarizes the results obtained for the conversions of **96**→**103** and **97**→**104** (Entries 5 and 6).

Having successfully completed the investigation on the conversion of Michael adducts to β-hydroxypropionitrile derivatives and further to acrylonitriles, the removal of the ketal protecting group was examined. Experimental results showed that the deprotection could be readily achieved without destruction of the rather labile acrylonitrile moiety. When exposed to p-toluenesulfonic acid in acetone at room temperature, both compounds **98** and **100** were found to undergo transketalization smoothly to give ketones **99** (81% yield) and **101** (97% yield) respectively.

In conclusion, cyanothiolacetates **21** were shown to undergo alkylation with various alkyl halides, Knoevenagel-type condensation with aldehydes and ketones, and Michael reaction with conjugated enones. The thiolester group of the products could be selectively reduced (in the case of Knoevenagel-type condensation product, the carbon-carbon double bond as well) with sodium borohydride to the alcohol level. Hence, by a two-step sequence various β-hydroxypropionitriles could be easily prepared utilizing cyanothiolacetate as a masked β-



99



101

hydroxypropionitrile carbanion equivalent. Furthermore, monosubstituted β-hydroxypropionitriles were readily dehydrated either directly with DCC or indirectly via a two-step sequence involving mesylation and elimination. Hence, cyanothiolacetate can also be conveniently used as a masked acrylonitrile unit.

EXPERIMENTAL

General

Melting points were determined [illegible] hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Varian HA-100, HA-100/Digilab, Bruker WH-80, Bruker WH-200 and WH-400 spectrometers and, except where otherwise stated, were obtained on solutions in deuterochloroform with tetramethylsilane as internal reference. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker HFx-90/Nicolet 1085 system or Bruker WH-200 and WH-400 spectrometers and were obtained on solutions in deuterochloroform using tetramethylsilane as internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometers. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 10% ethyl acetate in petroleum ether means 10 parts ethyl acetate by volume to 90 parts petroleum ether by volume.

Materials

Ether, benzene and 1,2-dimethoxyethane used for reactions were freshly distilled from lithium aluminum hydride. Toluene and ethyl acetate were distilled from calcium hydride. Absolute ethanol was obtained by distilling 98% ethanol over magnesium turnings in the presence of few crystals of iodine. Argon was passed through a purification train of Fieser's solution,[46] concentrated sulfuric acid, and potassium hydroxide pellets. Silica gel, 0.040-0.063 mm particle size, 230-400 mesh ASTM, was used as adsorbent for flash chromatography,[47] and silica gel, 60-120 mesh, was used as adsorbent for column chromatography. Thin-layer chromatography was carried out using Merck silica gel G (type 60). Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Commercially available sodium hydride (50% dispersion in oil) was used without further washing.

Commercially available methyl vinyl ketone, 2-cyclohexen-1-one, trans-3-penten-2-one, 2-cyclopenten-1-one, 3-methylene-2-norbornanone, and chlorotrimethylsilane were distilled before use. S-Benzyl, S-ethyl, and S-*t*-butyl cyanothiolacetates were prepared according to the method of Liu and Sabesan.[16] 4,4-Dimethyl-2-cyclohexen-1-one was prepared by the method of Djerassi.[48] 6-Methyl-2-cyclohexen-1-one was prepared according to the procedure of Stock and White.[49] cis-Tricyclo[$5.2.1.0^{2,6}$]deca-4,8-dien-3-one **77** was prepared by the method of Alder and Flock.[50]

S-Benzyl 2-benzyl-2-cyano-3-phenylthiolpropionate (25)

To a solution of S-benzyl cyanothiolacetate (**22**) (500 mg, 2.62 mmol) in 1,2-dimethoxyethane (10 mL) stirred at 0°C, was added sodium hydride (50% dispersion in oil; 280 mg, 6.54 mmol). The mixture was stirred for 10 min under an argon atmosphere. A solution of benzyl bromide (0.78 mL, 6.54 mmol) in 1,2-dimethoxyethane (1 mL) was added dropwise via a syringe and the mixture stirred for 7 h at room temperature. The reaction mixture was poured into ice-cold 1N aqueous hydrochloric acid, extracted with chloroform (4 × 20 mL) and washed with saturated aqueous sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was chromatographed on silica gel eluting with 50% benzene in petroleum ether to give dibenzyl derivative **25** (869 mg; 89% yield): m.p. 103-105°C (benzene-petroleum ether); ^{1}H nmr δ3.00 (d, 2H, J = 14 Hz, 2× -C<u>H</u>HPh), 3.35 (d, 2H, J = 14 Hz, 2× -CH<u>H</u>Ph), 4.00 (s, 2H, -S-CH_2-Ph), and 7.22 (m, 10H, aromatic protons); ir ($CHCl_3$) 1659 (C=O) and 3020-3100 cm^{-1} (aromatic); ms M$^+$ 371.1340 (calcd. for $C_{24}H_{21}NOS$: 371.1344). <u>Anal.</u> Calcd. for $C_{24}H_{21}NOS$: C, 77.63; H, 5.66; N, 3.77; O, 4.31; S, 8.63. Found: C, 77.85; H, 5.66; N, 3.76; O, 4.56; S, 8.55.

<u>S-Benzyl 1-cyano-cyclohexane-1 thiocarboxylate (**26**)</u>

A solution of cyanothiolester **22** (502 mg, 2.62 mmol) and 1,5-diiodopentane (0.47 mL, 3.14 mmol) in 1,2-dimethoxyethane (20 mL) was stirred at 0°C under an argon atmosphere for 15 min. Sodium hydride (50% dispersion in oil; 280 mg, 5.83 mmol) was added rapidly and mixture continued stirring at room temperature for 31.5 h. The reaction mixture was poured into ice-cold 1N aqueous hydrochloric acid solution and the resulting mixture extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. Column chromatography of the crude product using 40% benzene in petroleum ether as an eluent gave the pure cyclic compound **26** (209 mg, 31% yield): ^{1}H nmr δ1.00-2.00 (m, 10H, $-(CH_2)_5$), 4.13 (s, 2H, $-S-CH_2-Ph$), and 7.26 (m, 5H, aromatic protons); ir 1685 (C=O), 2240 (C≡N), and 3020-3060 cm^{-1} (aromatic); ms M$^+$ 259.1027 (calcd. for $C_{15}H_{17}NOS$: 259.1031).

S-Benzyl 2-butyl-2-cyanothiolhexanoate (28) and S-benzyl 2-cyanothiolhexanoate (27)

A mixture of S-benzyl cyanothiolacetate (**22**) (496 mg; 2.60 mmol) and sodium hydride (50% dispersion in oil; 125 mg, 2.60 mmol) in 1,2-dimethoxyethane (10 mL) was stirred at 0°C under an atmosphere of argon for 15 min. n-Butyliodide (0.3 mL, 2.60 mmol) was added dropwise by a syringe and the mixture stirred for 22 h at room temperature. Ice-cold 1N aqueous hydrochloric acid solution was added and the resulting mixture extracted with chloroform (4 × 20 mL). The extracts were washed with saturated aqueous sodium chloride solution, combined, dried, filtered, and concentrated. Purification of the residue on silica gel column chromatography (50% petroleum ether in benzene) gave the dibutyl compound **28** (210 mg; 27% yield): ^{1}H nmr δ0.88 (t, 6H, J = 8 Hz, 2× $-CH_3$), 4.18

(s, 2H, $-SCH_2-Ph$), and 7.28 (m, 5H, aromatic protons); ir 1605 (aromatic), 1680 (C=O), 2220 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M^+ 303.1657 (calcd. for $C_{18}H_{25}NOS$: 303.1657).

Further elution with the same solvent system afforded the mono-alkyl derivative **27** (212 mg; 23% yield): ^1H nmr $\delta 0.92$ (t, 3H, J = 6 Hz, $-CH_3$), 3.60 (t, 1H, J = 4 Hz, $-\overset{|}{C}HCN$), 4.20 (s, 2H, $-SCH_2-Ph$), and 7.30 (m, 5H, aromatic protons); ir 1600 (aromatic), 1675 (C=O), 2220 (C≡N), and 3040-3080 cm^{-1} (aromatic); ms M^+ 247.1018 (calcd. for $C_{14}H_{17}NOS$: 247.1031).

Further elution with 40% petroleum ether in benzene afforded the unreacted thiolester **22** (38.4 mg; 8% recovery).

S-Benzyl 2-cyano-2-isopropyl-3-methylthiolbutanoate (30) and S-benzyl 2-cyano-3-methylthiolbutanoate (29)

S-Benzyl thiolester **22** (515 mg, 2.69 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) (freshly distilled) and solution cooled to 0°C. Sodium hydride (50% dispersion in oil; 194 mg, 4.04 mmol) was added and solution stirred for 10 min under an argon atmosphere. Then, 2-iodopropane (0.27 mL, 2.69 mmol) was added dropwise *via* a syringe, and mixture continued stirring for

50 h at room temperature. The reaction mixture was quenched with ice-cold 1N aqueous hydrochloric acid solution, washed with saturated sodium chloride solution, and extracted with dichloromethane (4 × 20 mL). Extracts were combined, dried, filtered, and concentrated. Column chromatography of the residue on silica gel eluting with 50% benzene in petroleum ether gave the following products in order of elution from column. Dialkylated product **30** as a colorless oil (40.2 mg; 5% yield): ^{1}H nmr δ1.03, 1.10 (both d, 6H each, 7 Hz each, 2× $(CH_3)_2$), 4.32 (s, 2H, $-S-CH_2-Ph$), and 7.30 (m, 5H, aromatic protons); ir 1680 (C=O), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 275.1347 (calcd. for $C_{16}H_{21}NOS$: 275.1344). Monoalkylated product **29** as a colorless oil (146 mg; 23% yield): ^{1}H nmr δ1.09, 1.16 (both d, 6H, 3 Hz each, $-CH(CH_3)_2$), 3.58 (d, 1H, J = 6 Hz, $-\overset{|}{C}H-CN$), 4.30 (s, 2H, $-S-CH_2-Ph$), and 7.44 (m, 5H, aromatic protons); ir 1675 (C=O), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 233.0877 (calcd. for $C_{13}H_{15}NOS$: 233.0874).

Further elution with 40% petroleum ether in benzene afforded the recovered starting thiolester **22** (117 mg; 23% recovery).

S-*t*-Butyl 2-cyano-2-allyl-4-thiolpentenoate (**31**)

A solution of cyanothiolester **23** (488 mg, 3.11 mmol) and sodium hydride (50% dispersion in oil; 373 mg, 7.78 mmol) in 1,2-dimethoxyethane (10 mL) was stirred at 0°C for 10 min under an argon atmosphere. Then 3-bromopropene (0.67 mL, 7.78 mmol) was added slowly *via* a syringe and mixture stirred for 3 h at room temperature. The reaction mixture was then quenched with ice-cold water and poured into a 1N aqueous hydrochloric acid and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution and organic layer was dried, filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate in petroleum ether as an eluent to give the diallyl derivative **31** (508 mg; 69% yield): ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 2.48 (dd, 2H, J = 14 Hz, J' = 8 Hz, H_a and H_c), 2.68 (dd, 2H, J = 14 Hz, J' = 8 Hz, H_b and H_d), 5.23 (dd, 2H, J = 17 Hz, J' = 2 Hz, H_e and H_i), 5.24 (ddd, 2H, J = 11 Hz, J' = 2 Hz, J" = 1 Hz, H_f and H_g), 5.80 (ddt, 2H, J = 16 Hz, J' = 11 Hz, J" = 7 Hz, H_j and H_k); ir 1675 (C=O), 2240 (C≡N), and 3080 cm^{-1} (olefin stretch); ms M^+ −56 181.0559 (calcd. for $C_9H_{11}NOS$: 181.0561). Anal. Calcd. for $C_{13}H_{19}NOS$: C, 65.82; H, 8.02; N, 5.91; O, 6.75; S, 13.50. Found: C, 65.97; H, 8.22; N, 5.85; O, 6.80; S, 13.38.

S-t-Butyl 1-cyano-cyclohexane-1-thiocarboxylic acid (**32**)

A. Using sodium hydride as a base

A solution of cyanothiolester **23** (499 mg, 3.18 mmol) and sodium hydride (50% dispersion in oil; 336 mg, 7.00 mmol, in tetrahydrofuran (10 mL) was stirred at 0°C under an argon atmosphere for 15 min. A dropwise addition of 1,5-diiodopentane (0.56 mL, 3.82 mmol) was followed and mixture stirred for 30 h at room temperature. The mixture was then quenched with 1N aqueous hydrochloric acid solution, extracted with dichloromethane (4 × 20 mL) and the extracts washed with saturated sodium chloride solution. Extracts were combined, dried, filtered, and concentrated. The residue was subjected to column chromatography by elution with 50% benzene in petroleum ether to give the cyclic compound **32** (377 mg; 53% yield). One recrystallization from petroleum ether afforded pure white crystals (m.p. 35-36°C): ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 1.60-2.00 (m, 10H, $-(CH_2)_5-$); ir ($CHCl_3$) 1680 (C=O) and 2240 cm^{-1} (C≡N); ms M^+ 225.1178 (calcd. for $C_{12}H_{19}NOS$: 225.1187).

Further elution with 40% petroleum ether gave unconsumed thiolester (100 mg; 20% recovery).

B. Using lithium t-butoxide as a base

To a solution of cyanothiolester **23** (502 mg, 3.20 mmol), lithium t-butoxide (563 mg, 7.04 mmol) and hexamethylphosphoramide (HMPA) (1.22 mL, 7.04 mmol) in tetrahydrofuran (10 mL) at 0°C with stirring, was added 1,5-diiodopentane (0.57 mL, 3.84 mmol). After the mixture had been stirred for 17 h at room temperature under an argon atmosphere, ice-cold 1N hydrochloric acid solution was added, extracted with dichloromethane (4 × 20 mL) and the extracts washed with saturated sodium chloride solution. Similar purification as in method A afforded the cyclic compound **32** (552 mg; 77% yield). Spectral results (^{1}H nmr and ir) were identical to those obtained by method A (vide supra).

S-t-Butyl 2-butyl-2-cyanothiolhexanoate (**34**) and S-t-butyl 2-cyanothiolhexanoate (**33**)

A. From 1-iodobutane

At 0°C, a solution of cyanothiolester **23** (500 mg, 3.18 mmol) and lithium t-butoxide (407 mg, 5.09 mmol) in dry tetrahydrofuran (10 mL) was stirred under an argon atmosphere for 10 min. HMPA (0.95 mL, 5.43 mmol) was added <u>via</u> a syringe followed by addition of 1-iodobutane (0.58 mL, 5.09 mmol) and mixture continued stirring at 0°C for 72 h. The reaction was quenched with ice-cold 1N aqueous hydrochloric acid solution. The organic layer extracted with dichloromethane (4 × 20 mL) and the extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude oily product was chromatographed on silica gel by flash column chromatography, by eluting with 40% petroleum ether in benzene to give the dialkyl thiolester **34** (549 mg; 64% yield): ^{1}H nmr δ0.94 (t, 6H, J = 6 Hz, 2× $-CH_3$), 1.50 (s, 9H, $-C(CH_3)_3$), 1.40-2.20 (m, 12H, 2× $-(CH_2)_3-$); ir 1680 (C=O) and 2250 cm^{-1} (C≡N); ms* M+18 287 (calcd. for $C_{15}H_{31}N_2OS^+$: 287.2157).

Further elution with the same solvent system gave the monoalkyl thiolester **33** (137 mg; 20% yield): ^{1}H nmr δ0.94 (t, 3H, J = 6 Hz, $-CH_3$), 1.50 (s, 9H, $-C(CH_3)_3$), 3.50 (t, 1H, J = 7 Hz, $-\overset{|}{C}H-CN$); ir 1690 (C=O) and 2250 cm^{-1} (C≡N); ms* M+18 231 (calcd. for $C_{11}H_{23}N_2OS^+$: 231.1531).

Further elution with the same solvent system afforded the unreacted thiolester **23** (65.06 mg; 13% recovery).

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*Chemical ionization mass spectrum using NH_3 as a carrier gas.

B. From 1-bromobutane

At 0°C, a solution of thiolester **23** (498 mg, 3.17 mmol) and lithium t-butoxide (406 mg, 5.07 mmol) in dry tetrahydrofuran (10 mL) was stirred under an argon atmosphere for 10 min. HMPA (0.85 mL, 5.07 mmol) was added slowly and after 10 min followed by addition of 1-bromobutane (0.54 mL, 5.07 mmol) dropwise *via* a syringe. The mixture was stirred for 38 h at 0°C and quenched with ice-water. Extraction and purification were carried out as in method A, which gave the dialkylated compound **34** (175 mg; 20% yield), and the monoalkylated compound **33** (170 mg; 25% yield). Starting material **23** (190 mg; 38% recovery) was also obtained. Spectral data (^{1}H nmr and ir) of these compounds were identical with those reported in method A (*vide supra*).

C. From 1-chlorobutane

At 0°C, a solution of cyanothiolester **23** (499 mg, 3.18 mmol) and lithium t-butoxide (657 mg, 8.27 mmol) in freshly distilled tetrahydrofuran (10 mL) was stirred under an argon atmosphere for 10 min. HMPA (1.44 mL, 8.27 mmol) was added and after 10 min, followed by addition of 1-chlorobutane (0.86 mL, 8.27 mmol) by means of a syringe. The mixture was heated to reflux for 32 h. Isolation and purification were carried out as in method

A. Dibutyl derivative **34** (11 mg; 0.6% yield), monobutyl derivative **33** (241 mg; 36% yield) and unreacted thiolester **23** (192 mg; 61% recovery) were obtained. The ^{1}H nmr spectra for all these compounds were identical with those already reported in method A (vide supra).

S-t-Butyl 2-benzyl-2-cyano-3-phenylthiolpropanoate (**36**) and S-t-butyl 2-cyano-3-phenylthiolpropanoate (**35**)

A. Using lithium t-butoxide as a base

A solution of cyanothiolester **23** (508 mg, 3.23 mmol), lithium t-butoxide (285 mg, 3.56 mmol) and HMPA (0.62 mL, 3.56 mmol) in freshly distilled tetrahydrofuran (10 mL) was stirred for 10 min at 0°C. Benzyl bromide (0.42 mL, 3.56 mmol) was added dropwise via a syringe. After the mixture had been stirred for 4 days at room temperature under an argon atmosphere, ice-cold 1N aqueous hydrochloric acid solution was added. The organic layer was extracted with dichloromethane (4 × 20 mL) and extracts washed with saturated sodium chloride solution. The extracts were combined, dried, filtered, and concentrated. Purification of the crude material by column chromatography on silica gel (50% benzene in petroleum ether) followed by multiple development preparative thin-layer chromatography afforded the dibenzyl derivative **36** (552 mg; 51% yield) as pure white crystals: m.p. 92-95°C (ether); ^{1}H nmr δ1.34 (s, 9H, -C$(CH_3)_3$), 3.00 (d, 2H, J = 14 Hz, 2× -C$\underline{H}$HPh), 3.37 (d, 2H, J = 14 Hz, 2× -CH$\underline{H}$Ph), and 7.32 (s, ~~10H,~~ aromatic protons); ^{13}C nmr δ195.4, 136.1, 134.1, 133.7, 132.4, 130.3, 129.1, 128.6, 127.9, 127.6, 126.6, 124.9, 118.8, 59.1, 43.6 and 34.4; ir (CHCl$_3$) 1610 (aromatic), 1670 (C=O), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 337.1502 (calcd. for $C_{21}H_{23}NOS$: 337.1500). Anal. Calcd. for $C_{21}H_{23}NOS$: C, 74.74; H, 6.88; N, 4.15; O, 4.74; S, 9.48. Found: C, 74.78; H, 6.83; N, 4.14; O, 4.78; S, 9.39.

Further elution with the same solvent system gave the monobenzyl derivative **35** as a light yellow oil (129 mg; 16% yield); ^{1}H nmr δ1.48 (s, 9H, -C$(CH_3)_3$), 3.20 (d, 1H, J = 8 Hz, -C$\underline{H}$H-Ph), 3.23 (d, 1H, J = 6 Hz, -CH$\underline{H}$-Ph), 3.70 (dd, 1H, J = 8 Hz, J' = 6 Hz, -$\overset{|}{\text{C}}$HCN), and 7.31 (m, 5H, aromatic protons); ir 1685 (C=O), 2250 (C≡N), and 3040-3060 cm^{-1} (aromatic); ms M$^+$ 247.1026 (calcd. for $C_{14}H_{17}NOS$: 247.3544).

Further elution with the same solvent system gave the unconsumed thiolester **23** (47.56 mg; 9% recovery).

B. Using lithium hydride as a base

To a solution of cyanothiolester **23** (500 mg, 3.18 mmol) in freshly distilled tetrahydrofuran (10 mL) at −5°C, was added lithium hydride (43 mg, 5.41 mmol) followed by HMPA (0.94 mL, 5.41 mmol) with stirring under an argon atmosphere. Benzyl bromide (0.64 mL, 5.41 mmol) was added dropwise *via* a syringe and the mixture stirred for 26 h at −5°C. The usual work-up and purification as in method A afforded the following compounds in order of chromatographic separation. The dibenzyl derivative **36** (547 mg; 46% yield), the monobenzyl derivative **35** (196 mg; 17% yield), and the unconsumed thiolester **23** (93 mg; 19% recovery). The ^{1}H nmr spectra of these compounds were identical with those obtained by method A (*vide supra*).

S-*t*-Butyl 2-cyano-2-isopropyl-3-methylthiolbutanoate (**38**) and S-*t*-butyl 2-cyano-3-methylthiolbutanoate (**37**)

A. From 2-iodopropane

A solution of cyanothiolester **23** (456 mg, 2.90 mmol) and lithium *t*-butoxide (680 mg, 7.25 mmol) in freshly distilled tetrahydrofuran (10 mL) was stirred under an argon atmosphere at 0 °C for 10 min. HMPA (1.26 mL, 7.25 mmol) was added followed by dropwise addition of 2-

iodopropane (0.72 mL, 7.25 mmol) and the mixture stirred for 48 h at 0°C. Ice-cold 1N aqueous hydrochloric acid solution was added and the organic layer extracted with dichloromethane (4 × 20 mL) and the extracts washed with saturated sodium chloride solution. The extracts were combined, dried, filtered, and concentrated. The crude material was purified by silica gel column chromatography using 20% petroleum ether in benzene as an eluent to give the diisopropyl thiolester **38** (60 mg; 9% yield): ^{1}H nmr δ1.06 (d, 6H, J = 8 Hz, $(C\underline{H}_3)_2CH-$), 1.22 (d, 6H, J = 8 Hz, $(C\underline{H}_3)_2CH-$), 1.50 (s, 9H, $-C(CH_3)_3$), 2.30 (m, 2H, 2× $(CH_3)_2C\underline{H}-$); ir 1680 cm^{-1} (C=O); ms M^+ - 60 181.1831 (calcd. for $C_{12}H_{23}N$: 181.1830).

Further elution with the same solvent system gave the monoisopropyl thiolester **37** (285 mg; 49% yield): ^{1}H nmr δ1.10 (d, 6H, J = 6 Hz, $(C\underline{H}_3)_2CH-$), 1.50 (s, 9H, $-C(CH_3)_3$), 2.10-2.50 (m, 1H, $(CH_3)_2C\underline{H}-$), 3.37 (d, 1H, J = 6 Hz, $-\overset{|}{C}HCN$); ir 1690 (C=O) and 2250 cm^{-1} (C≡N); ms* M+18 217 (calcd. for $C_{10}H_{21}N_2OS^+$: 217.1375).

Further elution with the same solvent system afforded the unreacted thiolester **23** (139 mg; 30% recovery).

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*Chemical ionization mass spectrum using NH_3 as a carrier gas.

B. From 2-bromopropane

A solution of S-t-butyl cyanothiolacetate **(23)** (250 mg, 1.59 mmol) and lithium t-butoxide (318 mg, 3.98 mmol) in freshly distilled tetrahydrofuran (10 mL) was stirred under an argon atmosphere at 0°C for 10 min. HMPA (0.69 mL, 3.98 mmol) was added followed by dropwise addition of 2-bromopropane (0.37 mL, 3.98 mmol) and the mixture stirred for 15 h at room temperature. Usual work-up and purification as in method A afforded the diisopropyl derivative **38** (17 mg; 4% yield), the monoisopropyl derivative **37** (163 mg; 52% yield), and the unreacted thiolester **23** (89 mg; 35% recovery). The ^1H nmr spectra for all these compounds were identical with those of previously reported compounds in method A (vide supra).

C. From 2-bromopropane at refluxing temperature

The procedure was the same as in method B except the reaction was heated at refluxing temperature for 5 h. The products were obtained as follows after column chromatography: the diisopropyl derivative **38** (24 mg; 6% yield); the monoisopropyl derivative **37** (130 mg; 41% yield); the unreacted thiolester **23** (64 mg; 25% recovery). The ^1H nmr spectra for all these compounds were identical as have already been reported in method A (vide supra).

S-*t*-Butyl 2-cyano-2-octylthioldecanoate (**40**) and S-*t*-butyl 2-cyanothioldecanoate (**39**)

A. Using lithium *t*-butoxide as a base

A solution of cyanothiolester **23** (400 mg, 2.55 mmol) and lithium *t*-butoxide (225 mg, 2.81 mmol) in freshly distilled tetrahydrofuran (10 mL) was stirred under an argon atmosphere at 0°C for 10 min. HMPA (0.49 mL, 2.81 mmol) was added followed by dropwise addition of *n*-octyl bromide (0.48 mL, 2.81 mmol) *via* syringe. The mixture was stirred at 5°C for 40.5 h. Ice-cold 1N aqueous hydrochloric acid solution was added and the organic layer extracted with dichloromethane (4 × 20 mL) and the extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The residue was purified by silica gel flash column chromatography using 40% benzene in petroleum ether as an eluent to give the dioctyl derivative **40** (20.56 mg; 2% yield): ^{1}H nmr δ0.85 (brt, 6H, $J = 6$ Hz, 2 × CH_3), 1.20-2.20 (m, 28H, 2×-$(CH_2)_7$-), 1.46 (s, 9H, -$C(CH_3)_3$); ir 1680 cm^{-1} (C=O); ms M$^+$ 381.3040 (calcd. for $C_{23}H_{43}NOS$: 381.3065).

Further elution with the same solvent system gave the monooctyl derivative **39** (77.56 mg; 11% yield): ^{1}H nmr δ0.88 (brt, 3H, J = 6 Hz, $-CH_3$), 1.20-2.10 (m, 14H, $-(CH_2)_7-$), 1.50 (s, 9H, $-C(CH_3)_3$), 3.48 (t, 1H, J = 7 Hz, $-\overset{|}{C}H-CN$); ir 1685 (C=O) and 2260 cm^{-1} (C≡N); ms M$^+$ -57 212.1109 (calcd. for $C_{11}H_{18}NOS$: 212.1109).

Further elution with 40% petroleum ether in benzene afforded the unconsumed thiolester **23** (328 mg; 82% recovery).

B. Using lithium hydride as a base

To a solution of S-t-butyl cyanothiolacetate (**23**) (498 mg, 3.17 mmol) in freshly distilled tetrahydrofuran (10 mL) was added lithium hydride (30 mg, 3.80 mmol) at -5°C under an argon atmosphere. HMPA (0.66 mL, 3.80 mmol) was added followed by dropwise addition of n-octylbromide (0.66 mL, 3.80 mmol) via a syringe. After stirring at -5°C for 48 h, the reaction mixture was worked up and products isolated as described in method A. The dioctyl derivative **40** (25 mg; 2% yield), the monooctyl derivative **39** (230 mg; 27% yield), and the unreacted thiolester **23** (255 mg; 51% recovery) were obtained. The ^{1}H nmr spectra of all these compounds were identical with previously reported compounds as described in method A (vide supra).

S-t-Butyl 2-benzyl-2-cyano-4-methylthiolpentanoate (**42**)

To a solution of 2-cyano-4-methylthiolpentanoate **41** (182 mg, 0.85 mmol) in 1,2-dimethoxyethane (10 mL), was added sodium hydride (50% dispersion in oil; 40 mg, 0.85 mmol) and mixture stirred at 0°C under an argon atmosphere for 10 min. Benzyl bromide (0.10 mL, 0.85 mmol) was added slowly via a syringe. After the mixture had been stirred for 9.5 h at room temperature, ice-cold 1N aqueous hydrochloric acid solution was added and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated solution of sodium chloride, dried, filtered, and concentrated in vacuo. The crude product was purified by distillation (50°C/1 torr) to give a yellowish oil of compound **42** (218 mg; 85% yield): ^{1}H nmr δ0.94 (d, 3H, J = 6 Hz, isopropyl CH_3-), 1.03 (d, 3H, J = 6 Hz, isopropyl CH_3-), 1.40 (s, 9H, $-C(CH_3)_3$), 2.92 (d, 1H, J = 14 Hz, -C<u>H</u>H-Ph), 3.20 (d, 1H, J = 14 Hz, -CH<u>H</u>-Ph), 7.30 (m, 5H, aromatic protons); ir 1580, 1620 (aromatic), 1690 (C=O), 2260 (C≡N), and 3010-3100 cm^{-1} (aromatic); ms M$^+$ 303.1651 (calcd. for $C_{18}H_{25}NOS$: 303.1657).

trans-S-t-Butyl 2-cyano-2-ethyl-5-phenyl-4 thiolpentenoate (44)

Cyanothiolester **43** (139 mg, 0.51 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 5 min. Sodium hydride (50% dispersion in oil; 24 mg, 0.51 mmol) was added and after 10 min, followed by addition of ethyl iodide (0.04 mL, 0.51 mmol). After stirring for 22 h at room temperature, the mixture was poured into ice-cold 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL) and the organic layer washed again with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel using 10% ether in petroleum ether as an eluent gave dialkylated product **44** (103 mg; 66% yield): ^{1}H nmr δ1.10 (t, 3H, J = 7 Hz, $\underline{CH_3}$-CH_2-), 1.49 (s, 9H, -C(CH_3)$_3$), 1.96 (dq, 2H, J = 22 Hz, J' = 7 Hz, CH_3-$\underline{CH_2}$-), 2.74 (m, 2H, allylic -CH_2-), 6.18 (dt, 1H, J = 16 Hz, J' = 7 Hz, PhCH=C$\underline{H}$-), 6.56 (br d, 1H, J = 16 Hz, PhC$\underline{H}$=CH-), and 7.30 (m, 5H, aromatic protons); ir 690, 745 (monosubstituted benzene), 1670 (C=O), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 301.1485 (calcd. for $C_{18}H_{23}NOS$: 301.1500).

trans-S-t-Butyl 2-cyano-2-allyl-5-phenyl-4 thiolpentenoate (45)

Cyanothiolester **43** (103 mg, 0.37 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 10 min followed by addition of sodium hydride (50% dispersion in oil; 21 mg, 0.42 mmol). After 10 min stirring 3-bromopropene (0.04 mL, 0.44 mmol) was added and stirred for 16 h at room temperature. Ice-cold 1N aqueous hydrochloric acid solution was added and the organic layer extracted with dichloromethane (4 × 10 mL) and the extracts washed with aqueous sodium chloride solution. The combined extract was dried, filtered, and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/petroleum ether) to afford compound **45** (63.94 mg; 54% yield): ^1H nmr δ1.44 (s, 9H, $-C(CH_3)_3$), 2.50-3.00 (m, 4H, allylic protons, unresolved), 5.24 (dd, 1H, J = 16 Hz, J' = 2 Hz, vinylic proton H_a), 5.26 (dd, 1H, J = 10 Hz, J' = 2 Hz, vinylic proton H_b), 5.82 (ddt, 1H, J = 16 Hz, J' = 10 Hz, J" = 7 Hz, vinylic proton H_c), 6.16 (dt, 1H, J = 16 Hz, J' = 7 Hz, vinylic proton H_d), 6.55 (br d, 1H, J = 16 Hz, vinylic proton H_e), and 7.32 (m, 5H, aromatic protons); ir 1605 (C=C), 1670 (C=O), 1750-1785 (overtones), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 313.1495 (calcd. for $C_{19}H_{23}NOS$: 313.1500).

S-*t*-Butyl 2-cyano-5-phenyl-2, 4*E*-thiolpentadienoate (**46**)

A mixture of S-*t*-butyl cyanothiolacetate (**23**) (501 mg, 3.18 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (356 mg, 3.13 mmol) in dry tetrahydrofuran (10 mL) was stirred at 0°C under an argon atmosphere for 10 min. *trans*-Cinnamaldehyde (0.27 mL, 2.12 mmol) was added dropwise by means of a syringe and stirring continued for 13 h at room temperature. The mixture was then quenched with 1N aqueous hydrochloric acid solution. The organic layer was extracted with dichloromethane (4 × 20 mL) and the extracts were washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10% ether/petroleum ether) to give yellow crystals of **46** (540 mg; 94% yield), m.p. 82-85°C (petroleum ether). The ^{1}H nmr showed a mixture of two regioisomers (1:2 ratio from integration). The following spectral data were recorded on the mixture of isomers; ^{1}H nmr δ1.46 (s, 9H, $-C(CH_3)_3$, from minor isomer), 1.56 (s, 9H, $-C(CH_3)_3$, from major isomer), 7.30 (m, 5H, aromatic protons from major isomer), 7.42 (m, 5H, aromatic protons from minor isomer), and 7.71 (complex, 3H, overlapped between three vinylic protons); ir ($CHCl_3$) 1558, 1576, 1605 (olefinic stretch), 1662 (C=O), 2211 (C≡N), and 2964-3040 cm^{-1} (aromatic); ms M$^+$ 271.1031 (calcd. for $C_{16}H_{17}NOS$: 271.1031). Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.85; H, 6.27; N, 5.17; S, 11.81. Found: C, 71.00; H, 6.24; N, 5.17; S, 11.89.

S-*t*-Butyl 2-cyano-4-methyl-2-thiolpentenoate (**47**)

To a stirred solution of S-*t*-butyl cyanothiolacetate (**23**) (996 mg, 6.34 mmol) in dry tetrahydrofuran (20 mL) at 0°C, was added DABCO (850 mg, 7.61 mmol) and mixture stirred for 10 min at 0°C under an argon atmosphere. Isobutyraldehyde (0.70 mL, 7.61 mmol) was added by a syringe. After stirring at room temperature for 5 h the mixture was poured into aqueous 1N hydrochloric acid solution, extracted with dichloromethane (4 × 30 mL) and the extracts washed with aqueous sodium chloride solution. The combined extract was dried, filtered, and concentrated. The residue was purified by molecular distillation using Kugelrohr apparatus (112°C oven temperature at 0.8 torr) to afford the pure condensed product **47** (847 mg; 66% yield) as a single regioisomer according to the ^{1}H nmr spectrum; ^{1}H nmr δ1.15 (d, 6H, J = 6 Hz, $(\underline{CH_3})_2CH-$), 1.51 (s, 9H, $-C(CH_3)_3$), 2.96 (m, 1H, $(CH_3)_2\underline{CH}-$), and 7.32 (d, 1H, J = 10 Hz, $-CH{=}\overset{|}{C}CN$); ir 1610 (trisubstituted C=C), 1665 (C=O), and 2240 cm^{-1} (C≡N); ms M$^+$ 211.1035 (calcd. for $C_{11}H_{17}NOS$: 211.1031). Anal. Calcd. for $C_{11}H_{17}NOS$: C, 62.56; H, 8.06; N, 6.64; S, 15.17. Found: C, 62.63; H, 8.13; N, 6.62; S, 15.13.

S-t-Butyl 2-cyano-2-cyclohexylidenethiolacetate (**48**)

To a stirred solution of S-t-butyl cyanothiolacetate (**23**) (502 mg, 3.20 mmol) in dry tetrahydrofuran (10 mL) at 0°C, was added DABCO (607 mg, 5.42 mmol) and stirred for 10 min under an argon atmosphere. Cyclohexanone (0.56 mL, 5.43 mmol) was added via a syringe. After stirring at room temperature for 20 h, ice-cold 1N aqueous hydrochloric acid solution was added and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate/skelly B) to give α,β-unsaturated thiolester **48** (657 mg; 87% yield);

^{1}H nmr δ1.54 (s, 9H, $-C(CH_3)_3$), 1.58 (br t, 2H, J = 6 Hz, $-CH_2-\overset{|}{C}=$), and 1.77 (br t, 2H, J = 6 Hz, $-CH_2-\overset{|}{C}=$); ir 1590 (tetrasubstituted C=C), 1670 (C=O), and 2220 cm^{-1} (C≡N); ms M$^+$ 237.1186 (calcd. for $C_{13}H_{19}NOS$: 237.1187).

S-t-Butyl 2-cyano-3-methyl-2-thiolnonenoate (**49**)

Cyanothiolester **23** (541 mg, 3.45 mmol) was dissolved in dry tetrahydrofuran (15 mL) and mixture stirred for 10 min at 0°C under an argon atmosphere. DABCO (655 mg, 5.85 mmol) was added and stirred for another 15 min followed by addition of 2-octanone (0.92 mL, 5.85 mmol) via a syringe. After stirring for 25 h at room temperature the reaction was quenched with ice-cold aqueous 1N hydrochloric acid solution, and the resulting mixture extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated. The crude product was chromatographed on silica gel (10% ethyl acetate/petroleum ether) to give the α,β-unsaturated thiolester **49** (392 mg; 57% yield) as a mixture of isomers (ca. 1:1 ratio according to ^{1}H nmr spectrum); ^{1}H nmr δ0.89 (brt, 3H, J = 6 Hz, $\underline{CH_3}-CH_2-$), 1.54 (s, 9H, $-C(CH_3)_3$), 2.32 (s, 1/2× 3H, $CH_3-\overset{|}{C}=$), 2.40 (s, 1/2× 3H, $CH_3-\overset{|}{C}=$), and 2.62 (dt, 2H, J =

25 Hz, J' = 7 Hz, CH$_2$-$\overset{|}{C}$=); ir 1580 (tetrasubstituted C=C), 1660 (C=O) and 2210 cm^{-1} (C≡N); ms M$^+$ 267.1659 (calcd. for $C_{15}H_{25}NOS$: 267.1657).

8-(Cyano-*t* butylthiocarbonylmethylene)-1,5-dimethylbicyclo-[4.4.0]-deca-4-ene (**51**)

Cyanothiolester **23** (458 mg, 2.92 mmol) and DABCO (330 mg, 2.95 mmol) were dissolved in freshly distilled tetrahydrofuran (10 mL) and stirred under an argon atmosphere at room temperature for 10 min. Then anhydrous sodium sulfate (622 mg, 4.38 mmol) was added followed by slow addition of a solution of the ketone **50** (261 mg, 1.46 mmol) in tetrahydrofuran (1 mL). The mixture was stirred at room temperature for 48 h. Ice-cold 1N aqueous hydrochloric acid solution was added and the resulting mixture extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel (40% benzene in petroleum ether) afforded an isomeric mixture of the condensed products **51** (332 mg; 71% yield). The following spectral data were recorded on the mixture of regioiosomers; ^{1}H nmr δ0.90 (s, 3H, angular -CH$_3$), 1.52, 1.54 (both s, total 9H, $-C(CH_3)_3$), and 5.38 (br s, 1H, $\overset{|}{H}C{=}C$); ir 1375 (*t*-butyl), 1670 (C=O), and 2240 cm^{-1} (C≡N); ms M^+ 317.1814 (calcd. for $C_{19}H_{27}NOS$: 317.1813).

trans-S-*t*-Butyl 2-cyano-5-phenyl-4-thiolpentenoate (**43**)

To a solution of unsaturated thiolester **46** (80.45 mg, 0.29 mmol) in absolute ethanol (5 mL) at 0°C, was added sodium borohydride (2.75 mg, 0.07 mmol) and the mixture stirred for 2.5 h from 0°C to room temperature. The reaction mixture was poured into ice-cold saturated aqueous ammonium chloride solution, extracted with dichloromethane (4 × 10 mL) and the extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was chromatographed on silica gel eluting with 10% ether in petroleum ether to give γ,δ-unsaturated thiolester **43** (66 mg; 83% yield): ^1H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 2.87 (dd, 2H, J = 8 Hz, J' = 6 Hz, $-C\underline{H_2}-\overset{|}{C}H-CN$), 3.62 (t, 1H, J = 7 Hz, $-\overset{|}{C}HCN$), 6.14 (dt, 1H, J = 16 Hz, J' = 8 Hz, $-CH{=}C\underline{H}-CH_2-$), 6.57 (d, 1H, J = 16 Hz, $Ph-C\underline{H}{=}CH-$), and 7.30 (m, 5H, aromatic protons); ir 1600 (aromatic), 1670 (C=O), 2240 (C≡N), and 3020-3080 cm^{-1} (aromatic); ms M^+ 273.1184 (calcd. for $C_{16}H_{19}NOS$: 273.1187).

S-*t*-Butyl 2-cyano-4-methylthiolpentanoate (**41**)

To a solution of the condensed product **47** (199 mg, 0.94 mmol) in absolute ethanol (5 mL) at 0°C, was added sodium borohydride (8.94 mg, 0.24 mmol) and the mixture stirred for 45 min under an argon atmosphere. The solution was then poured into ice-cold saturated ammonium chloride solution and extracted with chloroform (4 × 10 mL). The extracts were washed with sodium chloride saturated solution, dried, filtered, and concentrated. The crude product was purified by column chromatography (10% ethyl acetate/petroleum ether) to afford the pure saturated product **41** (182 mg; 91% yield); ^{1}H nmr δ0.94 (d, 3H, J = 4 Hz, $\underline{CH_3}\text{-}\overset{|}{C}H\text{-}$), 1.02 (d, 3H, J = 4 Hz, $\underline{CH_3}\text{-}\overset{|}{C}H\text{-}$), 1.52 (s, 9H, $-C(CH_3)_3$), and 3.53 (dd, 1H, J = 8 Hz, J' = 6 Hz, $-\overset{|}{C}HCN$); ir 1690 (C=O) and 2260 cm^{-1} (C≡N); ms* M$^+$ +18 231 (calcd. for $C_{11}H_{23}N_2OS^+$: 231.1531).

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*Chemical ionization mass spectrum using NH_3 as a carrier gas.

S-t-Butyl 2-cyano-2-cyclohexylthiolacetate (52)

A mixture of α,β-unsaturated thiolester **48** (199 mg, 0.83 mmol) and sodium borohydride (7.96 mg, 0.21 mmol) in absolute ethanol (5 mL) was stirred under an argon atmosphere at 0°C for 45 min. The mixture was then poured into ice-cold saturated ammonium chloride solution and extracted with chloroform (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate/petroleum ether) to give a light yellow oil of saturated thiolester **52** (194 mg; 97% yield); ^{1}H nmr δ1.51 (s, 9H, $-C(CH_3)_3$), and 3.40 (d, 1H, J = 6 Hz, $-\overset{|}{C}HCN$); ir 1690 (C=O) and 2260 cm^{-1} (C≡N); ms M$^+$ 239.1334 (calcd. for $C_{13}H_{21}NOS$: 239.1344). Anal. Calcd. for $C_{13}H_{21}NOS$: C, 65.22; H, 8.84; N, 5.85; S, 13.39. Found: C, 65.40; H, 8.85; N, 5.59; S, 13.01.

S-t-Butyl 2-cyano-3-methylthiolnonanoate (53)

A mixture of α,β-unsaturated cyanothiolester **49** (102 mg, 0.38 mmol) and sodium borohydride (4 mg, 0.09 mmol) in absolute ethanol (5 mL) was stirred under an argon atmosphere for 45 min at 0°C. The mixture was poured into ice-cold saturated ammonium chloride solution, extracted with dichloromethane (4 × 10 mL) and the extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate/petroleum ether) which gave mixture of two diastereoisomers (ca. 1:1 ratio according to ^{1}H nmr integration) of saturated thiolester **53** (76.61 mg; 74% yield). The following spectral data were recorded on the mixture; ^{1}H nmr δ0.88 (br t, 3H, J = 7 Hz, $\mathrm{C\underline{H}_3{-}CH_2{-}}$), 1.06, 1.08 (both d, 6H, J = 7 Hz each, $\mathrm{\underline{CH_3}{-}\overset{|}{C}H{-}}$), 1.50 (s, 9H, $\mathrm{-C(CH_3)_3}$), 2.28 (m, 1H, $\mathrm{CH_3{-}\overset{|}{C}\underline{H}{-}}$), 3.40 (d, 1H, J = 5 Hz, $\mathrm{-\overset{|}{C}HCN}$, from one isomer), and 3.52 (d, 1H, J = 5 Hz, $\mathrm{-\overset{|}{C}HCN}$, from another isomer); ir 1680 (C=O) and 2240 cm^{-1} (C≡N); ms M$^+$ 269.1788 (calcd. for $\mathrm{C_{15}H_{27}NOS}$: 269.1813). Anal. Calcd. for $\mathrm{C_{15}H_{27}NOS}$: C, 66.86; H, 10.01; N, 5.20; S, 11.89. Found: C, 67.31; H, 10.18; N, 5.04; S, 11.81.

2-Benzyl-2-hydroxymethyl-3-phenylpropanecarbonitrile (54)

A solution of dibenzyl thiolester **25** (200 mg, 0.54 mmol) and sodium borohydride (100 mg, 2.63 mmol) in isopropyl alcohol (5 mL) (freshly distilled) was stirred at 0°C to room temperature for 24 h, under an argon atmosphere. The mixture was poured into ice-cold saturated solution of ammonium chloride and the resulting mixture extracted with chloroform (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated in vacuo. The crude product was subjected to column chromatography on silica gel eluting with 20% ether in benzene to afford the dibenzyl alcohol **54** (129 mg; 96% yield). Single recrystallization from 30% benzene in petroleum ether gave pure white crystals (m.p. 100-102°C): ^{1}H nmr δ2.95 (br s, 4H, 2× $-CH_2-Ph$), 3.53 (s, 2H, $-\underline{CH_2}-OH$), and 7.33 (m, 10H, aromatic protons); ir ($CHCl_3$) 1050 (C-O), 2220 ($C\equiv N$), 3000-3100 (aromatic), and 3490-3500 cm^{-1} (-OH); ms M$^+$ 251.1313 (calcd. for $C_{17}H_{17}NO$: 251.1310).

2-Hydroxymethyl hexanecarbonitrile (55)

A. From S-benzyl 2-cyanothiolhexanoate (27)

To a solution of thiolester **27** (127 mg, 0.51 mmol) in isopropyl alcohol (10 mL) at 0°C, was added sodium borohydride (66 mg, 1.74 mmol). The mixture was stirred at room temperature for 25 h under an argon atmosphere. Ice-cold water was added to the reaction mixture followed by saturated solution of ammonium chloride, and the resulting mixture extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Column chromatography of the residue (50% ethyl acetate/petroleum ether) gave an oily compound **55** (59.6 mg; 90% yield): ^1H nmr δ0.94 (t, 3H, J = 6 Hz, CH_3-), 1.54 (m, 6H, -$(CH_2)_3$-), 2.13 (br s, 1H, -OH), 2.75 (m, 1H, -$\overset{|}{C}$HCN), and 3.75 (d, 2H, J = 6 Hz, -$\underline{CH_2}$OH); ir 1070 (C-O), 2250 (C≡N), and 3400-3500 cm^{-1} (-OH); ms M^+ -30 97.0892 (calcd. for $C_6H_{11}N$: 97.0892).

B. <u>From S-*t*-butyl 2-cyanothiolhexanoate (**33**)</u>

A solution of thiolester **33** (101 mg, 0.474 mmol) and sodium borohydride (50 mg, 1.31 mmol) in absolute ethanol (10 mL) was stirred under an argon atmosphere for 24 h at room temperature. The same procedure for work-up and purification as mentioned in method A afforded an alcohol **55** (58.70 mg; 98% yield). The ^1H nmr spectrum obtained was found to be identical to that obtained by method A (*vide supra*).

2-Butyl-2-hydroxymethylhexanecarbonitrile (**56**)

A. <u>From S-benzyl 2-butyl-2-cyanothiolhexanoate (**28**)</u>

To a mixture of benzyl thiolester **28** (300 mg, 0.99 mmol) in isopropyl alcohol (5 mL) (freshly distilled) was added sodium borohydride (75 mg, 1.97 mmol) at 0°C. The mixture was stirred under an argon atmosphere for 11 h at room temperature, after which ice-cold water was added. Aqueous ammonium chloride saturated solution was added and the resulting mixture was extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated. Column chromatography of the residue on silica gel using 20% petroleum ether in benzene as an eluent, afforded the pure alcohol **56** (116 mg; 64% yield): ^1H nmr δ0.94 (br t, 6H, J = 6 Hz, 2× CH_3-), 2.00 (br s, 1H, -OH), and 3.68 (br s, 2H, $J_{w_{1/2}}$ = 4 Hz, -<u>CH_2</u>-OH); ir 1050 (C-O), 2240 (C≡N), and 3400-3500 cm^{-1} (-OH); ms M^+ -30 153.1519 (calcd. for $C_{10}H_{19}N$: 153.1517).

B. From S-t-butyl 2-butyl-2-cyanothiolhexanoate (**34**)

To a solution of S-t-butyl cyanothiolester **34** (111 mg, 0.41 mmol) in absolute ethanol (5 mL) at 0°C, was added sodium borohydride (83 mg, 2.18 mmol). The mixture was stirred for 19 h at room temperature under an argon atmosphere. The isolation and purification were carried out the same as described in method A to afford the pure alcohol **56** (68.61 mg; 90% yield). The ^1H nmr spectrum was identical to that already reported in method A (vide supra).

2-Hydroxymethyl-2-allyl-4-pentenecarbonitrile (**57**)

A solution of S-*t*-butyl thiolester **31** (178 mg, 0.75 mmol) and sodium borohydride (44 mg, 1.16 mmol) in absolute ethanol (5 mL) was stirred under an argon atmosphere from 0°C to room temperature for 11 h. Ice-cold aqueous saturated ammonium chloride solution was added and the resulting mixure extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product obtained was chromatographed on silica gel (eluted with 20% ethyl acetate in petroleum ether) to afford the pure alcohol **57** (89 mg; 80% yield): ^1H nmr δ2.08 (br t, 1H, -OH, disappeared upon D_2O exchange), 2.40 (d, 4H, J = 8 Hz, 2× $CH_2{=}CH{-}\underline{CH_2}$), 3.65 (br d, 2H, J = 6 Hz, $-C\underline{H_2}-OH$), 5.22 (dd, 2H, J = 17 Hz, J' = 1.5 Hz, H_eH_i), 5.24 (ddd, 2H, J = 11 Hz, J' = 1.5 Hz, J" = 1 Hz, H_fH_g), and 5.86 (ddt, 2H, J = 16 Hz, J' = 10.5 Hz, J" = 7 Hz, H_jH_k); ir 1590 (C=C), 2240 ($C\equiv N$), 3080 (C=C), and 3400-3500 cm^{-1} (-OH); ms M^+ 151.0990 (calcd. for $C_9H_{13}NO$: 151.0997).

1-Cyano-1-hydroxymethylcyclohexane (**58**)

To a solution of S-t-butyl cyanothiolester **32** (273 mg, 1.21 mmol) in absolute ethanol (5 mL) at 0°C, was added sodium borohydride (140 mg, 0.6 mmol). The mixture was stirred for 18 h at room temperature under an argon atmosphere. Ice-cold saturated ammonium chloride solution was added and the resulting mixture extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution and the combined extract was dried, filtered, and concentrated. Purification by silica gel column chromatography (20% petroleum ether in benzene) of the residue gave the cyclic alcohol **58** (159 mg; 94% yield): ^1H nmr δ1.00-2.25 (m, 10H, $-(CH_2)_5-$), and 3.51 (s, 2H, $-\underline{CH_2}OH$); ir 1050 (C-O), 2240 (C≡N), and 3400-3500 cm^{-1} (-OH); ms* M^+ +18 157 (calcd. for $C_8H_{17}N_2O^+$: 157.1341).

2-Hydroxymethyl-3-phenylpropanecarbonitrile (**59**)

A solution of S-t-butyl cyanothiolester **35** (123 mg, 0.50 mmol) and sodium borohydride (60 mg, 1.58 mmol) in

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[*] Chemical ionization mass spectrum using NH_3 ion as a carrier gas.

absolute ethanol (5 mL) was stirred under an argon atmosphere for 24 h at room temperature. The mixture was poured into ice-cold aqueous ammonium chloride solution and the resulting mixture extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was purified on silica gel flash column chromatography (50% ether/petroleum ether) to give the alcohol **59** (72.29 mg; 90% yield): ^1H nmr δ2.00 (complex, 1H, $-\overset{|}{C}HCN$), 3.00 (br s, 3H, overlapped between $PhCH_2$- and -OH), 3.80 (br s, 2H, $-\underline{CH_2}-OH$), and 7.30 (m, 5H, aromatic protons); ir 1070 (C-O), 1610 (aromatic), 2260 (C≡N), 3040-3100 (aromatic), and 3400-3500 cm^{-1} (-OH); ms M^+ 161.0841 (calcd. for $C_{10}H_{11}NO$: 161.0841).

2-Hydroxymethyl-3-methylbutanecarbonitrile (**60**)

A solution of S-*t*-butyl cyanothiolester **37** (182 mg, 0.91 mmol) and sodium borohydride (108 mg, 2.80 mmol) in absolute ethanol (5 mL) was stirred under an argon atmosphere for 15 h at room temperature. The mixture was quenched with ice-cold saturated solution of ammonium chloride and the resulting mixture extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was subjected to flash column chromatography on silica gel by eluting with 40% ethyl acetate in petroleum ether to give the alcohol **60** (94.66 mg; 91% yield) as a colorless oil: ^{1}H nmr δ1.09 (d, 6H, J = 6 Hz, $(\underline{CH_3})_2$-CH-), 2.00 (m, 1H, -$C\underline{H}(CH_3)_2$), 2.50 (br d, 1H, -OH), 2.65 (dt, 1H, J = 7 Hz, J' = 6 Hz, $-\overset{|}{C}HCN$), and 3.80 (dd, 2H, J = 6 Hz, J' = 2 Hz, -$C\underline{H_2}$-OH); ir 2250 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+-30 83.0735 (calcd. for C_5H_9N: 83.0735).

2-Hydroxymethyldecanecarbonitrile (**61**)

A mixture of S-t-butyl cyanothiolester **39** (197 mg, 0.73 mmol) and sodium borohydride (98 mg, 2.58 mmol) in absolute ethanol (5 mL) was stirred under an argon atmosphere from 0°C to room temperature for 1 h. The mixture was poured into saturated solution of ammonium chloride, extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was purified by silica gel column chromatography using 40% petroleum ether in benzene as an eluent, to give the alcohol **61** (133 mg; 99% yield) as a clear oil: ^{1}H nmr δ0.88 (t, 3H, J = 6 Hz,

$-CH_3$), 1.84 (br s, 1H, -OH), 2.74 (tt, 1H, J = 7 Hz, J' = 2 Hz, $-\overset{|}{C}HCN$), and 3.76 (dd, 2H, J = 6 Hz, J' = 2 Hz, $-C\underline{H_2}-OH$); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+ 183.1600 (calcd. for $C_{11}H_{21}NO$: 183.1623).

2-Benzyl-2-hydroxymethyl-4-methylpentanecarbonitrile (**62**)

A mixture of dialkylated thiolester **42** (217 mg, 0.71 mmol) and sodium borohydride (54 mg, 1.42 mmol) in absolute ethanol (10 mL) was stirred at room temperature for 13 h under an argon atmosphere. The mixture was poured into an aqueous saturated ammonium chloride solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrat[illegible] The residue was chromatographed on silica gel (30% ethyl acetate/petroleum ether) to give an alcohol **62** (139 mg; 90% yield): ^{1}H nmr δ1.05 (d, 6H, J = 7 Hz, $(\underline{CH_3})_2CH-$), 1.50 (br d, 2H, J = 6 Hz, $(CH_3)_2CH-\underline{CH_2}-$), 2.98 (s, 2H, $PhCH_2-$), 3.63 (br d, 2H, J = 6 Hz, $-C\underline{H_2}-OH$), and 7.33 (m, 5H, aromatic protons); ir 1580, 1600 (aromatic), 2240 (C≡N), 3040-3100 (aromatic), and 3400-3500 cm^{-1} (-OH); ms M^+ 217.1464 (calcd. for $C_{14}H_{19}NO$: 217.1467). Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.31; H, 8.93; N, 6.29.

trans-2-Ethyl-2-hydroxymethyl-5-phenyl-4-pentenecarbonitrile (**63**)

Dialkyl thiolester **44** (92 mg, 0.30 mmol) was dissolved in absolute ethanol (5 mL) and sodium borohydride (69 mg, 1.82 mmol) was added. The mixture was stirred for 19 h at room temperature under an argon atmosphere. The reaction was quenched with ice-cold saturated ammonium chloride solution and the resulting mixture extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. Column chromatography of the residue on silica gel (30% ethyl acetate/petroleum ether) gave the pure alcohol **63** (59.03 mg; 92% yield); ^1H nmr δ1.07 (t, 3H, J = 7 Hz, $\underline{CH_3}-CH_2-$), 1.74 (dq, 2H, J = 7 Hz, J' = 2 Hz, $CH_3\underline{CH_2}-$), 2.18 (br s, 1H, -OH, disappeared upon D_2O exchange), 2.54 (d, 2H, J = 8 Hz, $-CH_2-\overset{|}{\underset{|}{C}}-CN$), 3.66 (br d, 2H, $J_{w_{1/2}}$ = 4 Hz, $-\underline{CH_2}-OH$), 6.18 (dt, 1H, J = 16 Hz, J' = 7 Hz, $PhCH=C\underline{H}-$), 6.56 (br d, 1H, J = 16 Hz, $Ph\ \underline{CH}=CH-$), and 7.30 (m, 5H, aromatic protons); ir 690, 750 (monosubstituted benzene), 1580 (C=C), 2240 ($C\equiv N$), 3040-3100 (aromatic), and 3400-3500 cm^{-1} (-OH); ms M^+ 215.1312 (calcd. for $C_{14}H_{17}NO$: 215.1310).

trans-2-Hydroxymethyl-2-allyl-5-phenyl-4-pentene carbonitrile (**64**)

Cyanothiolester **45** (62.98 mg, 0.20 mmol) was dissolved in absolute ethanol (5 mL) and sodium borohydride (31.49 mg, 0.83 mmol) was added. The mixture was stirred for 10 h at room temperature under an argon atmosphere. The mixture was then added with ice-cold saturated ammonium chloride solution and extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give the pure alcohol **64** (39.56 mg; 85% yield): ^1H nmr δ1.90 (br s, 1H, -OH, disappeared upon D_2O exchange), 2.46 (d, 2H, J = 7 Hz, H_1H_2), 2.58 (d, 2H, J = 7 Hz, H_3H_4), 3.74 (br s, 2H, -C<u>H</u>$_2$OH), 5.24 (dd, 1H, J = 16 Hz, J' = 2 Hz, vinylic proton H_a), 5.26 (dd, 1H, J = 10 Hz, J' = 2 Hz, vinylic proton H_b), 5.82 (ddt, 1H, J = 16 Hz, J' = 10 Hz, J" = 7 Hz, vinylic proton H_c), 6.16 (dt, 1H, J = 16 Hz, J' = 7 Hz, vinylic proton H_d), 6.55 (br d, 1H, J = 16 Hz, vinylic proton H_e), and 7.35 (m, 5H, aromatic protons); ir 690-760 (monosubstituted benzene), 1630 (C=C), 2240 (C≡N), 3040-3100 (aromatic), and 3400-3500 cm^{-1} (-OH); ms M^+ 227.1302 (calcd. for $C_{15}H_{17}NO$: 227.1310).

2-Hydroxymethyl-3-methylnonanecarbonitrile (**65**)

A. From direct reduction of **49**.

α,β-Unsaturated cyanothiolester **49** (258 mg, 0.96 mmol) was dissolved in absolute ethanol (10 mL) at 0°C, followed by addition of sodium borohydride (129 mg, 3.39 mmol). The mixture was stirred for 50 min at 0°C under an argon atmosphere and then quenched with ice-cold saturated ammonium chloride solution followed by extraction with dichloromethane (4 × 10 mL). The extracts were washed with sodium chloride aqueous solution. The combined extract was dried, filtered, and concentrated. The crude product was purified by column chromatography (30% ethyl acetate/petroleum ether) to give the alcohol **65** (168 mg; 95% yield): ^1H nmr δ0.90 (br t, 3H, J = 6 Hz, $C\underline{H}_3\text{-}CH_2\text{-}$), 1.07 (d, 3H, J = 8 Hz, $C\underline{H}_3\text{-}\overset{|}{C}H\text{-}$), 2.04 (br s, 1H, -OH, disappeared upon D_2O exchange), 1.76 (m, 1H, -CH-CN), and 3.86 (br dd, 2H, $J_{w_{1/2}}$ = 14 Hz, $\text{-}C\underline{H}_2\text{-}OH$); ir 2240 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+-1 182.1535 (calcd. for $C_{11}H_{20}NO$: 182.1545).

B. From reduction of saturated thiolester **53**

Saturated thiolester **53** (180 mg, 0.67 mmol) was dissolved in absolute ethanol (5 mL) and sodium borohydride (76 mg, 2.01 mmol) was added at 0°C. The mixture, after stirring for 1 h under an argon atmosphere at room temperature, was worked up and crude product purified as in method A to give the alcohol **65** (105 mg; 92% yield). The ^1H nmr spectrum of the resulting alcohol was identical to that reported in method A (*vide supra*).

trans-2-Hydroxymethyl-5-phenyl-4-pentenecarbonitrile (**66**)

A mixture of unsaturated thiolester **46** (326 mg, 1.20 mmol) in absolute ethanol (10 mL) was stirred at 0°C for 10 min under an argon atmosphere. Sodium borohydride (163 mg, 4.29 mmol) was added. After stirring for 55 min at 0°C, the reaction mixture was quenched with ice-cold aqueous saturated ammonium chloride solution. The organic layer was extracted with dichloromethane (4 × 20 mL) and the extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was subjected to silica gel column chromatography (30% ethyl acetate/petroleum ether) to give the alcohol **66** (176 mg; 78% yield): ^1H nmr δ2.10 (br t, 1H, J = 6 Hz, -OH), 2.62 (dd, 2H, J = 8 Hz, J' = 6 Hz, $-\underline{CH_2}-\overset{|}{C}HCN$), 2.91 (dt, 1H, J = 14 Hz, J' = 6 Hz, $-\overset{|}{C}HCN$), 3.86 (dd, 2H, J = 6 Hz, J' = 5 Hz, $-\underline{CH_2}-OH$), 6.20 (dt, 1H, J = 16 Hz, J' = 8 Hz, Ph-CH=$\underline{CH}$-), 6.61 (d, 1H, J = 16 Hz, Ph-$\underline{CH}$=CH-), and 7.30 (m, 5H, aromatic protons); ir 700-750 (monosubstituted benzene), 1600 (aromatic), 2260 (C≡N), 3040-3100 (aromatic), and 3400-3500 cm^{-1} (-OH); ms M^+ 187.1004 (calcd. for $C_{12}H_{13}NO$: 187.0997).

2-Hydroxymethyl-4-methylpentanecarbonitrile (**67**)

A mixture of α,β-unsaturated cyanothiolester **47** (302 mg, 1.43 mmol) and sodium borohydride (80 mg, 2.11 mmol) in absolute ethanol (10 mL) was stirred under an argon atmosphere at 0°C for 15 min. The mixture was poured into ice-cold saturated ammonium chloride solution and extracted with chloroform (4 × 10 mL). The extracts were washed again with saturated sodium chloride solution, combined, dried, filtered, and concentrated. Flash column chromatography on residue (30% ethyl acetate/petroleum ether) gave pure colorless oil of the alcohol **67** (152 mg; 84% yield): ^1H nmr δ0.95 (d, 3H, J = 7 Hz, isopropyl $-CH_3$), 1.02 (d, 3H, J = 4 Hz, isopropyl $-CH_3$), 1.30-2.00 (m, 3H, overlapped between $-\underline{CH_2}-\overset{|}{C}HCN$ and $(CH_3)_2\underline{CH}$- protons), 2.35 (br s, 1H, -OH, disappeared upon D_2O

exchange), 2.88 (ddt, 1H, J = 10.5 Hz, J' = J" = 6 Hz, -$\overset{|}{C}$HCN), and 3.80 (br d, 2H, J = 7 Hz, -$\underline{CH_2}$OH); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+ 127.0986 (calcd. for $C_7H_{13}NO$: 127.0997).

2-Cyclohexyl-2-hydroxymethylethanecarbonitrile (**68**)

To a solution of α,β-unsaturated thiolester **48** (386 mg, 1.63 mmol) in absolute ethanol (10 mL) was added sodium borohydride (193 mg, 5.08 mmol). After the mixture had been stirred for 30 min at 0°C under an argon atmosphere, it was poured into ice-cold saturated ammonium chloride solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with sodium chloride aqueous solution, combined, dried, filtered, and concentrated. The resulting crude alcohol was purified by flash column chromatography (50% ethyl acetate/skelly B) to afford the pure alcohol **68** (244 mg; 98% yield): ^{1}H nmr δ1.22-2.00 (m, 11H, cyclohexyl protons), 2.65 (td, 1H, J = J' = 6 Hz, -$\overset{|}{C}$HCN), and 3.86 (dd, 2H, J = 7 Hz, J' = 1.5 Hz, -$\underline{CH_2}$-OH); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+ 153.1153 (calcd. for $C_9H_{15}NO$: 153.1154).

2-Methylidenedecanecarbonitrile (**69**)

A. From compound **61** *via* a mesylate

To a solution of cyanoalcohol **61** (103 mg, 0.56 mmol) in freshly distilled chloroform (5 mL) was added methanesulfonyl chloride (0.13 mL, 1.68 mmol), and the mixture stirred for 5 min at 0°C under an argon atmosphere. Triethylamine (0.39 mL, 2.80 mmol) was added slowly *via* a syringe and mixture continued stirring for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure and resulting yellow solids redissolved in benzene (5 mL). A 0.5 mL of 1,8-diazabicyclo-(5.4.0)undec-7-ene (DBU) was added and the mixture heated at reflux under an argon atmosphere for 4 h. The mixture was then cooled to room temperature, poured into 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed successively with aqueous saturated sodium carbonate solution, saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was purified by flash column chromatography (10% petroleum ether in benzene) to give the olefin **69** (86.62 mg; 94% yield): ^{1}H nmr δ0.90 (t, 3H, J = 6 Hz, CH_3-), 2.25 (br t, 2H, J = 7 Hz, $-CH_2-\overset{|}{C}=$), 5.65 (dd, 1H, J = J' = 1 Hz, $C=C\underline{H}H$), and 5.80 (d, 1H, J = 1 Hz, C=CH*H*); ir 1630 (C=C) and 2130 cm^{-1} (C≡N); ms M$^+$ 165.1477 (calcd. for $C_{11}H_{19}N$: 165.1517). *Anal.* Calcd. for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 80.21, H, 11.59, N, 8.09.

B. *From compound **61** by direct dehydration using dicyclohexylcarbodiimide (DCC)*

A solution of cyanoalcohol **61** (128 mg, 0.70 mmol) and dicyclohexylcarbodiimide (DCC) (217 mg, 1.05 mmol) in the presence of a catalytic amount of copper(I) chloride in dry ether (5 mL) was heated at reflux for 24 h under an argon atmosphere. The mixture was then cooled to room temperature, filtered through a sintered glass funnel (4-8 µ), and the filtrate evaporated. The residue was dissolved in 10% benzene in petroleum ether, filtered, and concentrated. The resulting crude product was then chromatographed on silica gel (flash column chromatography) using 30% petroleum ether in benzene as an eluent to give a colorless oil of the olefin **69** (98.39 mg; 85% yield). The ^{1}H nmr spectrum was consistent with that obtained from two-step method A (*vide supra*).

2-Methylidene-5-phenyl-*trans*-4-pentenecarbonitrile (**70**)

A mixture of cyanoalcohol **66** (178 mg, 0.95 mmol) and

DCC (294 mg, 1.43 mmol) in the presence of a trace amcunt of copper(I) chloride in dry ether (10 mL) was heated at reflux for 15 h under an argon atmosphere. The mixture was cooled to room temperature, filtered through a sintered glass funnel (4-8 μ) and filtrate concentrated in vacuo. The residue obtained was dissolved in petroleum ether, filtered, and filtrate concentrated. The crude product was then purified by flash column chromatography (10% ethyl acetate/petroleum ether) to give the olefin **70** (110 mg; 69% yield): ^1H nmr δ3.16 (dd, 2H, J = 7 Hz, J' = 2 Hz, $-CH_2-\overset{|}{C}=$), 5.82 (br d, 1H, $J_{w_{1/2}}$ = 3 Hz, C=C$\underline{H}$H), 5.94 (br d, 1H, $J_{w_{1/2}}$ = 3 Hz, C=CH$\underline{H}$), 6.16 (dt, 1H, J = 16 Hz, J' = 8 Hz, Ph-CH=C$\underline{H}$-CH_2-), 6.56 (d, 1H, J = 16 Hz, PhC$\underline{H}$=CH-), and 7.30 (m, 5H, aromatic protons); ir 1600-1630 (aromatic), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M$^+$ 169.0885 (calcd. for $C_{12}H_{11}N$: 169.0891). Anal. Calcd. for $C_{12}H_{11}N$: C, 85.21; H, 6.51; N, 8.28. Found: C, 85.26; H, 6.65; N, 8.16.

2-Cyclohexyl-2-methylideneethanecarbonitrile (71)

A mixture of cyanoalcohol **68** (231 mg, 1.51 mmol) and DCC (466 mg, 2.26 mmol) in the presence of a trace amount of copper(I) chloride in freshly distilled ether (10 mL) was heated at reflux under an argon atmosphere for 18.5

h. The reaction mixture was cooled to room temperature and filtered through sintered glass funnel (4-8 μ) and filtrate concentrated. The residue was dissolved in n-pentane, filtered, and concentrated. Column chromatography of the crude product (10% ethyl acetate/petroleum ether) on silica gel gave pure acrylonitrile derivative **71** (72 mg; 80% yield): ^{1}H nmr δ5.71 (dd, 1H, J = 2 Hz, J' = 1 Hz, $C{=}C\underline{H}H$), and 5.81 (d, 1H, J = 2 Hz, $C{=}CH\underline{H}$); ir 1620 (C=C) and 2220 cm^{-1} (C≡N); ms M$^+$ 135.1044 (calcd. for $C_9H_{13}N$: ([illegible]35.1048). Anal. Calcd. for $C_9H_{13}N$: C, 80.00; H, 9.6[illegible] N, 10.37. Found: C, 79.80; H, 9.84; N, 10.38.

3-Methyl-2-methylidenenonanecarbonitrile (72)

Cyanoalcohol **65** (160 mg, 0.87 mmol) was dissolved in freshly distilled ether (10 mL) followed by addition of DCC (268 mg, 1.30 mmol) and a trace amount of copper(I) chloride. The mixture was heated at reflux for 18 h under an argon atmosphere, cooled to room temperature and filtered through a sintered glass funnel (4-8 μ). The filtrate, after concentration was subjected to molecular distillation using a Kugelrohr apparatus at 60°C (oven temperature)/0.5 torr followed by flash column chromatography (50% benzene/petroleum ether) to give a colorless oil of the olefin **72** (101 mg; 70% yield): ^1H nmr δ0.90 (br t, 3H, J = 7 Hz, $C\underline{H}_3-CH_2-$), 1.18 (d, 3H, J = 8 Hz, $\underline{CH}_3-\overset{|}{C}H-$), 2.36 (m, 1H, $CH_3-\overset{|}{C}\underline{H}-$), 5.70 (d, 1H, J = 2 Hz, $C{=}C\underline{H}H$), and 5.80 (d, 1H, J = 2 Hz, $C{=}CH\underline{H}$); ir 1630 (C=C) and 2260 cm^{-1} (C≡N); ms M^+-57 108.0810 (calcd. for $C_7H_{10}N$: 108.0813). Anal. Calcd. for $C_{11}H_{19}N$: C, 79.93; H, 11.59; N, 8.48. Found: C, 79.98; H, 11.47; N, 8.25.

2-Methylidene-3-phenylpropanecarbonitrile (73)

A solution of cyanoalcohol **59** (57 mg, 0.35 mmol) and DCC (109 mg, 0.53 mmol) in dry ether (5 mL) in the presence of a trace amount of copper(I) chloride, was heated at reflux under an argon atmosphere for 19 h. The mixture was cooled to room temperature, diluted with ether, and filtered through a sintered glass funnel (4-8 μ). The filtrate was evaporated and residue dissolved in 10% benzene/petroleum ether, filtered, and concentrated. The crude product was then purified on silica gel column chromatography (50% benzene/petroleum ether) to give the acrylonitrile derivative **73** (26.15 mg; 52% yield): ^1H nmr δ3.56 (s, 2H, $PhCH_2-$), 5.69 (br s, 1H, $C{=}C\underline{H}H$), 5.91 (d, 1H, J = 1 Hz, $C{=}CH\underline{H}$), and 7.30 (m, 5H, aromatic protons); ir 700-730 (monosubstituted benzene), 945 (vinyl), 1620 (C=C), 2240 (C≡N), and 3040-3100 cm^{-1} (aromatic); ms M^+

143.0733 (calcd. for $C_{10}H_9N$: 143.0735).

3-(t-Butylthiocarbonyl-cyanomethyl)-1-cyclohexanone (**75**)

A. Using 1.0 equiv. of 1,4-diazabicyclo[2.2.2]octane (DABCO) and 0.8 equiv. of 2-cyclohexen-1-one

S-t-butyl cyanothiolacetate (**23**) (500 mg, 3.18 mmol) was dissolved in freshly distilled 1,2-dimethoxyethane (10 mL) and stirred under an argon atmosphere for 10 min at 0°C. Then 1,4-diazabicyclo[2.2.2]octane (357 mg, 3.18 mmol) was added and stirred for another 10 min followed by slow addition of 2-cyclohexen-1-one (0.26 mL, 2.65 mmol). After stirring for 36 h at room temperature, the mixture was poured into ice-cold 1N aqueous hydrochloric acid solution, and extracted with chloroform (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was chromatographed on silica gel (10% ethyl acetate/petroleum ether) to give a diastereomeric mixture of the 1,4-adduct **75** (410 mg; 61% yield) (ca. 1:1 ratio from the ^{1}H nmr spectrum). The following spectral data were recorded on the mixture; ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.45 (d, 1/2 × 1H, J = 6 Hz,

-CHCN, from one isomer), and 3.60 (d, 1/2× 1H, J = 4 Hz, -CHCN, from another isomer); ir ($CHCl_3$) 1677 (thiolester C=O), 1715 (ketone C=O), and 2240 cm^{-1} (C≡N); ms M^+ 253.1137 (calcd. for $C_{13}H_{19}NO_2S$: 253.1136). Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53; O, 12.63; S, 12.65. Found: C, 61.38, H, 7.75; N, 5.28; O, 12.76; S, 12.46.

B. Adduct **75** by refluxing in ether

A mixture of S-t-butyl cyanothiolacetate (**23**) (476 mg, 3.03 mmol), DABCO (339 mg, 3.03 mmol), and 2-cyclohexen-1-one (0.24 mL, 2.53 mmol) in freshly distilled ether (15 mL) was heated at reflux for 35 h under an argon atmosphere. The reaction was cooled to room temperature, worked up, and purified as mentioned in method A. The adduct **75** was obtained in 48% yield (310 mg). The ^1H nmr spectrum was identical to that already reported in method A (vide supra).

C. Using 1.0 equiv. of DABCO and 2.5 equiv. of cyclohexen-1-one

Cyanothiolester **23** (381 mg, 2.42 mmol) was dissolved in distilled 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 5 min. DABCO (271 mg, 2.42 mmol) was added, and after 5 min stirring, 2-cyclohexen-1-one (0.58 mL, 6.05 mmol) was added via a syringe. After stirring for 36 h at room temperature, the reaction mixture was worked up and the crude product purified as in method A to give the Michael adduct **75** (544 mg; 54% yield). The ^1H nmr spectrum was identical to that reported in method A (vide supra).

D. Using 0.5 equiv. of DABCO and 1.5 equiv. of cyclohexen-1-one

Similar procedure was carried out as in method C, using cyanothiolester **23** (300 mg, 1.91 mmol), DABCO (106 mg, 0.96 mmol), and 2-cyclohexen-1-one (0.28 mL, 2.86 mmol) in distilled 1,2-dimethoxyethane (10 mL). Reaction was stirred at room temperature for 8 days under an argon atmosphere. After work-up and purification gave the 1,4-adduct **75** (253 mg; 52% yield). The ^1H nmr spectrum was identical to that found in method A (vide supra).

Further elution, during column chromatography, gave cyanothiolester **23** (48.36 mg; 16% recovery).

E. Using 0.3 equiv. of DABCO and 2.0 equiv. of cyclohexen-1-one

Similar procedure as mentioned in method C was carried out using cyanothiolester **23** (500 mg, 3.18 mmol), DABCO (106 mg, 0.95 mmol) and 2-cyclohexen-1-one (0.61 mL, 6.36 mmol) in distilled 1,2-dimethoxyethane (10 mL). The reaction was carried out for 7 days at room temperature.

The adduct **75** (483 mg; 58% yield) and also cyanothiolester **23** (92.33 mg; 18% recovery) were obtained. The ^{1}H nmr spectrum of **75** was identical to that reported in method A (vide supra).

F. Using sodium hydride as a base in the presence of chlorotrimethylsilane

Cyanothiolester **23** (348 mg, 2.21 mmol) was dissolved in benzene (8 mL) (freshly distilled over lithium aluminum hydride) and stirred at ~5°C under an argon atmosphere for 5 min. Chlorotrimethylsilane (0.22 mL, 1.73 mmol) (freshly distilled over calcium hydride) was added via a syringe followed by 2-cyclohexen-1-one (0.25 mL, 2.56 mmol) and stirred for 10 min. Sodium hydride (50% dispersion in oil; 154 mg, 3.20 mmol) was then added. After stirring for 17 h at room temperature, the reaction was quenched and worked up as in method A and the crude product purified by flash column chromatography (20% ethyl acetate/petroleum ether) followed by molecular distillation using Kugelrohr apparatus (60°C oven temperature at 1 torr) to give the adduct **75** (478 mg; 86% yield). Spectral data in all respect were identical to that previously reported in method A (vide supra).

G. Using sodium hydride as a base in the absence of chlorotrimethylsilane

Cyanothiolester **23** (92 mg, 0.58 mmol) was dissolved in freshly distilled benzene (8 mL) and stirred at ~5°C under an argon atmosphere for 5 min. Sodium hydride (50% dispersion in oil; 28 mg, 0.58 mmol) was added followed by dropwise addition of 2-cyclohexen-1-one (0.07 mL, 0.70 mmol). After stirring for 22 h at room temperature, the mixture was worked up as in method A. After purification on silica gel column chromatography (20% ethyl acetate/petroleum ether) of the crude product, gave the adduct **75** (132 mg; 90% yield). The ^{1}H nmr spectrum was consistent with that reported in method A (vide supra).

3-(t-Butylthiocarbonyl-cyanomethyl)-1-cyclopentanone (**76**)

A. Using DABCO as a base

A mixture of cyanothiolester **23** (497 mg, 3.17 mmol) and DABCO (354 mg, 3.17 mmol) in distilled 1,2-dimethoxyethane (10 mL) was stirred at 0°C for 5 min. 2-Cyclopenten-1-one (217 mg, 2.64 mmol) was added dropwise and mixture stirred for 6 h at room temperature. Ice-cold 1N aqueous hydrochloric acid solution was added and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution and the combined extract was dried, filtered, and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/petroleum ether) to give a diastereomeric mixture (1:1 ratio from ^{1}H nmr integration) of the adduct **76** (230 mg; 36% yield) which formed crystals on standing at room temperature (m.p. 57-60°C). The following spectral data were recorded on the mixture: ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.60 (d, 1/2× 1H, J = 7 Hz, $-\overset{|}{C}HCN$, from one isomer), and 3.67 (d, 1/2× 1H, J = 5 Hz, $-\overset{|}{C}HCN$, from another isomer); ir ($CHCl_3$) 1679 (thiolester C=O), 1747 (ketone C=O), and 2250 cm^{-1} ($C\equiv N$); ms M^+ 239.0980 (calcd. for $C_{12}H_{17}NO_2S$: 239.0980).

B. *Using sodium hydride as a base in the presence of chlorotrimethylsilane*

Cyanothiolester **23** (320 mg, 2.03 mmol) was dissolved in freshly distilled benzene (10 mL) and stirred at ~5°C under an argon atmosphere for 5 min. 2-Cyclopenten-1-one (0.14 mL, 1.69 mmol) was added followed by chlorotrimethylsilane (0.23 mL, 1.82 mmol) *via* a syringe. After 10 min stirring, sodium hydride (50% disperson in oil; 136 mg, 2.84 mmol) was added and the mixture stirred for 3 h at ~10°C. The reaction mixture was poured into ice-cold 5% aqueous sulfuric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with sodium chloride saturated solution, combined, concentrated, and dissolved in methanol (30 mL). Aqueous potassium fluoride solution (0.5 g/15 mL) was added and shaken for 10 min in a separatory funnel. The mixture was extracted with dichloromethane (4 × 20 mL), and the combined extract dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give a mixture of diastereomers (1:1 ratio from ^{1}H nmr integration) of **76** (406 mg, 100% yield). The ^{1}H nmr spectrum was identical to that already reported in method A (vide supra).

C. Using sodium hydride as a base in the absence of chlorotrimethylsilane

Cyanothiolester **23** (102 mg, 0.65 mmol) was dissolved in freshly distilled benzene (10 mL) and cooled to 5°C. 2-Cyclopenten-1-one (0.05 mL, 0.54 mmol) was added and the mixture stirred for 10 min under an argon atmosphere. Sodium hydride (50% dispersion in oil; 44 mg, 0.91 mmol) was added and the reaction stirred for 3.5 h at ~15°C. Aqueous 1N hydrochloric acid solution was added and extracted with dichloromethane (4 × 20 mL), and the extracts washed again with saturated sodium chloride solution. The extracts were combined, dried, filtered, and concentrated. The residue was purified by flash column chromatography (30% ether/petroleum ether) to give the adduct **76** (121 mg; 93% yield). Its ^{1}H nmr spectrum was identical to that reported in method A (vide supra).

5-(t-Butylthiocarbonyl-cyanomethyl)-tricyclo[5.2.1.0^{2,6}]deca-8-ene-3-one (**78**)

A. Using DABCO as a base*

Cyanothiolester **23** (548 mg, 3.49 mmol) was dissolved in distilled 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 10 min. DABCO (389 mg, 2.66 mmol) was added followed by addition of tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one **77** (341 mg, 2.33 mmol). After stirring for 25 h at room temperature the reaction was quenched with 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with sodium chloride solution, dried, filtered, and concentrated. The crude product was purified by flash column chromatography (10% ethyl

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*When this reaction was repeated using tetrahydrofuran as a solvent, an 80% yield of the adduct **78** was obtained.

acetate/petroleum ether) to give a diastereomeric mixture of Micheal adduct **78** (552 mg; 78% yield). One recrystallization from 30% benzene-petroleum ether gave light yellow crystals (m.p. 81-85°C). The following spectral results were recorded on a mixture of diastereomers: ^{1}H nmr δ1.52 and 1.54 (both s, total 9H, $-C(CH_3)_3$), 3.54, 3.64 (both d, 1H each, J = 10 Hz each, $-\overset{|}{C}HCN$), and 6.20 (br s, 2H, $-\underline{CH}=\underline{CH}-$); ir ($CHCl_3$) 1675 (thiolester C=O), 1730 (ketone C=O), 2240 (C≡N), and 3060 cm^{-1} (C=C); ms M^+ 303.1292 (calcd. for $C_{17}H_{21}NO_2S$: 303.1293). <u>Anal.</u> Calcd. for $C_{17}H_{21}NO_2S$: C, 67.30; H, 6.98; N, 4.62; O, 10.55; S, 10.57. Found: C, 67.48; H, 7.15; N, 4.48; O, 10.47; S, 10.31.

B. <u>Using 4-dimethylaminopyridine as a base</u>

Cyanothiolester **23** (400 mg, 2.55 mmol) was dissolved in freshly distilled 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 10 min. 4-Dimethylaminopyridine (249 mg, 2.04 mmol) was added followed by addition of dienone **77** (248 mg, 1.70 mmol). The mixture was stirred for 26 h at room temperature, quenched with ice-cold 1N aqueous hydrochloric acid solution, and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The residue was purified on silica gel column chromatography (10% ethyl acetate/petroleum ether to give a diastereomeric mixture of Michael adduct **78** (383 mg; 74% yield). The ^{1}H nmr spectrum was found to be identical with that previously reported in method A (vide supra).

C. Using sodium hydride as a base in the presence of chlorotrimethylsilane

Cyanothiolester **23** (275 mg, 1.74 mmol) was dissolved in freshly distilled benzene (8 mL) and stirred at ~5°C for 5 min under an argon atmosphere. Chlorotrimethylsilane (0.20 mL, 1.56 mmol) was added followed by addition of dienone **77** (328 mg, 2.25 mmol) and mixture stirred for 10 min. Sodium hydride (50% dispersion in oil; 125 mg, 2.61 mmol) was added and the reaction mixture stirred for 23 h at room temperature. Ice-cold 1N aqueous hydrochloric acid solution was added and the mixture extracted with dichloromethane (4 × 20 mL). The extracts were washed again with saturated sodium chloride solution. The combined extract was concentrated, dissolved in methanol (30 mL), and shook with aqueous potassium fluoride solution (0.5 g/15 mL) for 10 min in a separatory funnel. The organic layer was extracted with dichloromethane (4 × 20 mL) and the combined extract dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to afford the Michael adduct **78** (442 mg; 84% yield). The ^{1}H nmr spectrum was found to be consistent with that previously reported in method A (vide supra).

D. Using sodium hydride as a base in the absence of chlorotrimethylsilane

Cyanothiolester **23** (100 mg, 0.64 mmol) was dissolved in freshly distilled benzene (10 mL) and cooled to 5°C. Sodium hydride (50% dispersion in oil; 46 mg, 0.96 mmol) was added and mixture stirred for 10 min under an argon atmosphere. Dienone **77** (112 mg, 0.77 mmol) was added and continued stirring for 25 h at room temperature. The reaction was quenched with 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was purified by flash column chromatography (20% ether/petroleum ether) to afford the Michael adduct **78** (95 mg; 49% yield). The ^{1}H nmr spectrum was consistent with that already reported in method A (vide supra).

S-*t*-Butyl 2-cyano-3-methyl-5-oxo-thiolhexanoate (**79**)

A. Using DABCO as a base

Cyanothiolester **23** (503 mg, 3.20 mmol) was dissolved in freshly distilled 1,2-dimethoxyethane (10 mL) and stirred under an argon atmosphere at 0°C for 5 min. DABCO (358 mg, 3.20 mmol) was added and stirred for 10 min followed by slow addition of 3-penten-2-one (0.78 mL, 8.00 mmol). The mixture was stirred at room temperature for 48 h, after which was quenched with ice-cold 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with sodium chloride solution, combined, dried, filtered, and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/petroleum ether) to give a diastereomeric mixture of the adduct **79** (285 mg; 37% yield) (*ca.* 1:2 ratio from ^1H nmr integration). Single recrystallization from 10% benzene-petroleum ether gave pure needle-shaped crystals (m.p. 42-43°C). The following spectral data were recorded on the mixture. The following signals are assigned for the major isomer: ^1H nmr δ1.07 (d, 3H, J = 6 Hz, $\underline{CH_3}-\overset{|}{C}H-$), 1.52 (s, 9H, $-C(CH_3)_3$), 2.28 (s, 3H, CH_3-CO-), and 3.90 (d, 1H, J = 4 Hz, $-\overset{|}{C}HCN$); the following signals are assigned for the minor isomer: ^1H

nmr δ1.13 (d, 3H, J = 6 Hz, $\underline{\mathrm{CH_3}}\text{-}\overset{|}{\mathrm{C}}\mathrm{H}\text{-}$), 1.49 (s, 9H, $-\mathrm{C(CH_3)_3}$), 2.12 (s, 3H, $\mathrm{CH_3\text{-}CO\text{-}}$), and 3.52 (d, J = 6 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HCN}$); ir 1685 (thiolester C=O), 1725 (ketone C=O), and 2260 $\mathrm{cm^{-1}}$ (C≡N); ms $\mathrm{M^+}$ 241.1138 (calcd. for $C_{12}H_{19}NO_2S$: 241.1136). Anal. Calcd. for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.94; N, 5.81; O, 13.27; S, 13.26. Found: C, 59.64; H, 7.95; N, 5.71; O, 13.16; S, 13.09.

B. Using sodium hydride as a base in the presence of chlorotrimethylsilane

Cyanothiolester **23** (271 mg, 1.73 mmol) was dissolved in freshly distilled benzene (8 mL) and stirred at 5°C under an argon atmosphere for 5 min. Chlorotrimethylsilane (0.20 mL, 1.56 mmol) was added followed by slow addition of 3-penten-2-one (0.14 mL, 1.43 mmol). Sodium hydride (50% dispersion in oil; 124 mg, 2.60 mmol) was added and stirred for 8 h at 10°C. The mixture was poured into ice-cold 1N aqueous hydrochloric acid solution, extracted with dichloromethane (4 × 20 mL) and extracts washed again with saturated solution of sodium chloride. The extracts were combined, concentrated, and dissolved in methanol (30 mL). Aqueous potassium fluoride solution (0.5 g/15 mL) was added and shook for 10 min in a separatory funnel. The organic layer was extracted with dichloromethane (4 × 20 mL) and combined extract dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give the Michael adduct **79** (216 mg; 62% yield). Spectral results of all respects were identical to that reported in method A (vide supra).

C. Adduct **79** by reaction at -20°C

Cyanothiolester **23** (209 mg, 1.33 mmol) was dissolved in freshly distilled toluene (8 mL) and stirred at -20°C under an argon atmosphere for 10 min. Chlorotrimethylsilane (0.15 mL, 1.20 mmol) was added followed by 3-penten-2-one (0.16 mL, 1.60 mmol) and mixture stirred for another 10 min. Sodium hydride (50% dispersion in oil; 96 mg, 2.00 mmol) was added and reaction stirred for 27 h at -20°C. The reaction mixture was worked up and crude product purified as mentioned in method B (vide supra), to give the adduct **79** (221 mg; 68% yield). The ^{1}H nmr spectrum was identical to that previously reported in method A (vide supra).

D. Using sodium hydride as a base in the absence of chlorotrimethylsilane

Cyanothiolester **23** (101 mg, 0.64 mmol) was dissolved in toluene (8 mL) (freshly distilled over calcium hydride) and stirred at -20°C for 5 min. 3-Penten-2-one (0.08 mL, 0.77 mmol) was added slowly _via_ a syringe and stirred for another 10 min. Sodium hydride (50% dispersion in oil; 50 mg, 0.96 mmol) was added and mixture stirred for [illegible] h at -20°C under an argon atmosphere. Then the reaction was poured into ice-cold 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was purified by flash column chromatography (30% ether/petroleum ether) to afford the Michael adduct **79** (89.17 mg; 58% yield). Its ^1H nmr spectrum was identical to that already reported in method A (_vide supra_).

3-(_t_-Butylthiocarbonyl-cyanoethyl)-2-norbornanone (**80**) and bis-adduct (**81**)

A. _Using DABCO as a base_

Cyanothiolester **23** (400 mg, 2.55 mmol) was dissolved in distilled 1,2-dimethoxyethane (10 mL) at 0°C. DABCO (229 mg, 2.04 mmol) was added and stirred for 10 min under an argon atmosphere. 3-Methylene-2-norbornanone (0.21 mL, 1.70 mmol) was added _via_ a syringe and solution stirred for 46 h at room temperature. The mixture was poured into aqueous 1N hydrochloric acid solution, extracted with dichloromethane (4 × 20 mL) and extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was chromatographed on silica gel (10% ethyl acetate/petroleum ether) to give a yellow oil of the 1,4-adduct **80** (53,40 mg; 11% yield) as a mixture of diastereomers, which crystallized on standing at room temperature (m.p. 65-69°C). The following spectral data were recorded on the mixture: ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.68 (dd, 1/2× 1H, J = 8 Hz, J' = 6 Hz, $-\overset{|}{C}HCN$, from one isomer), and 4.00 (dd, 1/2× 1H, J = 9 Hz, J' = 5 Hz, $-\overset{|}{C}HCN$, from another isomer); ir 1675 (thiolester C=O), 1740 (ketone C=O), and 2240 cm^{-1} (C≡N); ms M$^+$ 279.1290 (calcd. for $C_{15}H_{21}NO_2S$: 279.1293). Anal. Calcd. for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.02; O, 11.46; S, 11.45. Found: C, 64.55; H, 7.63; N, 4.93; O, 11.46; S, 11.23.

Further elution with the same solvent system gave yellow crystals (m.p. 58-60°C) corresponding to the bis-adduct **81** (198 mg; 14% yield): ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), and 1.7-3.1 (m, 21H, methine and methylene protons of two bicyclic rings); ir (CHCl$_3$) 1670 (thiolester C=O) and 1740 (2× ketone C=O); ms M$^+$ 401.2020 (calcd. for $C_{23}H_{31}NO_3S$: 401.2025).

B. Using 4-dimethylaminopyridine as a base

To a solution of cyanothiolester **23** (400 mg, 2.55 mmol) in distilled 1,2-dimethoxyethane (10 mL), was added 3-methylene-2-norbornanone (0.21 mL, 1.70 mmol) and the mixture stirred for 10 min under an argon atmosphere. 4-Dimethylaminopyridine (248 mg, 2.04 mmol) was added and the reaction mixture stirred for 24 h at room temperature. After work-up and purification as described in method A, the 1,4-adduct **80** (64.27 mg; 14% yield) was obtained. The ^1H nmr spectrum was found to be identical to that reported in method A (vide supra).

C. Using sodium hydride as a base in the presence of chlorotrimethylsilane

To a solution of cyanothiolester **23** (230 mg, 1.46 mmol) in freshly distilled benzene (10 mL) was added chlorotrimethylsilane (0.17 mL, 1.31 mmol) followed by addition of 3-methylene-2-norbornanone (0.15 mL, 1.21 mmol). The mixture was stirred for 10 min at 7°C under an argon atmosphere and sodium hydride (50% dispersion in oil; 105 mg, 2.19 mmol) was added. The reaction mixture was stirred for 2 h at 7°C. It was then poured into aqueous 5% sulfuric acid solution and extracted with dichloromethane (4 × 20 mL) and extracts washed again with aqueous sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude product was subjected to column chromatography (20% ethyl acetate/petroleum ether) to give an oil of adduct **80** (213 mg; 63% yield) which crystallized as white crystals on standing at room temperature. All spectral data, i.e. ^{1}H nmr, ir, and mass spectrum respectively, were found to be consistent with those already reported in method A (*vide supra*).

D. *Using sodium hydride as a base in the absence of chlorotrimethylsilane*

Cyanothiolester **23** (194 mg, 1.23 mmol) was dissolved in freshly distilled benzene (8 mL) and cooled to 7°C. 3-Methylene-2-norbornanone (0.12 mL, 1.02 mmol) was added *via* a syringe and stirred for 10 min under an argon atmosphere. Sodium hydride (50% dispersion in oil; 88 mg, 1.85 mmol) was added and the mixture stirred for 3 h at 7°C to room temperature. The reaction mixture was worked up as in method A and purified by flash column chromatography (20% ethyl acetate/petroleum ether) to give the 1,4-adduct **80** (202 mg; 71% yield). ^{1}H nmr spectrum was identical to that reported previously in method A (*vide supra*).

3-(Cyanoethylthiocarbonylmethyl)-1-cyclohexanone (82)*

Ethyl cyanothiolester **24** (402 mg, 3.12 mmol) was dissolved in distilled 1,2-dimethoxyethane (10 mL) and stirred at 0°C under an argon atmosphere for 5 min. 4-Dimethylaminopyridine (380 mg, 3.11 mmol) was added and after another 10 min stirring, 2-cyclohexen-1-one (0.20 mL, 2.08 mmol) was added _via_ a syringe. After the reaction mixture had been stirred for 19 h at room temperature, it was poured into ice-cold 1N aqueous hydrochloric acid solution and extracted with dichloromethane (4 × 20 mL). Extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to afford a diastereomeric mixture of the 1,4-adduct **82** (119 mg; 26% yield). The following spectral data were recorded on the mixture of diastereoisomers: ^{1}H nmr δ1.34 (t, 3H, J = 8 Hz, $\underline{CH_3}$-CH_2-), 3.02 (q, 2H, J = 6 Hz, CH_3-$\underline{CH_2}$-), 3.62 (d, 1/2× 1H, J = 5 Hz, $-\overset{|}{C}H-CN$, from one isomer), and 3.74 (d, 1/2×

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[*] For the preparation of this compound, other conditions were also used. For details see Table X.

1H, J = 4 Hz, $-\overset{|}{C}HCN$, from another isomer); ir 1675 (thiolester C=O), 1710 (ketone C=O), and 2240 cm^{-1} (C≡N); ms M$^+$ 225.0824 (calcd) for $C_{11}H_{15}NO_2S$: 225.08230.

6-Methyl-3-(*t*-butylthiocarbonyl-cyanomethyl)-1-cyclohexanone (**83**)

A. In the presence of chlorotrimethylsilane

Cyanothiolester **23** (293 mg, 1.86 mmol) was dissolved in freshly distilled benzene (10 mL) and cooled to 7°C. Chlorotrimethylsilane (0.21 mL, 1.67 mmol) was added followed by slow addition of 6-methyl-2-cyclohexen-1-one (245 mg, 2.23 mmol) and the mixture stirred for 5 min under an argon atmosphere. Sodium hydride (50% dispersion in oil; 134 mg, 2.79 mmol) was added and continued stirring for 16 h at room temperature. Aqueous 5% sulfuric acid solution (10 mL) was added and extracted with dichloromethane (4 × 20 mL) and extracts washed with saturated sodium chloride solution. The extracts were combined, concentrated, and dissolved in methanol (30 mL), followed by treatment with aqueous potassium fluoride solution (0.5 g/15 mL). Organic layer was extracted again with dichloromethane (4 × 20 mL) and extracts combined, dried, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave the 1,4-adduct **83** (408 mg; 82% yield) as a single isomer, which crystallized on refrigeration: ^{1}H nmr δ1.06 (d, 3H, J = 7 Hz, $\underline{\mathrm{CH}}_3$-$\overset{|}{\mathrm{C}}$H-), 1.54 (s, 9H, -C$(CH_3)_3$), and 3.44 (d, 1H, J = 5.5 Hz, -$\overset{|}{\mathrm{C}}$HCN); ^{13}C nmr δ209.2, 190.4, 114.9, 51.5, 50.6, 45.6, 44.5, 40.4, 33.4, 29.5, 27.9, 14.1; ir ($CHCl_3$) 1680 (thiolester C=O), 1710 (ketone C=O), and 2260 cm^{-1} (C≡N); ms M$^+$ 267.1290 (calcd. for $C_{14}H_{21}NO_2S$: 267.1293). Anal. Calcd. for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; O, 11.98; S, 11.97. Found: C, 62.72; H, 8.10; N, 5.12; O, 12.13; S, 11.59.

B. Adduct **83** in the absence of chlorotrimethylsilane

Cyanothiolester **23** (101 mg, 0.64 mmol) was dissolved in freshly distilled benzene (10 mL) and chilled to 5°C. Sodium hydride (50% dispersion in oil; 46 mg, 0.96 mmol) was added and the mixture stirred for 10 min under an argon atmosphere. 6-Methyl-2-cyclohexen-1-one (85 mg, 0.77 mmol) was added and the reaction stirred for 14 h at room temperature. Ice-cold 1N aqueous hydrochloric acid solution was added and extracted with dichloromethane (4 × 20 mL), followed by washing the extracts with saturated sodium chloride solution. Extracts were combined, dried, filtered, and concentrated. Flash column chromatography on the residue using 20% ethyl acetate in petroleum ether as an eluent gave the 1,4-adduct **83** (84 mg; 49% yield). The ^{1}H nmr spectrum was identical to that already reported in method A (vide supra).

3-(t-Butylthiocarbonyl-cyanomethyl)-4,4-dimethyl-1-cyclohexanone (84)

A. In the presence of chlorotrimethylsilane

Cyanothiolester **23** (282 mg, 1.79 mmol) was dissolved in freshly distilled benzene (10 mL) and cooled to 5°C. Chlorotrimethylsilane (0.20 mL, 1.61 mmol) was added followed by 4,4-dimethyl-2-cyclohexen-1-one (270 mg, 2.15 mmol) and the mixture stirred for 15 min under an argon atmosphere. Sodium hydride (50% dispersion in oil; 130 mg, 2.69 mmol) was added and reaction continued for 22 h at room temperature. Aqueous sulfuric acid solution was added and the resulting mixture was extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined and concentrated. The residue was dissolved in methanol (30 mL) and treated with aqueous potassium fluoride solution (0.5 g/15 mL) for 10 min. The organic layer was extracted with dichloromethane (4 × 20 mL), extracts combined, dried, filtered, and concentrated. Column chromatography of the residue on silica gel (20% ethyl acetate/petroleum ether) gave a colorless oil (which formed crystals on standing), of the adduct **84** (365 mg; 73% yield) as a single isomer. One recrystallization from 10% benzene in petroleum ether gave pure crystals (m.p. 74-77°C): ^1H nmr δ1.14, 1.22 (both s, 3H each, gem-dimethyl group), 1.52 (s, 9H, $-C(CH_3)_3$), and 3.74 (d, 1H, $J = 2$ Hz, $-\overset{|}{C}HCN$); ^{13}C nmr δ208.3, 191.2, 115.4, 50.6, 46.8, 46.6, 40.1, 37.7, 33.4, 29.5, 28.9, 19.9; ir 1680 (thiolester C=O), 1710 (ketone C=O), and 2250 cm^{-1} (C≡N); ms M^+ 281.1444 (calcd. for $C_{15}H_{23}NO_2S$: 281.1449). Anal. Calcd. for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; O, 11.38; S, 11.37. Found: C, 63.82; H, 8.26; N, 4.93; O, 11.54; S, 11.35.

B. Adduct **84** in the absence of chlorotrimethylsilane

To a solution of cyanothiolester **23** (101 mg, 0.64 mmol) in freshly distilled benzene (8 mL) at 5°C, was added sodium hydride (50% dispersion in oil; 46 mg, 0.96 mmol). After stirring for 10 min under an argon atmosphere, 4,4-dimethyl-2-cyclohexen-1-one (96 mg, 0.77 mmol) was added slowly as a solution in benzene (2 mL). The mixture was stirred for 25 h at room temperature, quenched with 1N aqueous hydrochloric acid solution, and extracted with dichloromethane (4 × 20 mL). The extracts were washed again with sodium chloride solution, combined, dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel (20% ethyl acetate/petroleum ether) afforded the 1,4-adduct **84** (82.19 mg; 46% yield). The ^{1}H nmr spectrum was found to be identical with that obtained from method A (*vide supra*).

S-*t*-Butyl 2-cyano-5-oxo thiolhexanoate (**85**) and S-*t*-butyl 3-acetyl-1-cyano-4-hydroxy-4-methylcyclohexanethiocarboxylate (**86**)*

Cyanothiolester **23** (254 mg, 1.62 mmol) was dissolved in distilled benzene (10 mL) and cooled to 7°C. Methyl vinyl ketone (0.11 mL, 1.35 mmol) was added slowly followed by chlorotrimethylsilane (0.19 mL, 1.46 mmol) and the mixture stirred for 15 min under an argon atmosphere. Sodium hydride (50% dispersion in oil; 115 mg, 2.43 mmol) was added and mixture stirred for another 3 h at ~10°C. Ice-cold 1N aqueous hydrochloric acid

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*Repeated reactions at -40°C (34 h), -60°C (44 h) using toluene (distilled over calcium hydride) afforded even poorer yields of 38% and 20% respectively together with the formation of 19% and 35% yields of dimeric material **86**.

solution was added and extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The residue was purified on silica gel column chromatography using 20% ethyl acetate in petroleum ether to give the 1,4-adduct **85** (148 mg; 48% yield): ^1H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 2.14 (s, 3H, CH_3-CO-), 2.63 (t, 2H, J = 7 Hz, $-CH_2CO-$), and 3.62 (dd, 1H, J = 8 Hz, J' = 6 Hz, -CHCN); ir 1685 (thiolester C=O), 1718 (ketone C=O), and 2250 cm^{-1} (C≡N); ms M$^+$ 227.0975 (calcd. for $C_{11}H_{17}NO_2S$: 227.0980).

Further elution with 30% ethyl acetate/petroleum ether gave the cyclic dimeric compound as a mixture of diastereomers **86** (62 mg; 8% yield). The following ^1H nmr was attributed to the major compound: ^1H nmr δ1.18 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$HOH), 1.50 (s, 9H, $-C(CH_3)_3$), and 2.17 (s, 3H, CH_3CO-); the following ^1H nmr was attributed to the minor compound: ^1H nmr δ1.25 (s, 3H, $\underline{CH_3}$-$\overset{|}{C}$HOH), 1.52 (s, 9H, $-C(CH_3)_3$), and 2.28 (s, 3H, CH_3CO-); ir 1680 (thiolester C=O), 1710 (ketone C=O), 2240 (C≡N), and 3500 cm^{-1} (-OH); ms M$^+$ 297.1391 (calcd. for $C_{15}H_{23}NO_3S$: 297.1399).

Transketalization reactions of ketocyanothiolesters

The reactions were carried out using the general procedure illustrated below with ketone **75**. All the reactions were found to be complete within 7 to 24 h. The crude products, without purification, were used directly for the subsequent reductions.

3-(*t*-Butylthiocarbonyl-cyanomethyl)-1,1-ethylenedioxo cyclohexane (**88**)

Ketone **75** (501 mg, 1.98 mmol) was dissolved in dry benzene (40 mL) and ethylene glycol (1.23 g, 19.8 mmol) and *p*-toluenesulfonic acid monohydrate (36.10 mg, 0.198 mmol) were added. The reaction flask was fitted with a Dean Stark water separator charged with type 3 Å molecular sieve in the take-off arm. The reaction mixture was heated at reflux for 7 h, then cooled to room temperature. Saturated aqueous bicarbonate solution (10 mL) was added and the resulting mixture extracted with dichloromethane (4 × 20 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered, and concentrated to afford a crude product **88** (596 mg). The following spectral data were recorded on the crude product without further purification: ^{1}H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.45, 3.49 (both d, 1H each, J = 7 Hz, J' = 6 Hz, $-\overset{|}{C}HCN$), and 3.95 (br s, 4H, $-O-CH_2CH_2-O-$); ir

($CHCl_3$) 1050-1100 (C-O), 1678 (C=O), and 2240 cm^{-1} ($C\equiv N$); ms M^+ 297.1409 (calcd. for $C_{15}H_{23}NO_3S$: 297.1399). Anal. Calcd. for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.80; N, 4.71; O, 16.15; S, 10.76. Found: C, 60.52; H, 7.76; N, 4.65; O, 16.21; S, 10.88.

The ketals **89-92** were shown to have the following spectral data. Compound **89**: ^1H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.60 (d, 1/2× 1H, J = 7 Hz, $-\overset{|}{C}HCN$, from one isomer), 3.67 (d, 1/2× 1H, J = 4 Hz, $-\overset{|}{C}HCN$, from another isomer), and 3.95 (br s, 2× 4H, $-O-CH_2CH_2-O-$); ir 1050-1100 (C-O), 1680 (C=O), and 2260 cm^{-1} ($C\equiv N$); ms M^+ 283.1239 (calcd. for $C_{14}H_{21}NO_3S$: 283.1242).

Compound **90**: ^1H nmr δ1.49, 1.54 (both s, 9H total, $-C(CH_3)_3$), 3.60, 3.65 (both d, 1H each, J = 10 Hz each, $-\overset{|}{C}HCN$), 3.90 (br s, 4H, $-OCH_2CH_2-O-$) and 6.20 (m, 2H, $-C\underline{H}=C\underline{H}-$); ir 1680 (C=O) and 2260 cm^{-1} ($C\equiv N$); ms M^+ 347.1557 (calcd. for $C_{19}H_{25}NO_3S$: 347.1555).

Compound **91**: The following ^1H nmr spectrum was attributed to the major isomer: ^1H nmr δ1.10 (d, 3H, J = 7 Hz, $\underline{CH_3}-\overset{|}{C}H-$), 1.36 (s, 3H, $CH_3-\overset{|}{\underset{|}{C}}-O-$), 1.52 (s, 9H, $-C(CH_3)_3$), 3.98 (s, 4H, $-OCH_2CH_2-O-$), and 4.26 (d, 1H, J = 4 Hz, $-\overset{|}{C}HCN$). The following ^1H nmr spectrum was attributed to the minor isomer: ^1H nmr δ1.22 (d, 3H, J = 7 Hz, $\underline{CH_3}-\overset{|}{C}H-$), 3.60 (d, 1H, J = 4 Hz, $-\overset{|}{C}HCN$), and 3.90

(br s, 4H, $-O-CH_2-CH_2O-$); ir 1680 (C=O) and 2250 cm^{-1} (C≡N); ms* M^++18 303 (calcd. for $C_{14}H_{27}N_2O_3S^+$: 303.1742). Anal. Calcd. for $C_{14}H_{23}NO_3S$: C, 58.92; H, 8.13; N, 4.91; S, 11.21. Found: C, 59.00; H, 8.16; N, 4.83; S, 11.04.

Compound **92**: ^1H nmr δ1.50 (s, 9H, $-C(CH_3)_3$), 3.50 (m, 1H, $-\overset{|}{C}HCN$), and 3.90 (m, 4H, $-OCH_2CH_2O-$); ir 1680 (C=O) and 2260 cm^{-1} (C≡N); ms M^+ 323.1558 (calcd. for $C_{17}H_{25}NO_3S$: 323.1555).

Reductions of ketal cyanothiolesters

The reactions were carried out using the general procedure as illustrated below with ketal cyanothiolester 88. Temperature and time used and % yields obtained for each case were shown in Table XII.

3-(1-Cyano-2-hydroxyethyl)-1,1-ethylenedioxocyclohexane (93)

Ketal thiolester **88** (248 mg, 0.84 mmol) was dissolved in absolute ethanol (5 mL) and sodium borohydride (124 mg,

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*Chemical ionization mass spectrum using NH_3 as a carrier gas.

3.26 mmol) was added. The reaction mixture was stirred under an argon atmosphere at room temperature for 1 h. It was then poured into ice-cold aqueous ammonium chloride solution and extracted with dichloromethane (4 × 20 mL) and extracts washed with saturated sodium chloride solution. The combined extract was dried, filtered, and concentrated. The crude material was purified by column chromatography on silica gel (50% ethyl acetate/petroleum ether) to give the mixture of diastereomeric alcohols **93** (163 mg; 93% yield, or 90% overall yield from the corresponding ketone **75**). The following spectral data were recorded on the diastereomeric mixture: ^{1}H nmr δ2.72 (dt, 1/2× 1H, J = 11 Hz, J' = 6 Hz, -$\overset{|}{\mathrm{C}}$HCN), and 3.82, 3.86 (both d, 2H each, J = 6 Hz each, -$\underline{\mathrm{CH_2}}$OH), and 3.95 (m, 4H, -$\mathrm{OCH_2CH_2O}$-); ir 2240 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M$^+$ 211.1209 (calcd. for $\mathrm{C_{11}H_{17}NO_3}$: 211.1208).

The alcohols **94-97** were shown to have the following spectral data. Compound **94**: ^{1}H nmr δ2.75 (m, 2H, -$\overset{|}{\mathrm{C}}$HCN and -OH protons), 3.80 (d, 2H, J = 6 Hz, -$\underline{\mathrm{CH_2}}$OH), and 3.90 (m, 4H, -$\mathrm{OCH_2CH_2O}$-); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M$^+$ 197.1043 (calcd. for $\mathrm{C_{10}H_{15}NO_3}$: 197.1052).

Compound **95**: ^{1}H nmr δ3.80 (m, 2H, -$\underline{\mathrm{CH_2}}$-OH), 3.90 (m, 4H, -$\mathrm{OCH_2CH_2O}$-), and 6.20 (m, 2H, -$\underline{\mathrm{CH}}$=$\underline{\mathrm{CH}}$-); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M$^+$ 261.1366 (calcd. for

$C_{15}H_{19}NO_3$: 261.1365).

Compound **96**: the following ^1H nmr was attributed to the major isomer: ^1H nmr δ1.10 (d, 3H, J = 6 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 1.32 (s, 3H, CH_3-$\overset{|}{C}$-O), 1.74 (d, 2H, J = 8 Hz, -CH_2-$\overset{|}{C}$-O-), 3.14 (td, 1H, J = 7 Hz, J' = 5 Hz, -$\overset{|}{C}$HCN), 3.80 (dd, 2H, J = 8 Hz, J' = 6 Hz, -$\underline{CH_2}$OH), and 3.97 (s, 4H, -OCH_2CH_2O-). The following ^1H nmr was attributed to the minor isomer: ^1H nmr δ1.20 (d, 3H, J = 8 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 1.32 (s, 3H, CH_3-$\overset{|}{C}$-O-), 1.82 (d, 2H, J = 9 Hz, -CH_2-$\overset{|}{C}$-O-), and 4.00 (s, 4H, -OCH_2-CH_2-O-); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+-15 184.0973 (calcd. for $C_9H_{14}NO_3$: 184.0974).

Compound **97**: ^1H nmr δ2.50 (br s, 1H, -OH), 2.70 (dt, 1H, J = 15 Hz, J' = 6 Hz, -CHCN), 3.76 (dd, 2H, J = 6 Hz, J' = 2 Hz, -$\underline{CH_2}$-OH), and 3.86 (m, 4H, -OCH_2CH_2O-); ir 2250 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+ 237.1359 (calcd. for $C_{13}H_{19}NO_3$: 237.1365).

3-(1-Cyanoethenyl)-1,1-ethylenedioxocyclohexane (**98**)

Ketal alcohol **93** (181 mg, 0.85 mmol) was dissolved in dry ether (5 mL) and DCC (262 mg, 1.27 mmol) and a trace amount of copper(I) chloride was added. The mixture was heated at reflux under an argon atmosphere for 16 h and was cooled to room temperature. The mixture was filtered through a sintered glass funnel (4-8 μ) and filtrate evaporated to dryness. The resulting residue was dissolved in 10% benzene/petroleum ether, filtered, and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/petroleum ether) to afford the acrylonitrile derivative **98** (129 mg; 79% yield): ^1H nmr $\delta 3.95$ (s, 4H, $-O-CH_2-CH_2-O-$), 5.70 (d, 1H, J = 2 Hz, $=C\underline{H}H$), and 5.82 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, $=CH\underline{H}$); ir 1080 (C-O) and 2220 cm^{-1} ($C\equiv N$); ms M^+ 193.1102 (calcd. for $C_{11}H_{15}NO_2$: 193.1103).

3-(1-Cyanoethenyl)-1-cyclohexenone (**99**)

Ketal **98** (62.51 mg, 0.32 mmol) was dissolved in acetone (5 mL) (reagent grade), and p-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) was added. The mixture was stirred under an argon atmosphere for 24 h at room temperature. The mixture was poured into aqueous solution of saturated sodium bicarbonate and extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel using 20% ethyl acetate in petroleum ether to afford the ketone **99** (39.07 mg; 81% yield) as a colorless oil: ^1H

nmr δ5.80 (d, 1H, J = 2 Hz, =C<u>H</u>H) and 5.94 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, =CH<u>H</u>); ir 1710 (C=O) and 2220 cm^{-1} (C≡N); ms M^+ 149.0839 (calcd. for $C_9H_{11}NO$: 149.0841).

3-(1-Cyanoethenyl)-1,1-ethylene dioxocyclopentane (**100**)

Ketal alcohol **94** (23.26 mg, 0.11 mmol) was dissolved in distilled ether (5 mL) followed by addition of DCC (33.0 mg, 0.16 mmol) and a trace amount of copper(I) chloride. The mixture was heated at reflux under an argon atmosphere for 31 h after which it was cooled to room temperature, filtered (sintered glass funnel, 4-8 μ), and filtrate concentrated. The crude product was purified by column chromatography using 20% ethyl acetate in petroleum ether as an eluent to give the olefin **100** (12.88 mg; 65% yield): ^1H nmr δ3.94 (s, 4H, O-C<u>H</u>$_2$-CH$_2$-O-), 5.75 (d, 1H, J = 2 Hz, =C<u>H</u>H), and 5.83 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, =CH<u>H</u>); ir 1110 (C-O) and 2220 cm^{-1} (C≡N); ms M^+-52 127.0759 (calcd. for $C_7H_{11}O_2$: 127.0759).

3-(1-Cyanoethenyl)-1-cyclopentanone (**101**)

A mixture of ketal **100** (67.16 mg, 0.37 mmol) and *p*-toluenesulfonic acid monohydrate (70.30 mg, 0.37 mmol) in acetone (5 mL) (reagent grade), was stirred under an argon atmosphere for 36 h at room temperature. Aqueous saturated sodium bicarbonate solution was added and extracted with dichloromethane (4 × 10 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel using 20% ethyl acetate in petroleum ether to give the ketone **101** (49.06 mg; 97% yield): ^{1}H nmr [illegible] 3.10 (tt, 1H, $-\overset{|}{C}H-$, unresolved), 5.84 (br s, 1H, $J_{w_{1/2}}$ [illegible] =CHH), and 5.95 (br s, 1H, $J_{w_{1/2}}$ [illegible] 2 Hz, =CHH); ir [illegible]20 (C=C), 1740 (C=O), and 2230 cm[illegible]N); ms M^+ 135.0683 (calcd. for C_8H_9NO: 135.0684).

5-(1-[illegible]noethenyl)-3,3-ethylenedioxo-tricyclo[5.2.1.0^{2,6}]-deca-8-ene (102)

A. By direct dehydration using DCC as a dehydrating agent

Ketal alcohol **95** (291 mg, 1.11 mmol) was dissolved in distilled ether (5 mL) and DCC (342 mg, 1.67 mmol) was added, followed by addition of a small amount of copper(I) chloride. The mixture was heated at reflux and stirred for 48 h under an argon atmosphere, and then cooled to room temperature. The solution was filtered (sintered glass funnel) and filtrate concentrated. The residue was dissolved in n-pentane, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to afford a clear yellow oil of the ketal olefin **102** (165 mg; 60% yield): ^1H nmr δ3.92 (m, 4H, $-O-CH_2-CH_2-O-$), 5.76 (d, 1H, J = 2 Hz, =C$\underline{H}$H), 5.86 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, =CH$\underline{H}$), 6.10 (dd, 1H, J = 6 Hz, J' = 4 Hz, -C$\underline{H}$=CH-), and 6.34 (dd, 1H, J = 6 Hz, J' = 3 Hz, -CH=C$\underline{H}$-); ^{13}C nmr δ138.4, 132.3, 132.1, 128.8, 126.5, 115.4, 92.1, 64.5, 64.0, 55.1, 53.2, 50.8, 44.8, 44.7, 43.6; ir 1080 (C-O), 1630 (C=C), and 2220 cm^{-1} (C≡N); ms M^+ 243.1256 (calcd. for $C_{15}H_{17}NO_2$: 243.1259). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.05; N, 5.76; O, 13.16. Found: C, 74.06; H, 7.20; N, 5.59; O, 13.28.

B. From ketal alcohol **95** *via* mesylate

Ketal alcohol **95** (249 mg, 0.95 mmol) was dissolved in dichloromethane (10 mL) and stirred for 5 min. Methanesulfonyl chloride (0.22 mL, 2.85 mmol) was added followed by triethylamine (0.66 mL, 4.75 mmol) and mixture stirred for 24 h at room temperature under an argon atmosphere. The mixture was evaporated to dryness in vacuo and the resulting orange precipitates were dissolved in dry benzene (5 mL) followed by addition of 1,8-diazabicyclo[5,4.0]undec-7-ene (DBU) (0.5 mL). The mixture was heated and stirred at reflux for 50 min and was then washed sequentially wih water, saturated sodium carbonate solution, and then with saturated sodium chloride solution. Organic layer was extracted with dichloromethane (4 × 20 mL) and extracts combined, dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel (20% ethyl acetate/petroleum ether) afforded a colorless oil of the olefin **102** (135 mg; 58% yield over two steps from the corresponding alcohol **95**). The ^{1}H nmr spectrum of olefin **102** [illegible] found to be identical to that obtained by direct method A (*vide supra*).

5,5-Ethylenedioxo-3-methyl-2-methylidenehexanecarbonitrile (**103**)

Ketal alcohol **96** (81 mg, 0.40 mmol) was dissolved in distilled ether (5 mL) and DCC (124 mg, 0.60 mmol) and copper(I) chloride (trace amount) were added. The mixture was heated at reflux under an argon atmosphere for 24 h and cooled to room temperature. The reaction mixture was filtered, concentrated, and the resulting residue dissolved in 10% benzene in petroleum ether. The insoluble urea solids were filtered and filtrate concentrated. The residue was further subjected to flash column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give the pure ketal olefin **103** (56 mg; 77% yield): ^{1}H nmr δ1.20 (d, 3H, J = 7 Hz, $\underline{CH_3}$-$\overset{|}{C}$H-), 1.36 (s, 3H, CH_3-$\overset{|}{C}$-O-), 2.70 (m, 1H, CH_3-$\underline{\overset{|}{C}H}$-), 3.96 (s, 4H, -O-$CH_2$-$CH_2$-O-), 5.70 (d, 1H, J = 2 Hz, =C$\underline{H}$H), and 5.78 (d, 1H, J = 2 Hz, =CH$\underline{H}$); ir 1050-1100 (C-O), 1630 (C=C), and 2220 cm^{-1} (C≡N); ms M$^+$-15 166.0868 (calcd. for $C_9H_{12}NO_2$: 166.0868).

3-(2-Cyano-2-propenyl)-2,2-ethylene dioxo-bicyclo[2.2.1]-heptane (104)

Ketal alcohol **97** (337 mg, 1.42 mmol) was dissolved in distilled ether (5 mL) and DCC (440 mg, 2.13 mmol) was added followed by a small amount of copper(I) chloride. The mixture was heated at reflux and stirred for 21 h under an argon atmosphere and then allowed to cool to room temperature. The solution was then filtered through a sintered glass funnel (4-8 μ) and filtrate concentrated. The residue was dissolved again in 10% benzene in petroleum ether, filtered, and filtrate concentrated. The resulting crude product was purified by flash column chromatography (10% ethyl acetate/petroleum ether) to give the pure ketal olefin **104** (271 mg; 87% yield): ^{1}H nmr δ2.20 (m, 5H, 3× -$\overset{|}{C}$H- and allylic protons), 3.80 (m, 4H,

$-O-CH_2-CH_2-O-$), 5.78 (br s, 1H, $J_{w_{1/2}}$ = 4 Hz, $=C\underline{H}H$), and 5.86 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, $=CH\underline{H}$); ir 1120 (C-O), 1620 (C=C), and 2238 cm^{-1} ($C\equiv N$); ms M^+ 219.1262 (calcd. for $C_{13}H_{17}NO_2$: 219.1259). <u>Anal.</u> Calcd. for $C_{13}H_{17}NO_2$: C, 71.19; H, 7.82; N, 6.39. Found: C, 71.06; H, 7.93; N, 6.23.

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THIOLESTERS IN ORGANIC SYNTHESIS. PART II.

TOTAL SYNTHESIS OF (±)-α-COSTAL

INTRODUCTION

The eudesmane group of sesquiterpenes **1** confronts organic chemists with a variety of interesting problems. β-Eudesmol (**2**) for example, is noteworthy for its role in the stereochemical correlation of terpenes and steroids.[1] The carbon framework of β-eudesmol, including the C-4 exocyclic methylene grouping, reappears in a number of its close relatives such as β-selinene (**3**), costol* (**4**), costal (**5**), and costic acid (**6**). These compounds differ only in the oxidation level of their C-7 substituent. On the other hand eudesmane sesquiterpenes have attracted much synthetic effort. The availability of new and improved methodologies has led to a large number of total syntheses of this class of natural products.

In most cases the required bicyclic system was formed by Robinson annelation leading to intermediates such as compound **7**.[2] In the other cases, new annelation procedures have been developed and applied. A few examples are discussed below.

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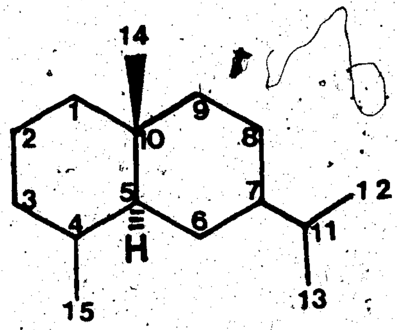
*Costol is also commonly known as sesquibenihiol.



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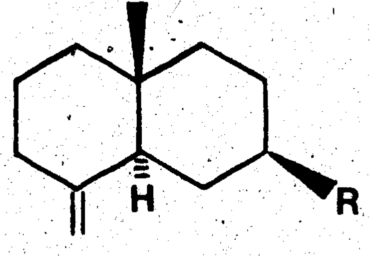


2. R = $(CH_3)_2COH$

3. R = $CH_2{=}CCH_3$

4. R = $CH_2{=}CCH_2OH$

5. R = $CH_2{=}CCHO$

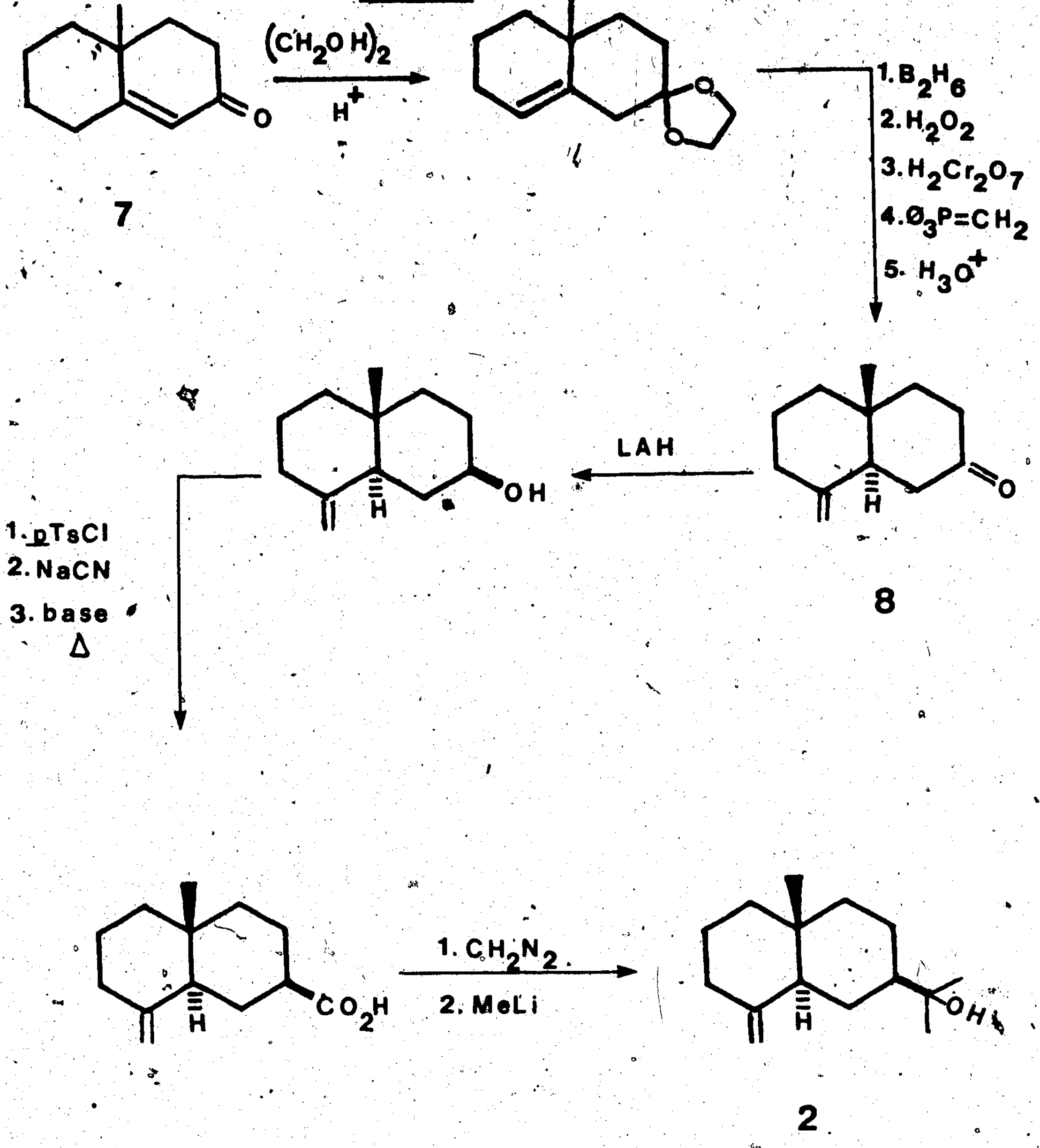
6. R = $CH_2{=}CCOOH$

Marshall and coworkers[3] have accomplished a total synthesis of β-eudesmol (**2**) by the use of decalone **8** as a common intermediate. This compound was prepared from enone **7** by an array of reactions as shown in Scheme I. Concurrently, a stereoselective total synthesis of β-eudesmol (**2**) and α-eudesmol (**9**) were also reported by Pinder et al.[4] Their key intermediates **10** and **11** were obtained respectively by Robinson-Mannich annelation of (+)-dihydrocarvone (**12**) and (-)-dihydrocarvone (**13**) with 1-diethylaminobutan-3-one methiodide.

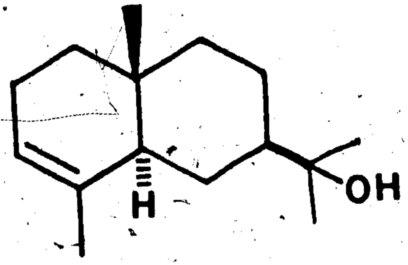
A novel synthetic approach leading to β-eudesmol was reported by Carlson and Zey.[5] Their approach consisted of the preparation of the key intermediate **14** by an intramolecular acylation reaction, and addition of lithium dimethyl copper(I) to produce a mixture of keto esters **15**. The trans isomer was further transformed into β-eudesmol as shown in Scheme II.

A versatile synthetic approach to the eudesmane class of sesquiterpenes was reported by Miller and Nash,[6] utilizing the key intermediate **17** obtained from dione **16**. The selective protection of the C-6 ketone carbonyl allowed sequential incorporation of substituents at C-1 and C-7 required for the construction of eudesmane sesquiterpenes. Furthermore, the control of the

Scheme I



7
(CH2OH)2
H+
1. B2H6
2. H2O2
3. H2Cr2O7
4. Ø3P=CH2
5. H3O+
O
8
LAH
OH
H
1. pTsCl
2. NaCN
3. base
Δ
CO2H
1. CH2N2
2. MeLi
OH
2



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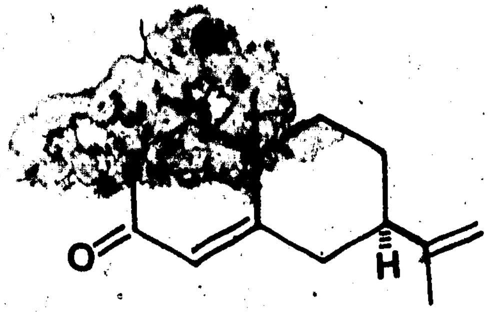

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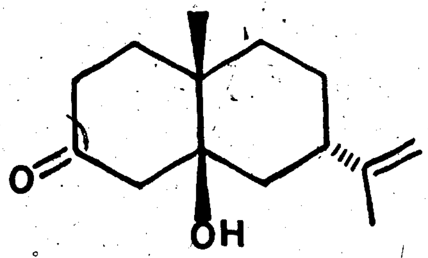

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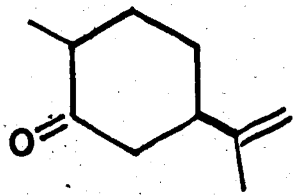

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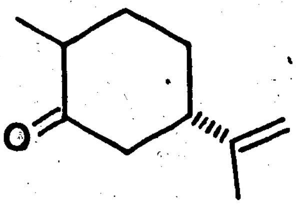

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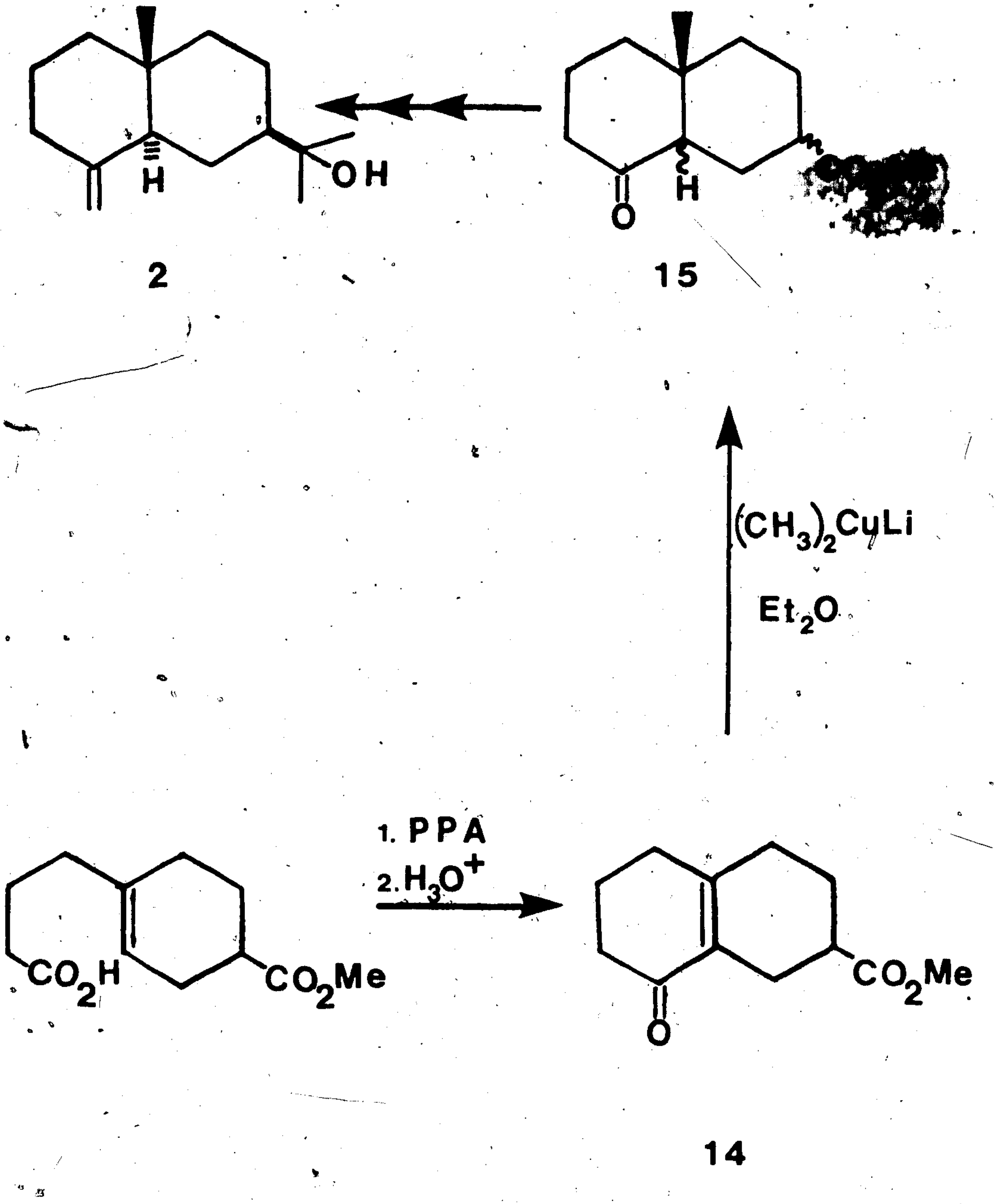
Scheme II

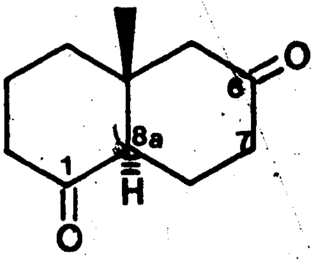


stereochemistry at C-8a and C-7 was permissible at a later stage by epimerization using the neighbouring carbonyl groups.

A formal total synthesis of β-eudesmol (**2**), atractylon (**20**), and isoalantolactone[7] (**21**) made use of, as the key step, the cationic cyclization of α,β-unsaturated ketone **18** leading eventually to the formation of enone **19** (Scheme III).[8]

More recently, a new annelation route to the bicyclic eudesmane skeleton has been developed by Wolinsky and coworkers.[9] They observed that treatment of olefin **22** with 3-butenoyl chloride in nitromethane in the presence of aluminum chloride gave rise to bicyclic enone **23** (Scheme IV). Subsequent modifications of this intermediate completed the total synthesis of β-selenene (**3**) and neointermedeol (**24**).

It is noted that in eudesmane sesquiterpenes as well as in many other terpenoid systems, a functionalized isopropyl side chain is often present. The introduction of such an isopropenyl unit can be achieved by two general approaches. One involves the use of a suitable starting material already possessing such a unit, and the other requires its incorporation at an adequate stage during the synthesis. A few examples of each approach are given below.



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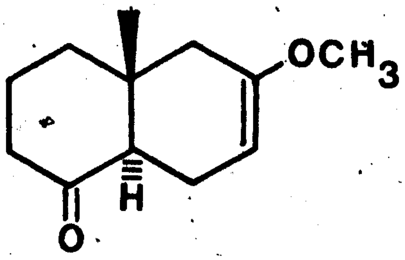

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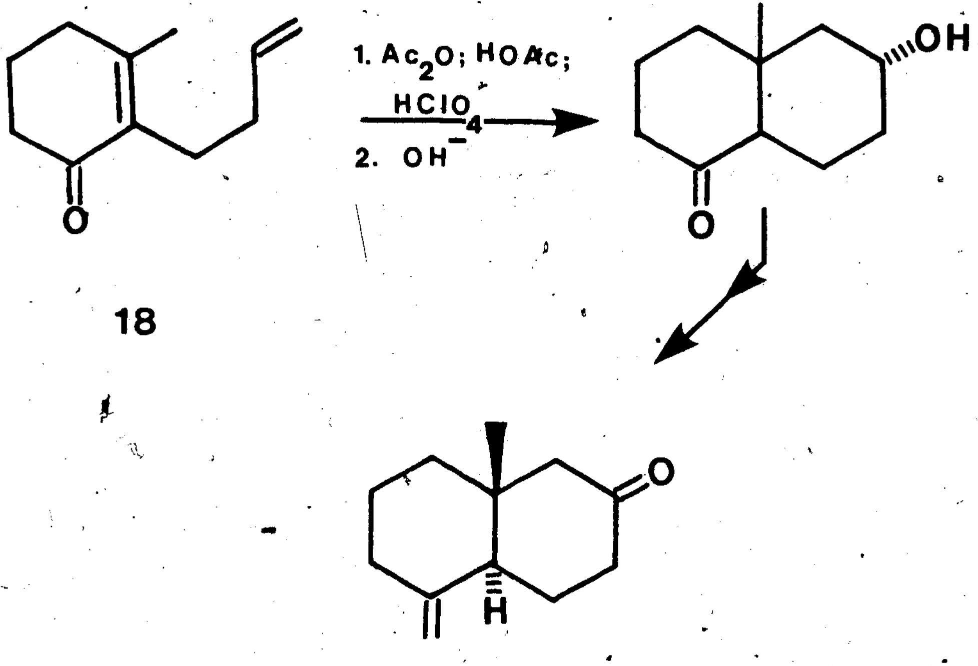
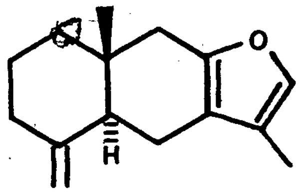
Scheme III



18

19



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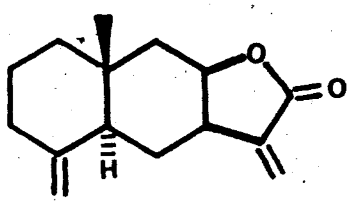
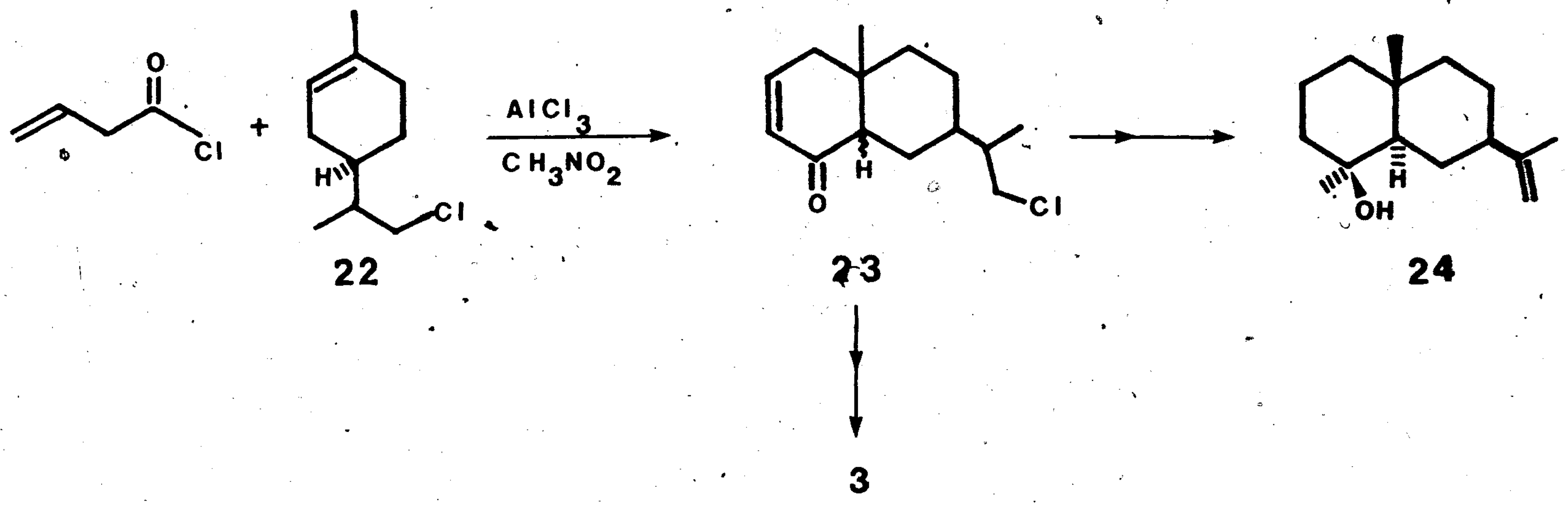


21

Scheme IV



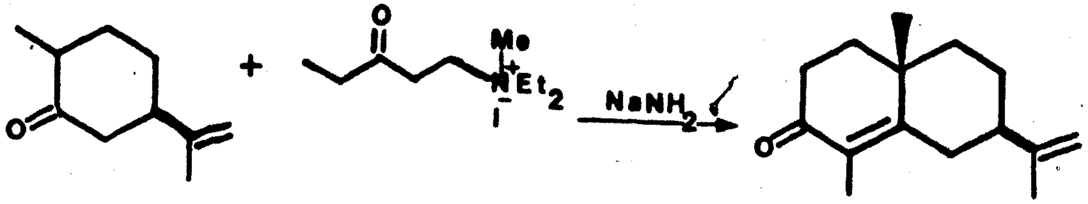
Examples of the first approach include the classical synthesis of α-cyperone (25) by Howe and McQuillin[10] who made use of (+)-dihydrocarvone (12) as a starting material to facilitate the construction of the target molecule as shown in Scheme V. In a similar fashion, epi-γ-silenene (26)[11] was synthesized starting with (+)-dihydrocarvone (12).

As described earlier, Pinder et al. synthesized β-eudesmol (2) using (−)-dihydrocarvone as a starting material. The required modification of the isopropenyl unit present in the starting material to an isopropyl alcohol unit was affected by a sequence of reactions further illustrated in Scheme VI.[12]

An alternative synthesis of α-cyperone (25) was achieved by Piers and Cheng[13] by the degradation of α-santonin (27). As outlined in Scheme VII the isopropenyl group required for α-cyperone was formed by modifying the lactone ring present in the starting material.

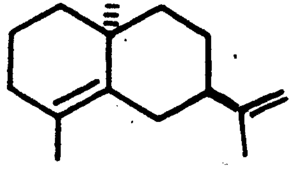
The second approach requires the installation of an isopropyl unit at a suitable stage during the synthesis. One example is Marshall's synthesis of β-eudesmol (2) in which an S_N2 replacement of an equatorial tosylate group with sodium cyanide was carried out as shown in Scheme I. Subsequent treatment of the resulting nitrile with

Scheme V



12

25



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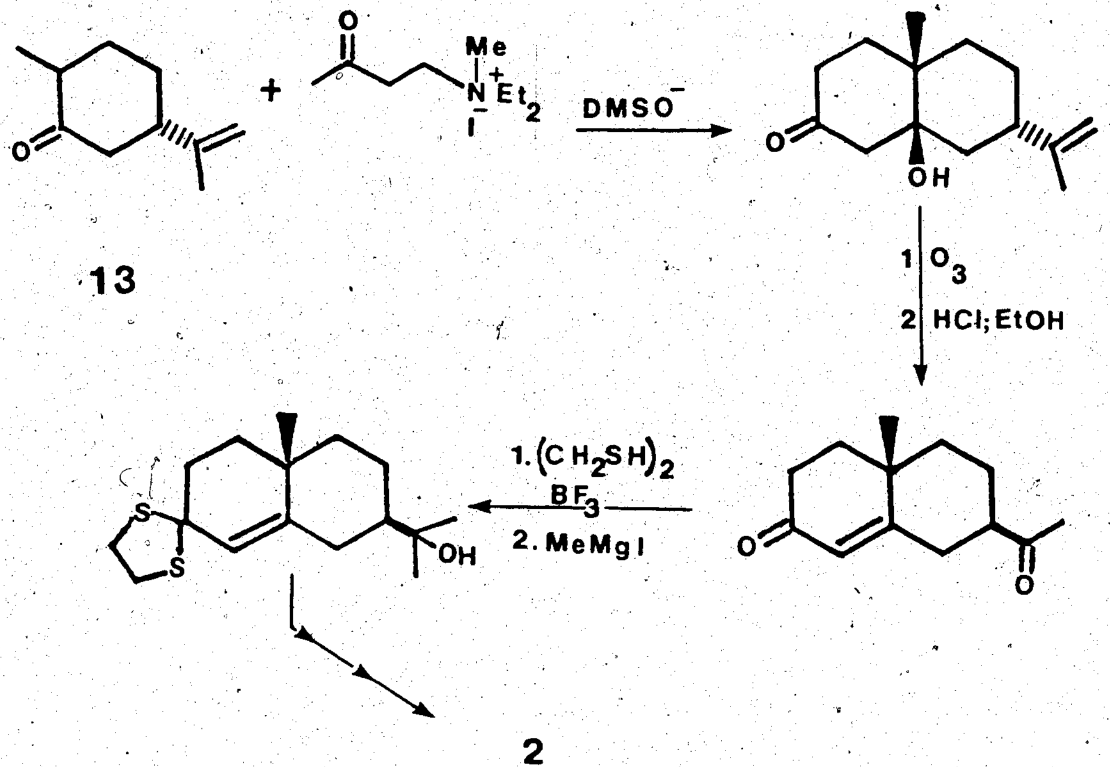
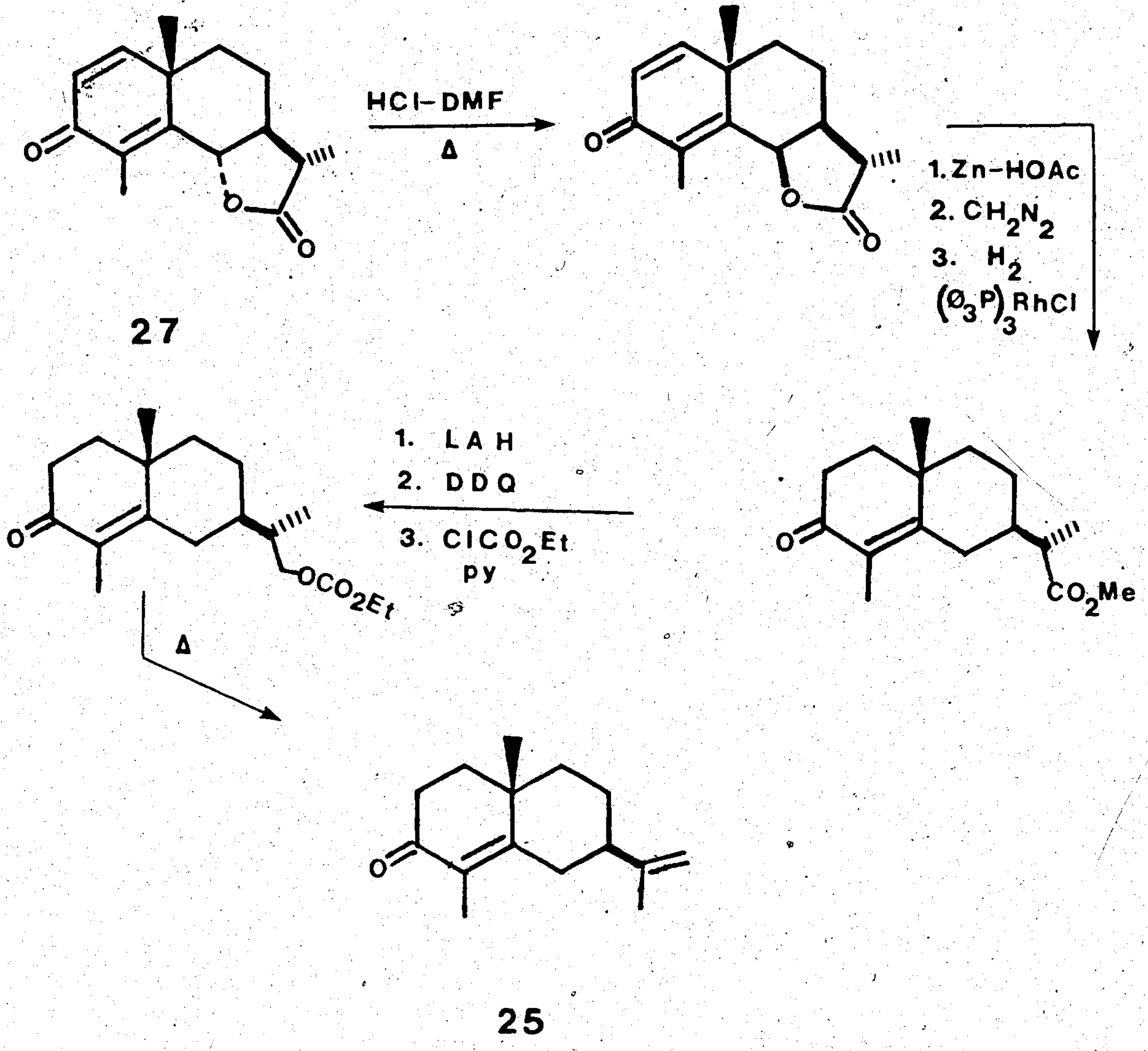
Scheme VI


O
Me
N
Et2
I
DMSO⁻
OH
1 O3
2 HCl; EtOH
O
O
1. (CH2SH)2
BF3
2. MeMgI
S
S
OH
13
2

Scheme VII

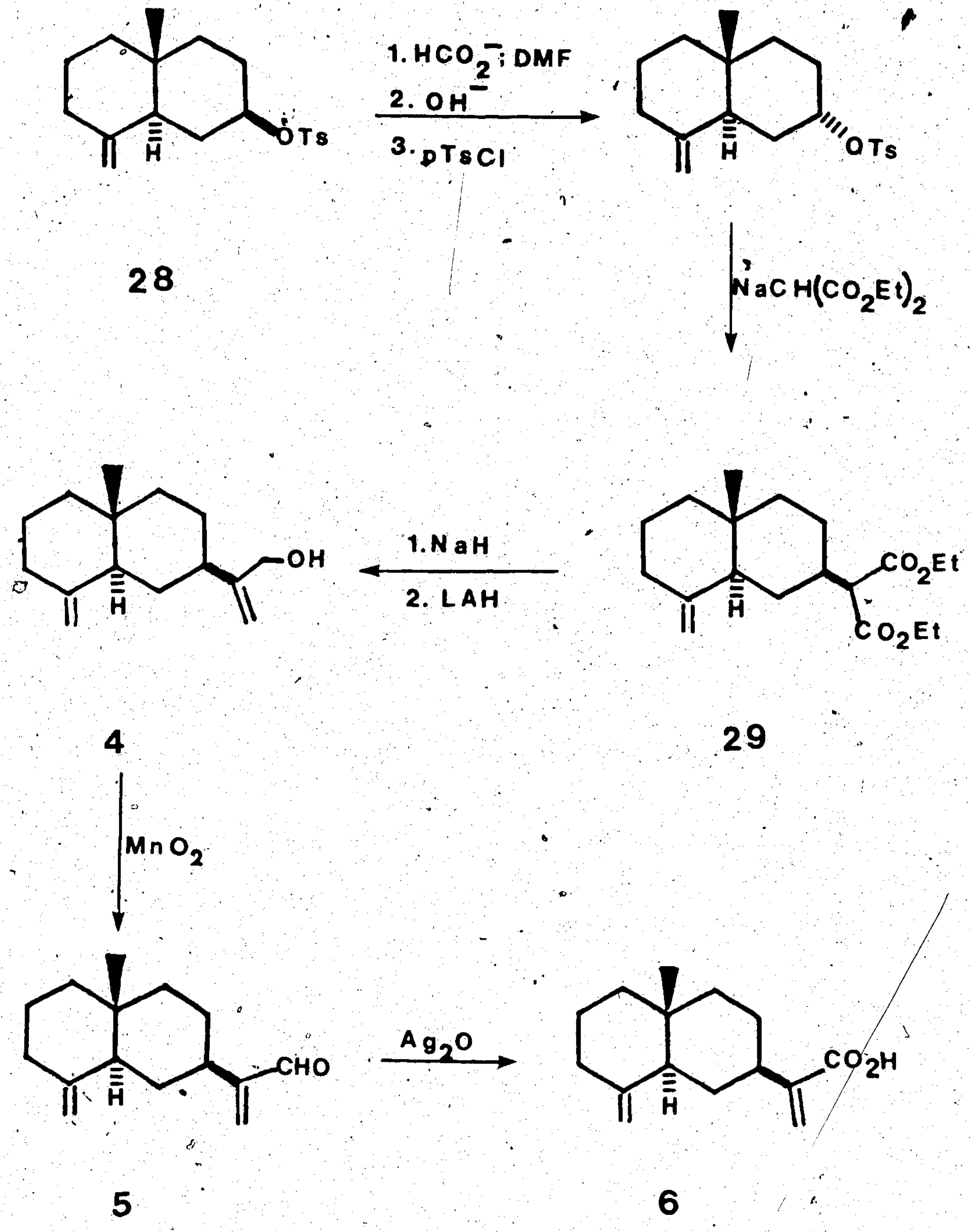

HCl–DMF
Δ
1. Zn–HOAc
2. CH₂N₂
3. H₂
(Ø₃P)₃RhCl
1. LAH
2. DDQ
3. ClCO₂Et
py
OCO₂Et
CO₂Me
Δ
27
25

alkali effected simultaneously the epimerization and hydrolysis of the cyano group. The carboxylic acid thus obtained was esterified with diazomethane. Treatment of the ester with methyl lithium gave the isopropanol group required for β-eudesmol (**2**). Alternatively,[14] epimerization of tosylate **28** by a three-step reaction sequence (Scheme VIII) followed by replacement with the sodium salt of diethylmalonate resulted in the formation of compound **29**. Lithium aluminum hydride reduction of the sodium salt of compound **29** effected the direct conversion of its malonate unit to a 1-hydroxy-2-propenyl moiety found in costol (**4**). Oxidation of **4** with manganese dioxide gave costal (**5**) which was further oxidized to costic acid (**6**) with silver oxide.

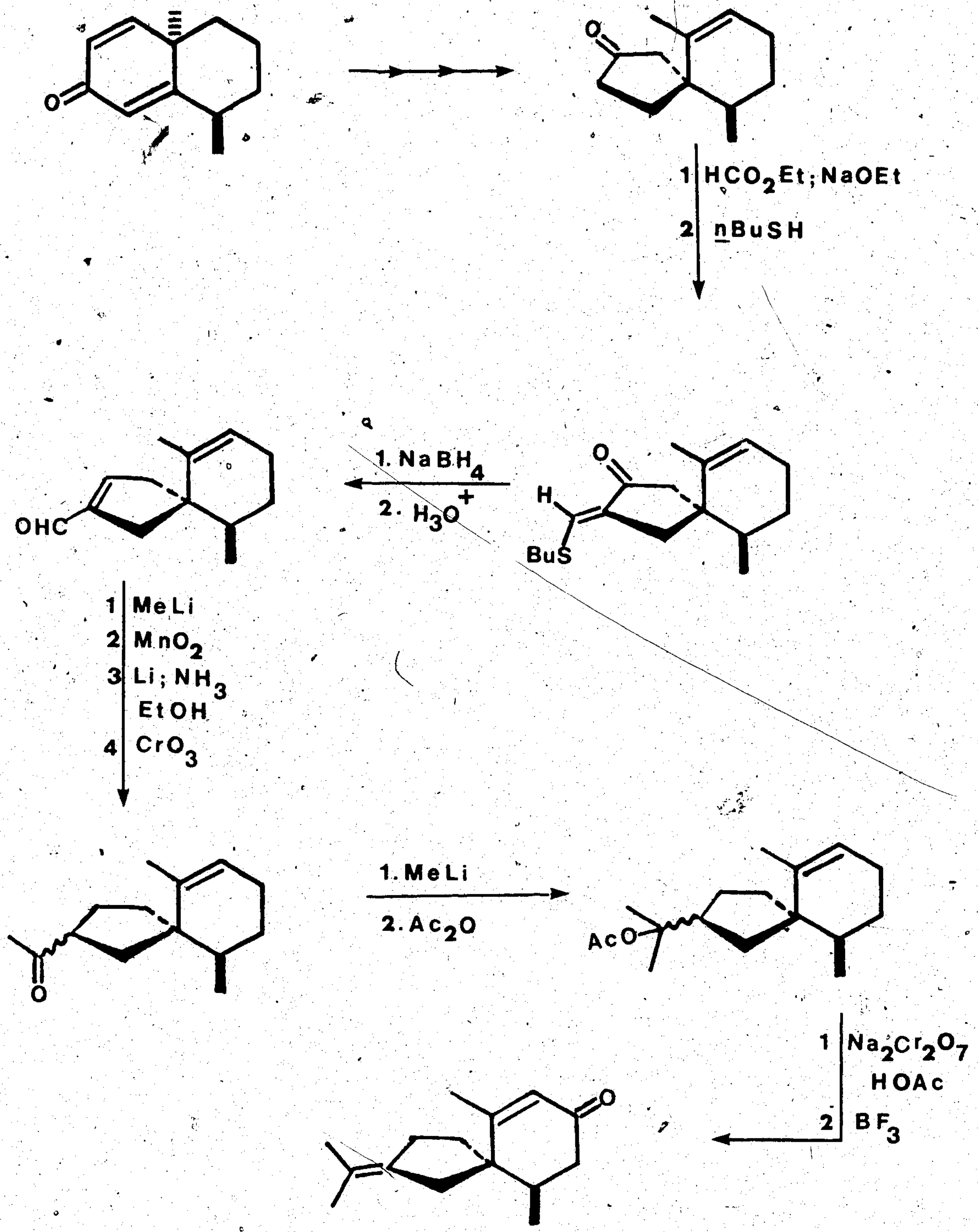
Other interesting methods used for the introduction of a functionalized isopropyl grouping are found in the syntheses of β-vetivone (**30**)[14] and linesol (**31**)[15] as shown in Schemes IX and X respectively . In the synthesis of α-bulnesene (**32**) and bulnesol (**33**)[16] (Scheme XI), the use of a ketone carbonyl to install a functionalized isopropenyl unit has been demonstrated.

During the course of our studies on cyanothiolesters (Part I of this thesis), we have established a methodology to facilitate the synthesis of β-hydroxypropionitrile and

Scheme VIII

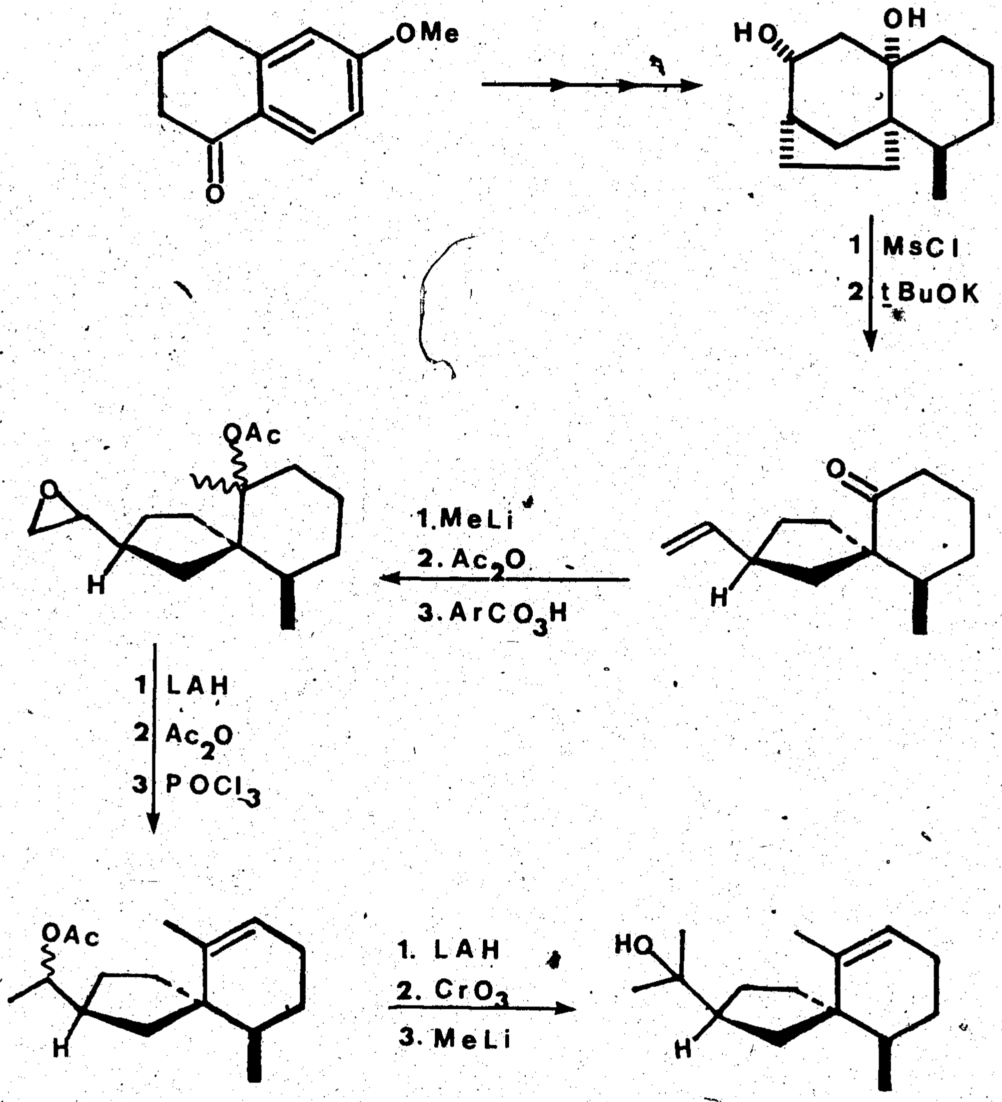

OTs
H
28
1. HCO$_2^-$; DMF
2. OH$^-$
3. pTsCl
OTs
H
NaCH(CO$_2$Et)$_2$
CO$_2$Et
CO$_2$Et
H
29
1. NaH
2. LAH
OH
H
4
MnO$_2$
CHO
H
5
Ag$_2$O
CO$_2$H
H
6

Scheme IX


O
1 HCO$_2$Et; NaOEt
2 nBuSH
O
H
BuS
1. NaBH$_4$
2. H$_3$O$^+$
OHC
1 MeLi
2 MnO$_2$
3 Li; NH$_3$ EtOH
4 CrO$_3$
O
1. MeLi
2. Ac$_2$O
AcO
1 Na$_2$Cr$_2$O$_7$ HOAc
2 BF$_3$
O

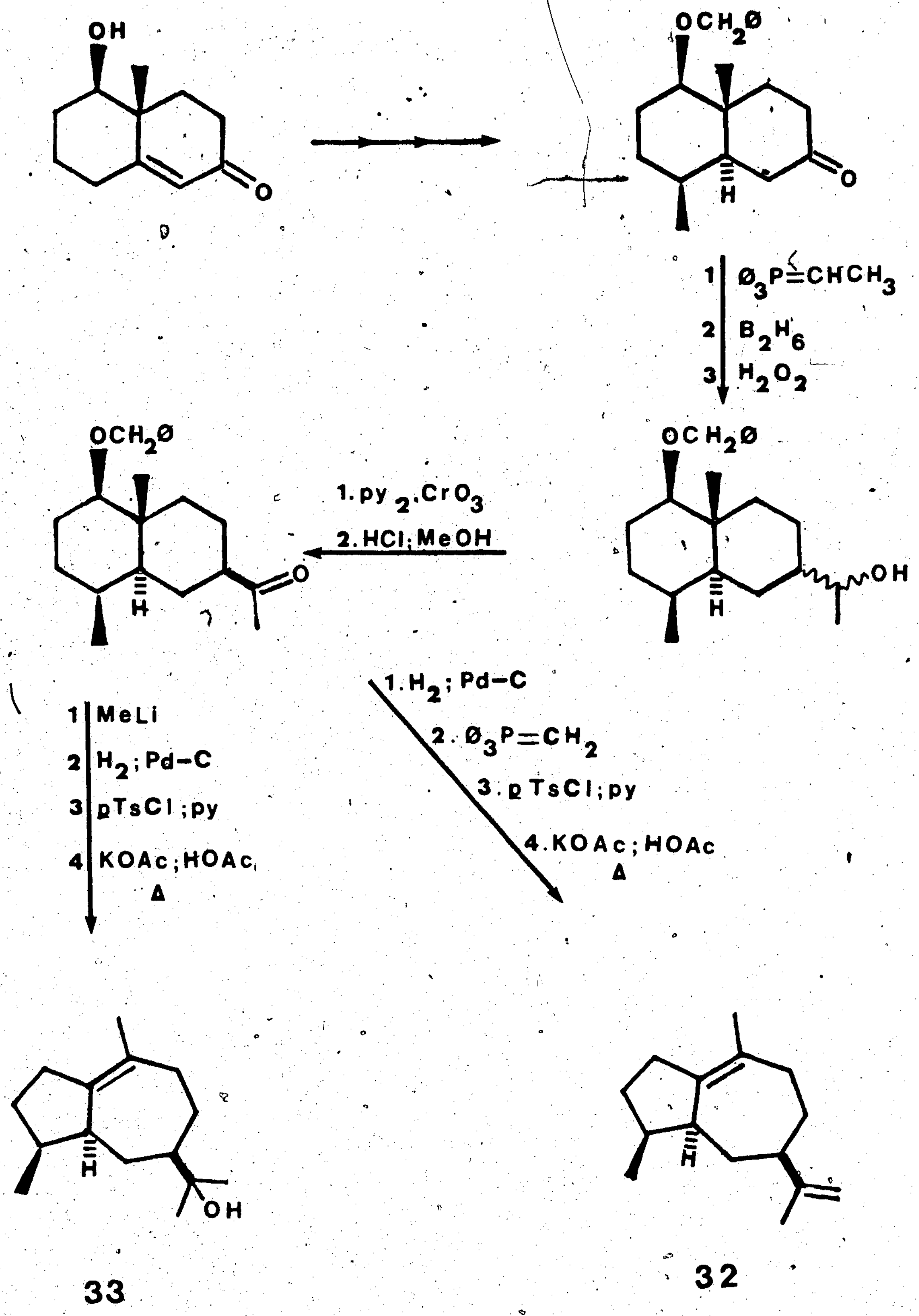
30

Scheme X


OMe
HO
OH
1 MsCl
2 tBuOK
O
OAc
H
1.MeLi
2. Ac2O
3. ArCO3H
H
1 LAH
2 Ac2O
3 POCl3
OAc
H
1. LAH
2. CrO3
3. MeLi
HO
H

31

Scheme XI


OH
O
OCH$_2$Ø
H
1 Ø$_3$P=CHCH$_3$
2 B$_2$H$_6$
3 H$_2$O$_2$
OCH$_2$Ø
H
OH
1. py$_2$.CrO$_3$
2. HCl; MeOH
OCH$_2$Ø
H
O
1 MeLi
2 H$_2$; Pd–C
3 pTsCl; py
4 KOAc; HOAc, Δ
1. H$_2$; Pd–C
2. Ø$_3$P=CH$_2$
3. pTsCl; py
4. KOAc; HOAc Δ
H
OH
33
H
32

acrylonitrile derivatives through the use of cyanothiolacetate as a masked β-hydroxypropionitrile carbanion equivalent. In essence, this method provides a convenient means for the incorporation of the highly functionalized isopropyl unit. In order to test the applicability of this method in the area of natural product synthesis, α-costal (**34**) was chosen as a target molecule.

α-Costal (**34**) is one of the constituents of the leaf oil of Thujopsis dolabrata Sieb. et Zucc. It was first isolated in 1965 by Ito and coworkers,[17] along with several other sesquiterpenes. This compound was found to be inseparable from its double bond isomer, β-costal* (**5**). The structure was assigned by chemical transformation of the mixture of **5** and **34** to the corresponding alcohols **4** and **35** by sodium borohydride reduction. The ir and ^{1}H nmr spectra of this mixture of alcohols were superimposable with those of costol (**4**)[18-20] except the presence of an extra band at 790 cm^{-1} in the ir spectrum and two signals at δ0.81 and δ5.25 in the ^{1}H nmr spectrum of the mixture. These spectral data suggested

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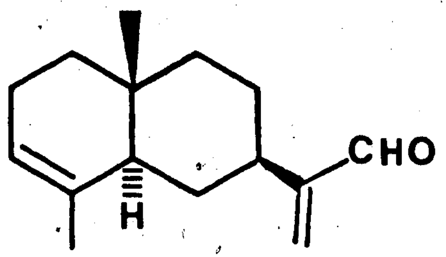
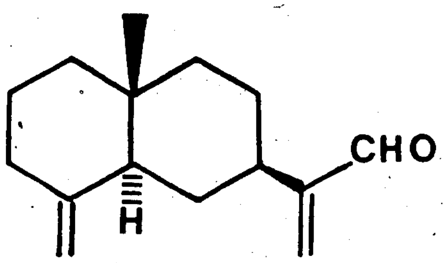
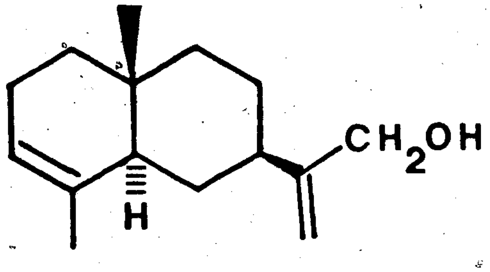
*In the original literature, α-costal was inadvertantly named as β-costal and vice versa.



34



5

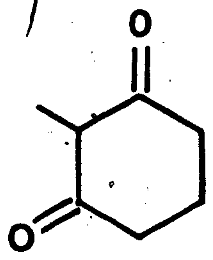


35

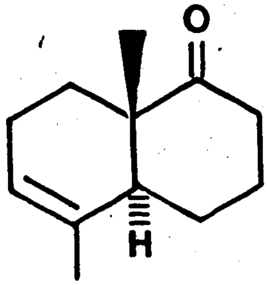
the presence of an endocyclic double bond in α-costal and accordingly the structure of its parent compound α-costal was tentatively assigned.

In the approach to the synthesis of α-costal, the most suitable starting compound appeared to be ketone **44** which was readily available from 2-methyl-1,3-cyclohexanedione **36**.[21,22] This compound already possesses some of the required features of the target molecule, such as a <u>trans</u> decalin system, the angular and vinylic methyl groups, and a trisubstituted double bond. The transformation of ketone **44** to α-costal (**34**) requires the incorporation of an acrolein unit to the carbon β to the ketone carbonyl. Involving the developed methods described previously in Part I of this thesis, this requirement could be achieved, in principle, by the three possible routes illustrated in Scheme XII.

Route **a** requires a 1,3-oxygen transposition of the ketone carbonyl. The resulting ketone is expected to undergo Knoevenagel-type condensation with cyanothiolacetate to facilitate the installation of the acrolein unit found in the target molecule. In route **b**, a leaving group will be introduced to the β-carbon of the ketone carbonyl. This is to be followed by an alkylation reaction with cyanothiolacetate. In route **c** the Michael

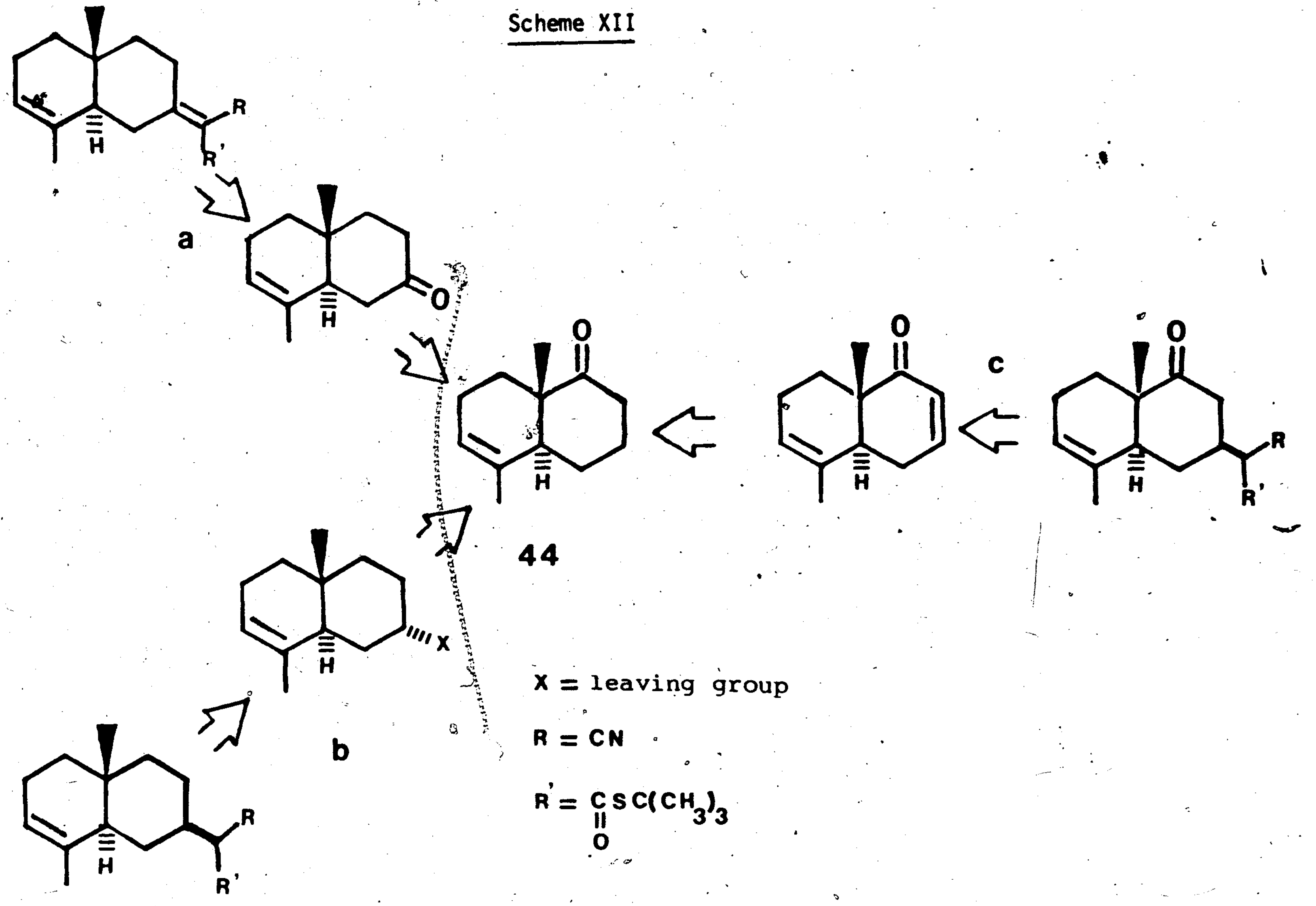


36



44

Scheme XII



44

X = leaving group

R = CN

R' = $\underset{\overset{\|}{O}}{C}SC(CH_3)_3$

addition of cyanothiolacetate is considered as a convenient means for the introduction of a highly functionalized isopropyl unit.

All of the outlined approaches were examined and, by the use of route a, the first total synthesis of α-costal (34) in racemic form has been achieved. Results are detailed in the following section.

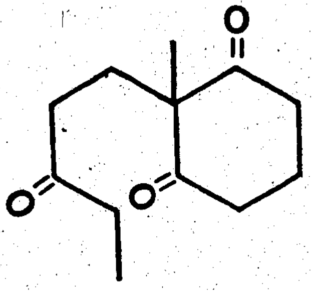
RESULTS AND DISCUSSION

The starting 2-methyl-1,3-cyclohexanedione (**36**) was prepared by hydrogenation of the mono sodium salt of 2-methyl resorcinol at room temperature under 50 psi pressure of hydrogen using 5% rhodium on alumina as a catalyst.[23] This procedure compares favorably with the traditional one by Mekler[24] which requires substantially higher pressure using Raney nickel as a catalyst. The crude product **36** obtained in 89% yield was subjected to subsequent reaction without further purification.

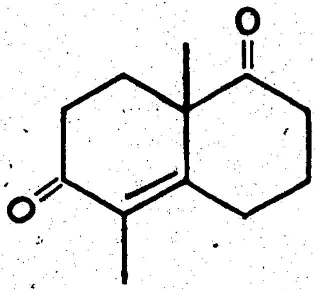
Enedione **38** was prepared by a slight modification of a reported procedure.[25] Treatment of diketone **36** with ethyl vinyl ketone in 1,2-dimethoxyethane at room temperature in the presence of 1,4-diazabicyclo[2.2.2]octane[26] gave trione **37** in 82% yield. Intramolecular aldol condensation of **37** with benzoic acid (1.1 equiv.) and triethylamine (0.7 equiv.) in refluxing benzene[27] resulted in the formation of crystalline enedione **38**, m.p. 40-42°C (lit.[25] m.p. 39-40°C), in 89% yield.

Ketalization of enedione **38** with an excess of ethylene glycol in the presence of a catalytic amount of either d-10-camphorsulfonic acid or anhydrous _p_-toluenesulfonic acid in refluxing benzene gave ketal **39** (82-88% yield). In the case of camphorsulfonic acid, a small amount (~6% yield) of diketal **40** was also formed. This by-product showed a molecular ion peak at 280.1671 in the mass spectrum and the absence of any carbonyl absorption bands in the ir spectrum. Furthermore, the ^1H nmr spectrum displayed a broad singlet at δ5.44 for a vinylic proton and a doublet (J = 7 Hz) at δ1.04 for a methyl group indicating that the double bond had migrated during the ketalization process.

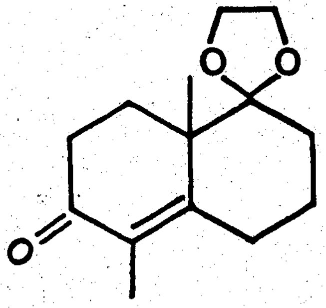
According to Ireland's procedure,[21] ketal enone **39** was subjected to Birch reduction[28-33] in liquid ammonia at -78°C with an excess of lithium metal in the presence of _t_-butyl alcohol. After the excess of lithium was destroyed with isoprene, ammonia was removed under reduced pressure, and the resulting lithium enolate was trapped directly with diethyl phosphorochloridate in THF at 0°C in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA). The yield obtained for the desired enol phosphate **41**[21] ranged from 50-69% which was comparable to that obtained by Ireland and Pfister[21] but considerably



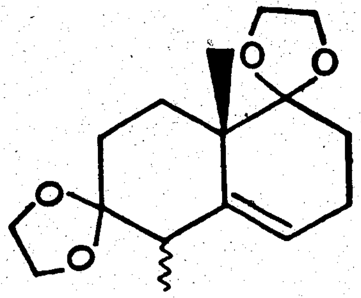
37



38



39



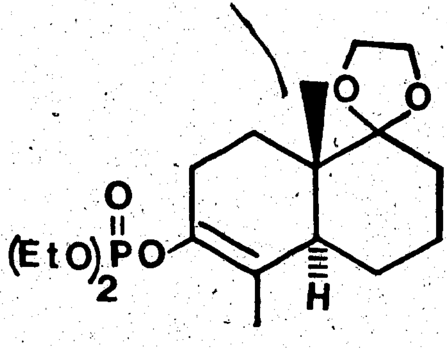
40

lower than that reported by Garver and van Tamelen.[22] The latter workers carried out the trapping process under similar conditions but in the absence of TMEDA. This procedure was repeated. Unfortunately, in our hands, the reported yield of better than 92% could not be achieved. Other than enol phosphate **41**, a variable amount (ca. 10-20%) of ketone **42** was also obtained. This compound, which was apparently formed by the protonation of the intermediate enolate ion, showed a strong absorption band at 1710 cm^{-1} in the ir spectrum due to the ketone carbonyl. In the ^{1}H nmr spectrum, a doublet at $\delta 1.00$ (J = 7 Hz) for the methyl group adjacent to the ketone, a sharp singlet at $\delta 1.25$ for the angular methyl group, and a multiplet at $\delta 3.95$ for the methylene protons of the ketal moiety were observed. These spectral data indicated the presence of the single stereoisomer. Since the compound was formed by the Birch reduction which is known to provide the thermodynamically more stable trans-decalin system and since the compound was recovered intact under epimerization conditions with sodium hydroxide, the stereochemistry of the compound was assigned as depicted. In spite of the extreme care undertaken in carrying out the reaction, the formation of ketone **42** could not be suppressed.

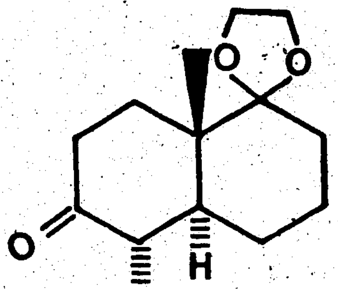
Ketal enol phosphate **41** underwent reductive elimination of the phosphate group smoothly when treated with lithium in ethylamine in the presence of t-butyl alcohol.[21] The resulting ketal olefin **43**, which was obtained in 84% yield, showed spectral data in agreement with those reported previously.[21]

Treatment of ketal **43** with 1.0 equiv. of p-toluenesulfonic acid in acetone at room temperature[34] for 16 h resulted in transketalization giving a quantitative yield of ketone **44**.[22] As discussed previously this compound already contained a number of important features found in α-costal (**34**), such as trisubstituted double bond and trans-fused decalin system along with two methyl groups in the required positions. In order to convert ketone **44** to the target molecule, it was necessary to incorporate an acrolein unit onto the β-carbon of the ketone carbonyl. As shown in Scheme XII, three routes are conceivable to fulfill this requirement. Regardless of the route to be undertaken it is necessary to activate the center to which the acrolein unit is to be attached. In order to achieve this, ketone **44** was converted to the α,β-unsaturated ketone **47** as follows.

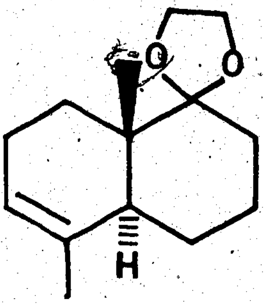
Ketone **44** was treated sequentially with lithium diisopropylamide and phenyl selenenyl chloride in THF at



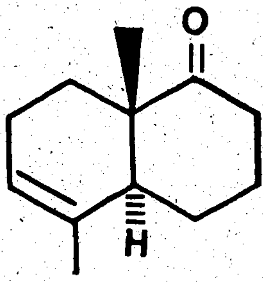
41



42



43



44

-78°C.[35] After 3 h, the reaction was complete and selenide **45** was isolated in 88% yield* as a single stereoisomer. The stereochemistry of the newly incorporated chiral center was deduced on the basis of the ^1H nmr spectrum which showed a signal at $\delta 4.54$ for the proton attached to this chiral center. The signal appeared as a doublet of doublets with coupling constants of 12 and 6 Hz indicating that the proton was axial and thus the phenylselenenyl substituent equatorial.

When selenide **45** was exposed to 30% hydrogen peroxide in THF at 0°C to room temperature for 5 h, the α,β unsaturated ketone **47** was isolated in 78% yield resulting from concomitant oxidation of the phenyl selenyl group and elimination of the resulting selenoxide. The ^1H nmr spectrum showed a doublet of doublets of doublets at $\delta 5.94$ with coupling constants of 11, 3, and 1.5 Hz for the vinylic proton H_a. The β-proton H_b of the enone system appeared at a low field of $\delta 6.90$ also as a doublet of doublets of doublets with coupling constants of 11, 6, and 2 Hz. The ir spectrum displayed an intense absorption band at 1690 cm^{-1} characteristic of a ketone carbonyl in

---

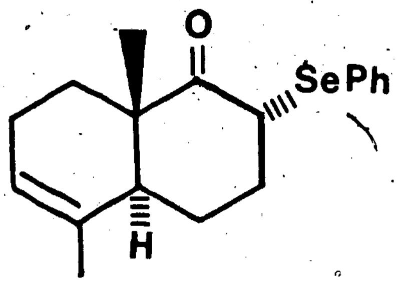
*When phenyl selenenyl bromide was used a lower yield (60-70%) was obtained.

conjugation with a double bond. The mass spectrum was in agreement with the required formula of $C_{12}H_{16}O$ showing a molecular ion peak at 176.1198.

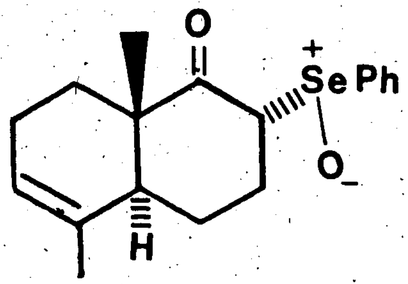
With enone **47** in hand, the three synthetic routes leading to α-costal (**34**) were individually explored as planned (Scheme XII). The first route under examination was route a in which a Knoevenagel-type condensation was conceived as a means for the introduction of a highly functionalized isopropyl unit required for the synthetic target.

Towards this end, enone **47** was converted to alcohol **49** by the use of Wharton's reaction.[36-38] Epoxidation of dienone **47** with 30% hydrogen peroxide in ethanol in the presence of sodium hydroxide[39-41] afforded epoxyketone **48** in 89% yield. This compound was obtained as a single stereoisomer in crystalline form, m.p. 54-55°C. The mass spectrum of this compound displayed a molecular ion peak at 192.1153 for the required formula of $C_{12}H_{16}O_2$. In the ir spectrum, absorption bands at 1270 and 1720 cm^{-1} were attributable for the oxirane ring and the ketone carbonyl respectively. The ^1H nmr spectrum displayed two singlets, one at $\delta 0.96$ for the angular methyl group and the other at $\delta 1.66$ for the vinylic methyl group. The vinylic proton appeared at $\delta 5.40$ as a multiplet whereas the two protons attached to the oxirane ring, H_a and H_b, appeared respectively at δ3.20 as a doublet and δ3.56 as a broad singlet. The stereochemistry of compound **48** could not be assigned unambiguously at this stage. However, the subsequent transformation requires its stereochemistry as shown resulting from the epoxidation of enone **47** from the less hindered side.

Initial attempts to induce the Wharton reaction on epoxy ketone **48** were carried out as follows using standard conditions. Hydrazine hydrate (2 equiv.) and acetic acid (0.2 equiv.) were added sequentially to a methanolic solution of epoxide **48** and the resulting solution was stirred for 3 h at room temperature. The results were found to be rather unsatisfactory; the desired product **49** was isolated only in 38% yield along with a substantial quantity of an unidentified material which appeared to be dimeric in nature (bis-hydrazone?) as suggested by its mass spectrum. When the reaction was carried out in neat hydrazine hydrate in the absence of glacial acetic acid at elevated temperature,[38] a poor yield (18%) of the rearrangement product **49** was obtained. To avoid the formation of the dimeric material, the reaction was performed with the following modifications. A dilute methanolic solution of epoxy ketone was added slowly to a



45



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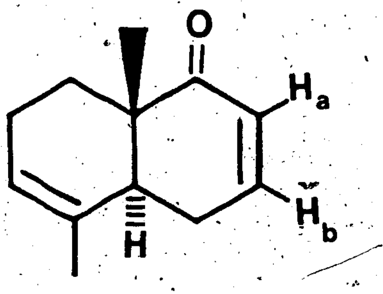
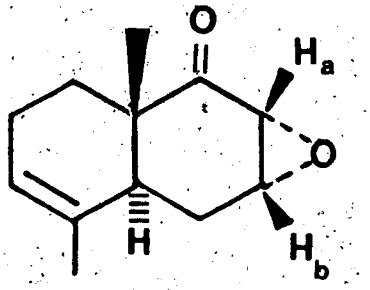


47



48

solution of hydrazine hydrate (5 equiv.) and glacial acetic acid (0.2 equiv.) in methanol. This experiment, involving the reverse addition and the use of a large excess of hydrazine hydrate, proved to be superior and the desired product was obtained in a much improved yield of 74%. In the ir spectrum, the allylic alcohol **49** showed a hydroxyl absorption at 3300-3400 cm^{-1} and the olefinic absorption band at 1650 cm^{-1}. The mass spectrum displayed a molecular ion peak at 178.1355 for the required formula $C_{12}H_{18}O$. In the ^1H nmr spectrum, the angular methyl group appeared as a singlet at δ0.86, a slight upfield shift as compared to its precursor, probably due to the shielding of the newly formed double bond. Also observed were the vinylic methyl at δ1.68 as a broad singlet and three vinylic protons at δ5.36, a multiplet for the C-6 proton, δ5.65, a doublet of doublets of doublets (J = 10, J' = 4, J" = 1.5 Hz) for the C-2 proton, and δ5.78, a doublet of doublets (J = 10, J' = 1 Hz) for the C-1 proton. The C-3 proton appeared as a broad triplet (J = 4 Hz) at δ4.22. Decoupling experiments showed that this proton was coupled with the C-1 and C-2 protons, with coupling constants of 1 and 4 Hz respectively. It was shown to be further coupled with the axial proton* on C-4 at δ2.72 with a rather small coupling constant of 2.5 Hz. On the basis of this observed small coupling constant the stereochemistry of compound **49** was deduced.

Oxidation of allylic alcohol **49** with pyridinium dichromate[42] in dichloromethane gave, after 4 h at room temperature, an 89% yield of dienone **50** which showed in the ir spectrum a prominent band at 1675 cm^{-1} for the conjugated enone carbonyl. In the ^1H nmr spectrum a doublet at δ6.83 (J = 10 Hz) and a doublet of doublets at δ5.86 (J = 10, J' = 1.5 Hz) were observed for the β and the α protons of the enone system respectively.

The conversion of enone **50** to the corresponding saturated ketone **52** requires the selective reduction of the double bond conjugated with the ketone carbonyl. In the presence of Wilkinson's catalyst (<u>tris</u>-triphenylphosphine rhodium(I) chloride),[43] hydrosilanes have been shown[44] to add to α,β-unsaturated ketones exclusively by 1,4-addition to give silyl enol-ethers which readily undergo hydrolysis[45] to give saturated

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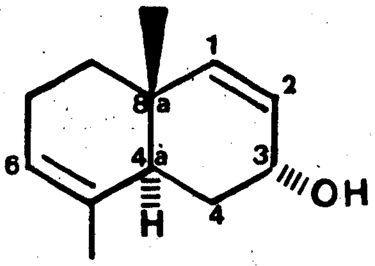
*This proton was found to be also coupled with the equatorial proton on the same carbon and the C-4a proton with coupling constants of 8 Hz each.

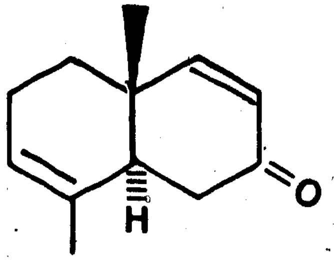
ketones. When enone **50** was subjected to hydrosilation with triethylsilane in the presence of Wilkinson's catalyst for 6 h at room temperature, silyl enol-ether **51** was isolated in quantitative yield. The ^{1}H nmr spectrum showed complex signals in the region of $\delta 0.5$-1 integrating for a total of fifteen protons for the three ethyl units attached to silicon atom. A broad singlet at $\delta 4.80$ was attributed to vinylic proton of the silyl enol-ether moiety. In the ir spectrum, the absence of any carbonyl absorption band and the appearance of a band at 1665 cm^{-1} due to the silyl enol-ether group were also in agreement with the assigned structure. The mass spectrum further confirmed the structure showing a molecular ion peak at 292.2224.

On exposure to tetra-n-butylammonium fluoride in THF, silyl enol-ether was converted smoothly to ketone **52** in 73% yield. A comparable yield was obtained when the hydrosilation product was directly subjected to the fluoride treatment without purification. Ketone **52** showed carbonyl absorption in the ir spectrum at 1710 cm^{-1} and molecular ion peak in the mass spectrum at 178.1356.

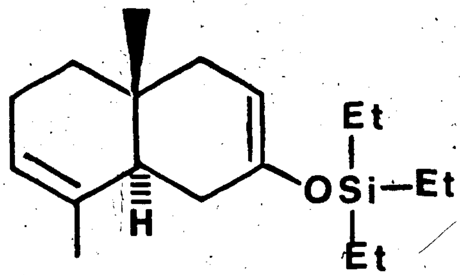
Having successfully prepared the saturated ketone **52** from **44** via an overall 1,3-oxygen transposition, its condensation with S-t-butyl cyanothiolacetate was



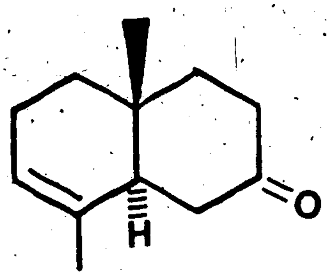
49



50

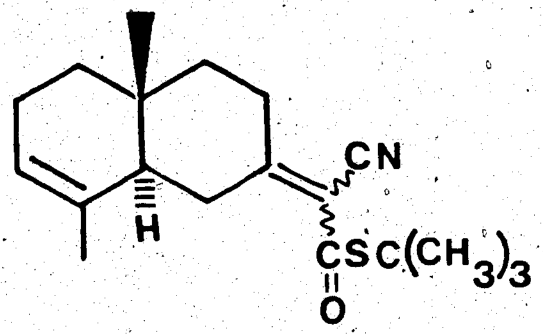


51

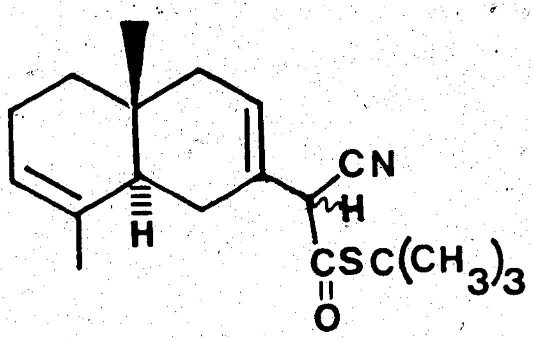


52

investigated. Initially, ketone **52** was treated with the latter reagent in THF in the presence of DABCO at room temperature. This set of conditions has been successfully used previously to effect the Knoevenagel-type condensation of S-_t_-butyl cyanothiolacetate with various ketones (Part I, Section 2). In the present case, however, the reaction was found to be not highly effective. The reaction did proceed rapidly, based on thin layer chromatographic analysis (tlc), but was found to be incomplete even at refluxing temperature for 15 h and only 21% yield of the desired product was formed. These results suggested that the reaction was probably reversible. In order to facilitate the product formation, water, which was produced during the condensation, needed to be removed. Towards this end, magnesium sulfate was added to the reaction mixture. Surprisingly, this resulted in the rapid consumption of the thiolester reagent, as shown by tlc, without substantial formation of the desired product for reasons which have yet to be determined. In further attempts, anhydrous sodium sulfate was used as a dehydrating agent. The experiment proved to be successful giving an isomeric mixture of **53** along with compound **54** in _ca_. 4:1 ratio in a total of 73% yield. The latter compound showed two vinylic protons in the ^{1}H nmr



53



54

spectrum, one at δ5.38 and the other at δ5.90, each as an unresolved multiplet. The spectrum also showed two broad singlets at δ4.75 and 4.05 integrating for a total of one proton due to the presence of the methine proton flanked by the thiolester and cyano groups. A strong thiolester absorption was observed in the ir spectrum at 1670 cm^{-1} and the molecular ion peak at 317.1813 in the mass spectrum further confirmed the structure of the compound.

The mixture of isomeric compounds **53** showed only a single vinylic proton at δ5.38 and the absence of any signals at _ca._ δ4.5 region indicating the presence of a tetrasubstituted double bond. In the ir spectrum, absorption band at 1670 cm^{-1} and 2240 cm^{-1} were also observed for the thiolester and cyano group respectively. The required molecular formula of $C_{19}H_{27}NOS$ was confirmed by its mass spectrum displaying a molecular ion peak at 317.1814.

To complete the syntheis of α-costal (**34**), it remained to modify the newly incorporated cyanothiolester unit to the required acrolein moiety preferably with control of the desired stereochemistry. Previously, it was shown that the carbon-carbon double bond of α,β-unsaturated cyanothiolester system present in the Knoevenagel-type condensation product could be selectively reduced with sodium borohydride under controlled conditions. In the presence of an excess of a reducing agent at higher temperature, further reduction of the thiolester to the alcohol level could also be simultaneously effected.

Initially, the selective reduction of the carbon-carbon double bond of compound **53** was examined in an attempt to determine the selectivity of the reduction. It was gratifying to find that when a mixture of **53** and **54** was subjected to sodium borohydride (1 mole equiv.) reduction at 0°C in ethanol, not only the reduction of the former compound was effected, the carbon-carbon double bond (β,γ to the cyanothiolacetate group) of the latter compound was also smoothly reduced. Apparently, the conditions were sufficient to effect the isomerization of the double bond into conjugation with cyano and thiolester groups. The reduction product **55** obtained in 74% yield was found to be homogeneous by tlc. However, the ^{1}H nmr spectrum indicated the presence of at least two diastereomers showing four doublets where two centered at $\delta 3.38$ (J = 8 Hz) and the other two at 3.70 (J = 12 Hz) in a ratio of 2:1 for the methine proton of the cyanothiolester group. Attempts to separate these diastereomers were totally fruitless and the stereochemistry of the reduction product at C-3 could not be determined with certainty until a later stage.

Further reduction of the cyanothiolacetate **55** with sodium borohydride in ethanol at room temperature gave an 88% yield of the corresponding alcohol **56** showing a strong hydroxy absorption band at 3400-3500 cm^{-1} and the disappearance of the carbonyl absorption in the ir spectrum. In the ^{1}H nmr spectrum a multiplet at δ3.90 attributable for the methylene protons adjacent to the hydroxyl group was displayed. The mass spectrum exhibited the molecular ion at 233.1778 confirming the required formula $C_{15}H_{23}O$.

Alcohol **56** also could be prepared directly from the mixture of **53** and **54** using an excess of sodium borohydride (4 mol equiv.) in ethanol at -40°C for 4 h and at room temperature for 12.5 h. The yield (91%) thus obtained for alcohol **56** was far superior to the two-step sequ[illegible]e.

The conversion of alcohol **56** to α-costal (**34**) requires further modification of the functionalized isopropyl side chain. Two required operations, i.e. dehydration and the conversion of the nitrile group to an aldehyde, could in principle be carried out in either sequence. The reduction of the nitrile was first examined using diisobutylaluminum hydride (DIBAL) as a reducing agent which is known to affect the direct conversion of a nitrile to an aldehyde.[46] However, under various conditions in the presence of an excess of DIBAL, the desired reduction did not occur and starting alcohol **56** was recovered intact presumably due to the competing acid-base reaction involving the hydroxyl group.

As a consequence of the above observation, alcohol **56** was subjected to dehydration. Treatment of **56** with dicyclohexylcarbodiimide (DCC) in refluxing ether in the presence of catalytic amount of copper(I) chloride[47,48] gave a mixture of cyanoolefins **57** and **58** in 2:1 ratio and in 94% total yield. These isomeric compounds were readily separated by Chromatotron using a solution of 5% ether in petroleum ether as a solvent. Both compounds showed in the ir spectrum, olefin absorption bands at 930 and 1620 cm^{-1} and nitrile absorption band at 2210 cm^{-1}. The epimeric nature of these compounds was further confirmed by the mass spectra, each of which showed a molecular ion peak (215.1676 for the major and 215.1663 for the minor) in accordance with the molecular formula of $C_{15}H_{21}N$. The stereochemistry of these two compounds were assigned after a careful examination of the ^{1}H nmr spectra. The major compound showed a multiplet at δ2.28 for the C-7 hydrogen atom*. By decoupling experiments, this proton was found to be coupled to the vinylic protons of the acrylonitrile moiety at δ5.74 (a doublet of doublets) and 5.82 (a broad doublet). Similarly, the C-7 proton of the minor isomer, which appeared at δ2.72 as a multiplet, was also shown to couple with the terminal vinylic protons observed at δ5.85 and 6.07, each as a doublet. It has been shown by ample examples that the axial and equatorial protons of cyclohexane and its derivatives (especially when rigid) are not equally shielded.[49,50] The axial proton normally absorbs at a much higher field than the equatorial counterpart with the relative chemical shift difference of ca. 0.2-0.8 ppm.[51] The fact that the C-7 proton of the major isomer appeared at a much higher field (δ2.28) than that of the minor isomer (δ2.72) by 0.48 ppm indicated the axial orientation of this proton. Accordingly, the stereochemistry of **57** and **58** was deduced as shown.

The predominant formation of epimer **57** possessing the desired stereochemistry was apparently a result of stereoselective reduction of the conjugated carbon-carbon double bond of compound **53** with sodium borohydride.

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*According to eudesmane skeleton numbering.

involving the addition of the hydride ion from the less hindered side of the molecule. In principle, the selectivity could be enhanced by the use of a bulkier reducing agent or by performing the sodium borohydride reduction at an even lower temperature.

Towards this end a mixture of compounds **53** and **54** was subjected to sodium borohydride reduction at -78°C. After 1.5 h, the tlc analysis showed that the reduction of the conjugated carbon-carbon double bond was complete. The reaction mixture was then allowed to warm up to room temperature to effect the further reduction of the thiolester group. To our dismay however, the product obtained was found to be completely identical with that obtained at higher temperature. Furthermore, dehydration of this material produces isomeric nitriles **57** and **58** again in 2:1 ratio.

In another attempt to improve the stereoselectivity, the mixture of compounds **53** and **54** was subjected to reduction with a bulky reducing agent <u>viz.</u> lithium tri-<u>t</u>-butoxyaluminum hydride[52,53] in THF for 3.5 h to give compound **55**. The material thus obtained was found to be again a mixture containing at least two diastereomers, but in a different ratio of 3:2. Further reduction of this material with sodium borohydride* resulted in the formation of alcohol **56** in 81% yield over two steps. Dehydration of the alcohol thus obtained using DCC-CuCl method gave isomeric nitriles **57** and **58** in 57% yield in a ratio of 1:2.8. Unexpectedly, the major product produced by this sequence was found to be the undesired isomer **58** resulting from the reduction of **53** from the more hindered side.

Nitriles **57** and **58** were individually treated with DIBAL (1.5 equiv.) at -78°C in toluene for 3 h. From epimer **57**, a reduction product was obtained in 54% yield. This compound showed the following ^{1}H nmr signals identical with those reported for α-costal (**34**): ^{1}H nmr (CCl_4) δ0.83 (s, 3H, angular $-CH_3$), 1.58 (s, 3H, $CH_3-\overset{|}{C}=$), 2.53 (m, 1H, $-C\underline{H}C=CH_2$), 5.28 (m, 1H, $HC=\overset{|}{C}-$), 5.90 (br s, 1H, $J_{w1/2}$ = 1.5 Hz, $-\overset{|}{C}=C\underline{H}H$), 6.21 (br s, 1H, $J_{w1/2}$ = 1.5 Hz, $-\overset{|}{C}=CH\underline{H}$), 9.52 (s, 1H, -CHO). In agreement with the

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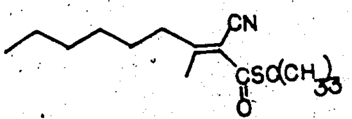
*In a model study, compound **i** was treated with an excess of lithium tri-t-butoxyaluminum hydride for 12 h at room temperature, a quantitative yield of compound **ii** was obtained without further reduction of its thiolester group.



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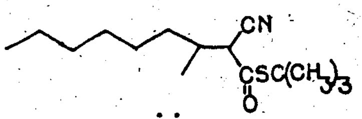
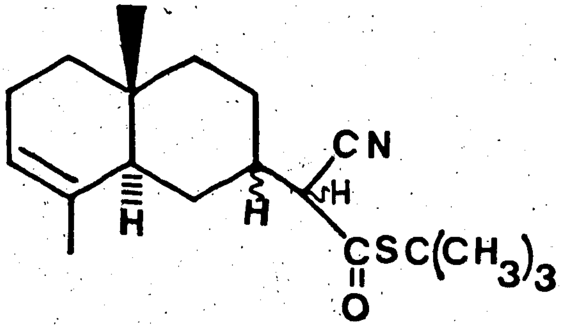


ii

structural features, the compound displayed in the ir spectrum, absorption bands at 2700 and 1694 cm^{-1} for the aldehyde group and at 1620 and 940 cm^{-1} for the double bonds, and in the mass spectrum, molecular ion peak at 218.1671 for $C_{15}H_{22}O$.

Reduction of nitrile **58** with DIBAL gave a 48% yield of compound **59**, epimeric with α-costal at C-7. Eip-α-costal thus obtained showed a mass spectrum similar to that of α-costal (**34**). In the ir spectrum, however, the positions of double bond (800 cm^{-1}) and carbonyl (2852 and 1697 cm^{-1}) absorptions were found to be quite different from those of the natural product. The major differences of the two compounds were however observed by the comparison of their ^1H nmr spectra. The two methyl singlets of the unnatural epimer were found at δ0.85 and 1.54. The proton of the isolated double bond appeared as a multiplet at δ5.34 while a singlet at δ6.11 and a doublet at δ6.48 ($J = 2$ Hz) were readily accountable for the terminal double bond protons. An aldehydic proton was also observed at δ9.48. More importantly the C-7 hydrogen atom appeared as a multiplet at δ3.04. The appearance of this proton at a much lower field ($\Delta\delta = 0.51$ ppm) when compared to the corresponding proton (δ2.53) in α-costal (**34**) further confirmed the stereochemical assignment.



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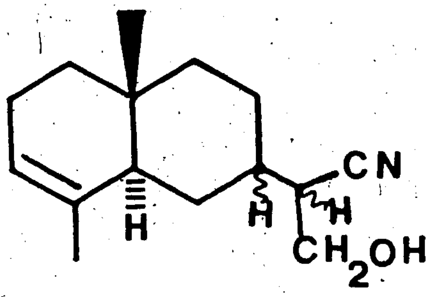

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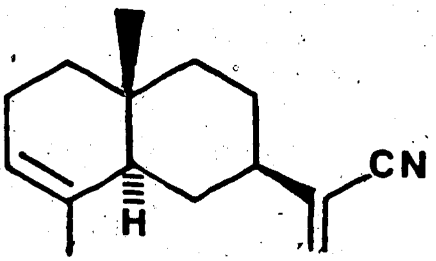

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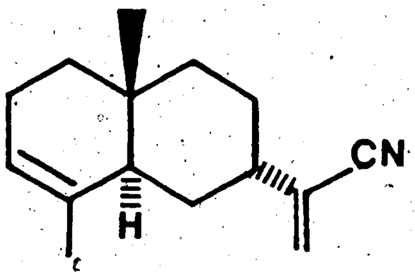

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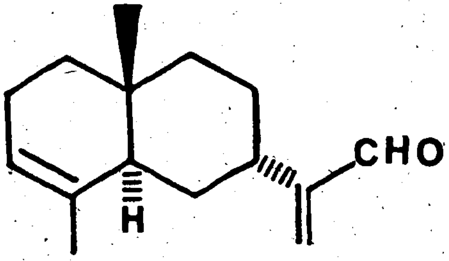


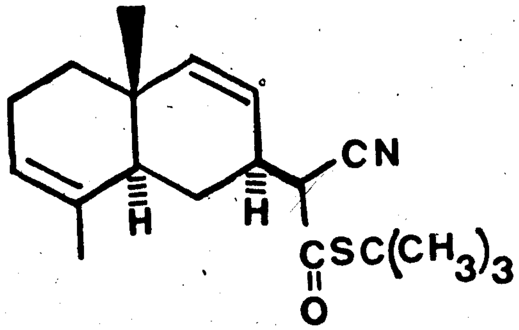
59

After completing the first total synthesis of α-costal (**34**) in a stereoselective manner, the other two possible routes outlined in Scheme XII were also examined. These were carried out in order to determine (i) the feasibility of these approaches leading to the natural product and (ii) the possible improvement of the total synthesis.

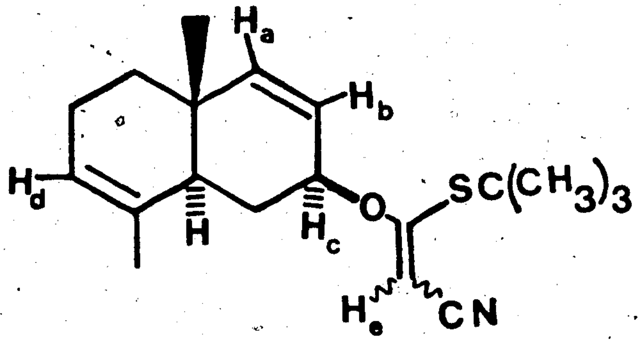
For route b, alcohol **49** which was produced as a single stereoisomer with a well defined stereochemistry, provided an interesting opportunity to carry out the total synthesis with complete stereochemical control. It is concievable that the replacement of the hydroxyl group with S-t-butyl cyanothiolacetate with inversion of stereochemistry could lead eventually to α-costal (**34**). Replacement reaction could be induced indirectly by first converting the hydroxyl into an adequate leaving group such as tosylate or mesylate with retention of stereochemistry. More interestingly, the displacement reaction could be directly carried out on alcohol **49** by invoking a Mitsunobu reaction.[54] The latter possibility was studied and the results are described below.

Allylic alcohol **49** and S-t-butyl cyanothiolacetate (2 equiv.) were sequentially added to a THF solution of 1.5 equiv. each of diethylazodicarboxylate (DEAD) and triphenyl phosphine (TPP). After 3.5 h at −35°C, an inseparable mixture of the desired compound **60** and its isomer **61** (*ca.* 2:1) was isolated in 54% yield. In addition to the signals corresponding to those of pure **61** (*vide infra*) the ^1H nmr spectrum of the mixture showed signals for vinylic protons at $\delta 5.50$ region and two doublets at $\delta 3.50$ and 3.58 ($J = 8$ Hz each) for the methine proton of the cyanothiolacetate moiety. On the basis of mechanistic considerations[55-57] of the Mitsunobu reaction, stereochemistry of each of these compounds were tentatively assigned.

Treatment of the mixture of **60** and **61** with sodium borohydride resulted in the selective reduction of compound **60** and the recovery of compound **61**. The alcohol **62** which was obtained in 78% yield based on the precursor **60** was readily separable from compound **61**. With the pure material available, the structure of compound **61** was readily deduced as follows: the mass spectrum indicated molecular formula of $C_{19}H_{27}NOS$, isomeric with the desired Mitsunobu reaction product **60**, displaying a molecular ion peak at 317.1806. In the ir spectrum, thiolester absorption was absent but a nitrile absorption was readily observed at 2210 cm^{-1}. The ^1H nmr spectrum showed singlets at $\delta 1.01$, 1.43, and 1.66 for the angular methyl



60

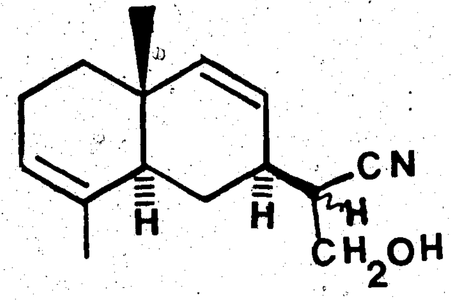


61

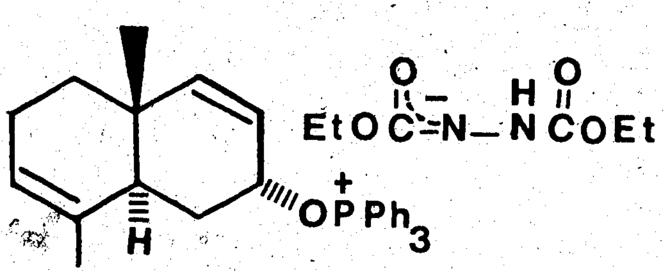
group, the t-butyl group and the vinylic methyl respectively. A further singlet was observed in the low field at δ5.00 attributable for the vinylic proton H_e. A broad doublet at δ5.82 for one proton and a complex signal at δ5.3-5.6 for a total of three protons were observed. These signals could be attributed to the two additional vinylic protons as well as the proton on the carbon bearing the oxygen atom.

Compound **62** was obtained as a mixture of two epimers in a ratio of 1:1. Hydroxyl and nitrile absorption bands appeared at 3400→3500 and 2260 cm^{-1} respectively in the ir spectrum. The required molecular formula of $C_{15}H_{21}NO$ was confirmed by mass spectrum show[illegible] molecular ion peak at 231.1617. In the ^1H nmr spectrum, unresolved signals at δ3.90 were attributable for the methylene group bearing the hydroxyl group. In agreement with the stereochemistry assigned to the precursor **60**, the methine proton on carbon bearing the side chain moiety appeared as a multiplet containing one large coupling constant of ~12 Hz characteristic for diaxial coupling.

Although the desired alcohol **62** could be prepared with complete stereochemical control, the yield of the Mitsunobu reaction (**49**→**60**) was rather unsatisfactory. To improve this reaction several modifications were made. In one experiment triethylamine (1.5 equiv.) was added in an attempt to facilitate the formation of the expected intermediate **63**. However, the major product obtained from this reaction in 87% yield was found to be compound **64** resulting from the addition of S-*t*-butyl cyanothiolacetate to DEAD. In another experiment a larger amount of DEAD and TPP (2.5 equiv. each) were stirred with alcohol **49** in THF for 10 h at room temperature prior to the addition of the thiolester reagent. This was carried out with the intention to produce the reaction intermediate **63** before the subsequent step was to take place. In this case, compound **65** was isolated in 50% yield. In a further modification, 2.5 equiv. each of DEAD and TPP were sequentially added to a solution of alcohol **49** and the thiolester in THF. After 24 h at -20°C, the major product which was found to be compound **66** was isolated in 58% yield. In a number of other experiments, diisopropyl azodicarboxylate[58] and/or tri-*n*-butyl phosphine were also used in place of DEAD and TPP respectively in attempts to enhance the selectivity. Results obtained were also disappointing. In all of these modifications the desired product **60** was formed in comparatively poorer yield than in the original experiment. It was previously observed that the Mitsunobu reaction using ethyl acetoacetate and



62

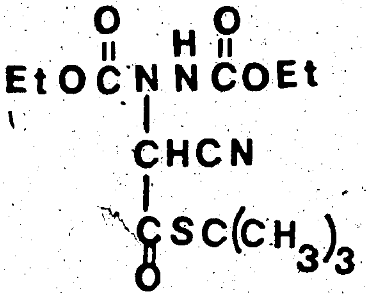


63

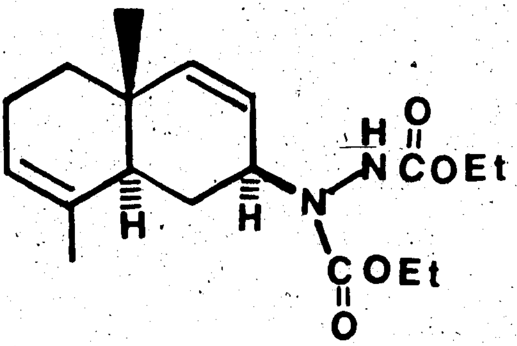
ethyl cyanoacetate gave only moderate yields of the desired products.[54,59] Our reagent was found to be unexceptional.

Concurrently with the attempted improvement of the Mitsunobu reaction, we also examined the selective reduction of the disubstituted double bond present in alcohol **62**, which was necessary towards the synthesis of α-costal. Selective hydrogenation was attempted under various conditions using one atmospheric pressure of hydrogen and 5% palladium on charcoal. When benzene or ethyl acetate or a combination of the two in various proportions was used as a solvent, the hydrogenation reaction did not occur even over a long period of reaction time, and the starting material was recovered intact. When ethanol was used as a solvent and the reaction worked up after 15 or 25 min interval, partial reduction occurred and the desired product **67** was produced along with the unreacted starting material. The hydrogenation was found to be difficult to control; after a somewhat longer reaction time of 1 h, the complete reduction of both double bonds was observed. Other methods which were expected to induce the selective reduction of the disubstituted double bond in the presence of a trisubstituted one were also explored. However, neither homogeneous hydrogenation using Wilkinson's catalyst[43,60] nor reduction with diimide,[61] produced from the potassium salt of azodicarboxylic acid and acetic acid in methanol, proved to be successful. In both cases, no reaction occurred. The fact that alcohol **67** could not be prepared effectively, and the disubstituted double bond in **67** could not be selectively reduced, further studies along route **b** were discontinued.

The synthesis of α-costal (**34**) by route c requires the Michael addition of S-*t*-butyl cyanothiolacetate to enone **47**. This was readily effected by treatment of the latter compound with the cyanothiolacetate (1.5 equiv.) and sodium hydride (2.2 equiv.) in the presence of chlorotrimethylsilane (1.4 equiv.) in refluxing benzene for 16 h. A 75% yield of the desired adduct **68** was obtained. This material was found to be a mixture of four diastereomers in approximately 2:2:1:1 ratio on the basis of ^{1}H nmr spectrum. This was evident from the fact that four doublets, each with a coupling constant of 5 Hz, were observed for the methine proton of the newly introduced group at δ3.44, 3.53, 3.46 and 3.64 integrating to a 2:2:1:1 ratio. In agreement with the assigned structure, two carbonyl absorption bands were observed, in the ir spectrum, at 1710 (ketone) and 1679 cm^{-1} (thiolester).


$\mathrm{EtOC(=O)N[NHC(=O)OEt]CH(CN)C(=O)SC(CH_3)_3}$

64



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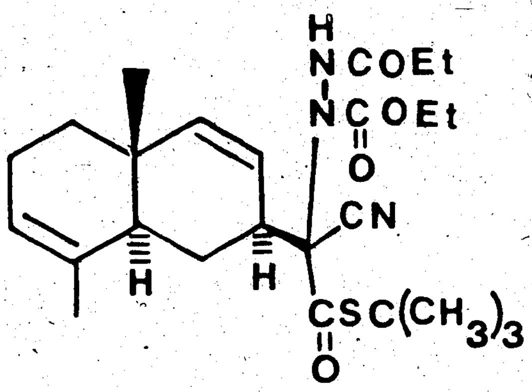

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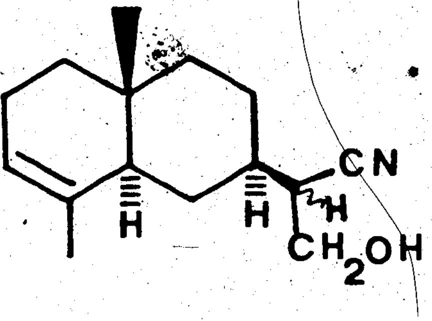
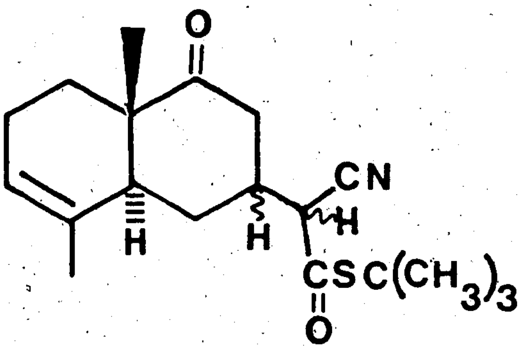


67

Also observed was a nitrile absorption at 2220 cm^{-1}. A molecular ion peak at 333.1765 in the mass spectrum confirmed the required molecular composition of $C_{19}H_{27}NO_2S$.

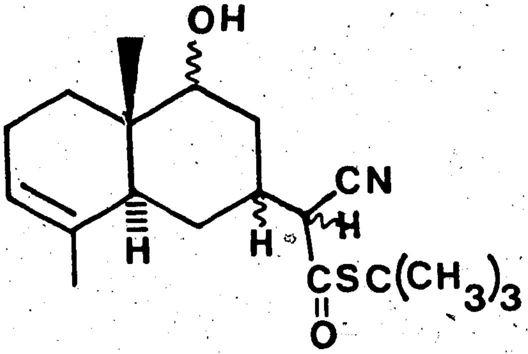
In order to remove its ketone carbonyl, compound **68** was subjected to a brief treatment (1.5 h) with sodium borohydride (2.2 mol equiv.) in ethanol at 0°C. The diastereomeric mixture of alcohols **69** obtained in 75% yield was further treated with methanesulfonyl chloride and triethylamine in chloroform at room temperature for 6 h to give mesylate **70**. The crude mesylate without purification was heated with anhydrous sodium iodide and zinc dust in refluxing N,N-dimethylformamide for 7 h in an attempt to replace the methanesulfonyloxy group with a hydrogen atom.[62,63] The reaction was found to be rather sluggish and the only product which could be isolated in a meaningful amount (14%) was the unexpected hydroxynitrile **71**.

The fact that the stereoselectivity of the Michael addition (**47→68**) was poor and the lack of simple solutions to effect the removal of the ketone carbonyl of the adduct made further exploration of route **c** to α-costal (**34**) unattractive.



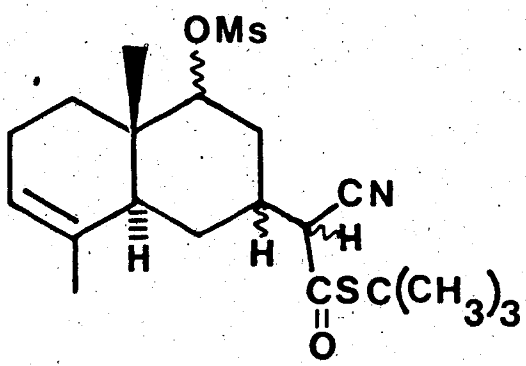
O
CN
H
H
H
CSC(CH3)3
O

68



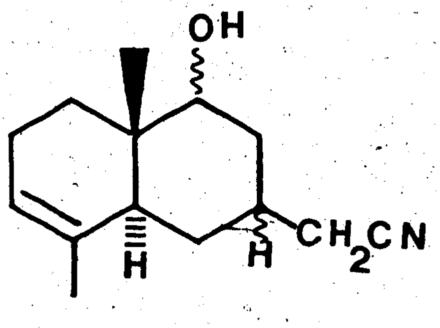
OH
CN
H
H
H
CSC(CH3)3
O

69



OMs
CN
H
H
H
CSC(CH3)3
O

70



OH
CH2CN
H
H

71

EXPERIMENTAL

General

Chromatotron model 7924 was used to separate the epimeric mixtures. For other general remarks, see Part I of this thesis.

Materials

1,2-Dimethoxyethane and tetrahydrofuran were freshly distilled over sodium metal in the presence of benzophenone as an indicator. Benzene and ether were freshly distilled over lithium aluminum hydride. Dichloromethane was washed with an equal volume of 10% aqueous sodium carbonate and distilled over powdered calcium chloride. Gaseous ammonia was passed through potassium hydroxide pellets and distilled over sodium metal. N,N,N',N'-Tetramethylethylenediamine was freshly distilled over sodium metal. Diethyl phosphorochloridate was freshly distilled over powdered lead carbonate.[64] Ethylamine was freshly distilled over powdered calcium hydride. Isoprene (Gold Label) was redistilled before use. Ethanol was freshly distilled over magnesium turnings and stored over 3Å molecular sieve. Diisopropylamine was distilled over calcium hydride. Argon was passed over a purification train of Fieser's solution,[65] concentrated sulfuric acid and potassium hydroxide pellets.

2-Methyl-1,3-cyclohexadione was prepared by a modified procedure by Sircar and Meyers.[23] S-_t_-Butyl cyanothiolacetate was prepared according to the reported procedure by Liu and Sabesan.[66] Lithium tri-_t_-butoxyaluminum hydride was freshly prepared according to the procedure by H.C. Brown and co-workers.[52,53]

2-Methyl-1,3-cyclohexadione (36)

2-Methylresorcinol (10 g, 0.08 mole) was dissolved in distilled water (70 mL) and sodium hydroxide (3.75 g, 0.09 mole) was added and mixture stirred until homogeneous in a fiberglass covered hydrogenation bottle. 5% Rhodium on alumina (1 g) was added and the bottle fitted in a parr hydrogenation apparatus. The mixture was stirred under 50 psi hydrogen pressure at room temperature for 9.5 h. The reaction mixture was then filtered through a sintered glass funnel and the filtrate acidified by dropwise addition of concentrated hydrochloric acid (~25 mL) to the pH of 5 to 4. The resulting solution was extracted with ethyl acetate (200 × 4 mL). The extracts were dried, filtered, and concentrated to give the crude dione **36** (9.10 g; 90% yield) which was subjected to further reaction without purification. Crude dione **36** showed the following ^1H nmr spectrum: ^1H nmr (DMSO) $\delta 1.62$ (s, 3H, CH_3-) and 1.75-2.5 (m, 6H, $-(CH_2)_2-$).

1-Methyl-1-(3-oxo-pentyl) cyclohexan-2,6-dione (**37**)

To a solution of 2-methyl-1,3-cyclohexadione (**36**) (19 g, 0.15 mole) in freshly distilled DME (300 mL), was added DABCO (19.38 g, 0.17 mole) and the solution chilled to 0°C and stirred for 15 min under an argon atmosphere. Ethyl vinyl ketone (17.3 mL, 0.17 mole) (freshly distilled) was added dropwise by means of a syringe and reaction mixture stirred for 12 h at room temperature. The mixture was poured into ice-cold 1N aqueous hydrochloric acid solution (~200 mL), extracted with dichloromethane (300 × 4 mL), and extracts washed with saturated solution of sodium chloride (~350 mL). The extracts were combined, dried, filtered, and concentrated. The crude product obtained was subjected to a reduced pressure at 60°C/1.5 torr, for 2 h to remove any excess of ethyl vinyl ketone. The crude product **37** (28.37 g; 90% yield) obtained was not purified further: ^1H nmr $\delta 1.02$ (t, 3H, J = 7 Hz, $\underline{CH_3}-CH_2-$), 1.26 (s, 3H, angular CH_3-), 1.8-2.9 (complex, 12H, 6× $-CH_2-$); ir 1715 (C=O) and 3500 cm^{-1} (enol -OH); ms M^+ 210.1258 (calcd. for $C_{12}H_{18}O_3$: 210.1256); Analytical sample was obtained by flash column chromatography (20% ethyl acetate/petroleum ether) of the crude; Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63; O, 22.83. Found: C, 69.03; H, 8.50; O, 22.57.

5,8a-Dimethyl-3,4,8,8a-tetrahydro-1,6[2H,7H] naphthalenedione (**38**)*

Trione **37** (3.95 g, 19 mmol) and benzoic acid (2.47 g, 20 mmol) were dissolved in xylene (20 mL) (freshly distilled over calcium hydride). After addition of triethylamine (2.0 mL, 14 mmol) the solution was heated to boiling whereby the water formed was azeotropically removed (by using Dean Stark apparatus). After refluxing for 22 h the solution was cooled and diluted with ether followed by sequential washing with water, 5% aqueous sodium bicarbonate solution, 2N aqueous sulfuric acid, and

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*These bicyclic compounds were named as naphthalene derivatives in accord with Chemical Abstract, unless otherwise specified.

water. The organic layer was dried, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (50% ether/petroleum ether) to give dienone **38** (3.23 g; 89% yield). Single recrystallization from ether afforded pure yellow crystals (m.p. 40-42°C): ^{1}H nmr δ1.38 (s, 3H, angular CH_3-) and 1.79 (s, 3H, $CH_3-\overset{|}{C}=$); ^{13}C nmr δ212.1, 197.7, 158.2, 130.8, 50.7, 37.4, 33.3, 29.7, 29.5, 27.3, 23.4, 21.6; ir 1610 (C=C), 1660 (conjugated C=O), and 1710 cm^{-1} (saturated C=O); ms M^+ 192.1149 (calcd. for $C_{12}H_{16}O_2$: 192.1150). Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; O, 16.65. Found: C, 74.89; H, 8.54; O, 16.94.

1,1 Ethylenedioxo-5,8a-dimethyl-1,2,3,4,8,8a hexahydro-6[7H] naphthalenone (**39**)* and 1,1,6,6-diethylenetetraoxo-5,8aβ-dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene (**40**)

d-10-Camphorsulfonic acid (50 mg, 0.20 mmol) and ethylene glycol (2 mL, 38.61 mmol) were dissolved in benzene (20 mL) and heated to reflux for 13 h in a three-neck flask connected to a Dean-Stark water separator.

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*The reaction was repeated using p-toluenesulfonic acid to give ketal **39** in 88% yield.

Approximately 10 mL of benzene was distilled off from the take-off arm charged with 3Å molecular sieve. The mixture was cooled to room temperature and dienone **38** (414 mg, 2.15 mmol) dissolved in benzene (10 mL) was added. The mixture was heated at reflux for 3 h under an argon atmosphere. The solution was then allowed to cool to room temperature, washed with ice-cold aqueous saturated solution of sodium bicarbonate, saturated sodium chloride solution respectively and extracted with ether (20 × 4 mL). The extracts were combined, dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in petroleum ether) to give a pure clear oil (crystallized on refrigeration) of ketal **39** (418 mg; 82% yield): ^1H nmr δ1.31 (s, 3H, angular CH_3-), 1.80 (s, 3H, $CH_3-\overset{|}{C}=$), 3.94 (br s, 4H, $-O-CH_2-CH_2-O$); ir 1040-1200 (C-O), 1618 (C=C), and 1670 cm^{-1} (C=O); ms M^+ 236.1410 (calcd. for $C_{14}H_{20}O_3$: 236.1412). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54; O, 20.32. Found: C, 71.06; H, 8.63; O, 20.06.

Further elution with the same solvent system afforded the diketal **40** (36 mg; 6% yield): ^1H nmr δ1.04 (d, 3H, J = 7 Hz, $\underline{C}H_3-\overset{|}{C}H-$), 1.28 (s, 3H, angular CH_3-), 3.95 (m, 8H, 2× $-OCH_2-CH_2-O$), and 5.44 (br s, 1H, $-CH=\overset{|}{C}-$); ir 1040-1180 cm^{-1} (C-O); ms M$^+$ 280.1671 (calcd. for $C_{16}H_{24}O_4$: 280.1675).

1,1-Ethylenedioxo-5,8aβ-dimethyl-1,2,3,4,4aα,5,8,8a-octahydro-6[7]-naphthalenone (42) and 6-diethyl phosphoryloxy-1,1-ethylenedioxo-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (41)*

To a solution of lithium wire (169 mg, 0.02 g-atom) in dry ammonia (35 mL) (distilled over sodium metal), a solution of ketal enone **39** (1.52 g, 6.35 mmol) in dry ether (25 mL) containing *t*-butyl alcohol (0.50 mL, 5.31 mmol), was added dropwise *via* a syringe and stirred under an argon atmosphere for 1.5 h at -78°C. Excess lithium was destroyed by dropwise addition of isoprene (freshly distilled) until the blue color discharged. The mixture was warmed to room temperature and ammonia and excess isoprene were removed under reduced pressure using a hypodermic syringe connected to a pump in which the needle of the syringe was inserted through a rubber septum of the reaction flask. The resulting cloudy solution was cooled

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The stereochemical designations used in this and all other chemical names used in this section denote *relative* stereochemistry. All compounds used and obtained were racemic.

to 0°C and a solution of N,N,N',N'-tetramethylethylenediamine (13 mL) (distilled over sodium metal) in dry ether (22 mL) was added slowly. After stirring for 5 min under an argon atmosphere, diethyl phosphorochloridate (3 mL, 20.76 mmol) was added slowly as a solution in ether (10 mL). After stirring for 5 h the mixture was quenched with ice-cold water, extracted with ether (50 × 4 mL) and washed again with water. The combined extract was dried, filtered, and concentrated *in vacuo*. The crude product was chromatographed on flash silica gel (40% petroleum ether in ether) to give, ketone **42** (151 mg; 10% yield) as a clear yellow oil: ^1H nmr δ1.02 (d, 3H, J = 8 Hz, $C\underline{H}_3$-$\overset{|}{C}H$-), 1.25 (s, 3H, angular CH_3-), and 3.9-4.0 (m, 4H, -OCH_2CH_2O-); ir 1050-1200 (C-O) and 1710 cm^{-1} (C=O); ms M^+ 238.1565 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

Further elution with 30% petroleum ether in ether gave a pure yellow oil of enol phosphate **41** (1.65 g, 69% yield): ^1H nmr δ0.98 (s, 3H, angular CH_3-), 1.38 (2×t, 6H, J = 7 Hz, 2× $\underline{C}H_3CH_2O$-), 1.63 (br s, 3H, CH_3-$\overset{|}{C}$=), 3.95 (s, 4H, -OCH_2CH_2O-), and 4.16 (2×qd, 4H, J = J' = 7 Hz, $CH_3\underline{CH_2}$-O-$\overset{|}{\underset{|}{P}}$=O); ir 1270 (O=$\overset{|}{P}(OEt)_2$), 1370 (-P-O-C-) and 1690 cm^{-1} (C=C); ms M^+ 374.1851 (calcd. for $C_{18}H_{31}O_6P$: 374.1858).

1,1-Ethylenedioxo-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (43)

Ethylamine (200 mL) was distilled fr[illegible]lcium hydride into a reaction vessel under an atmosphere of argon at 0°C. Small pieces of lithium wire (2.0 g, 0.29 g-atom) were added and the mixture was stirred for 1 h to effect solution. Then a solution of ketal phosphate **41** (10.59 g, 28 mmol) and t-butyl alcohol (4.5 mL, 48 mmol, dried over type 3Å molecular sieves) in THF (194 mL) (freshly distilled over sodium metal/benzophenone), was added dropwise over 1 h with stirring. After stirring for 2 h at 0°C, ethylamine was removed under reduced pressure, and water was added dropwise to discharge the blue color and the reaction mixture was poured into ice-cold water. The resulting mixture was extracted with ether (200 × 4 mL) and the extracts were washed with ice-cold water until the washings were neutral. The extracts were combined, dried, filtered, and concentrated. Flash column chromatography on silica gel (30% ether in petroleum ether) of the crude product afforded a pure ketal olefin **43** as a colorless oil (5.22 g; 84% yield): ^1H nmr δ0.92 (s, 3H, angular CH_3-), 1.63 (br s, 3H, $CH_3-\overset{|}{C}=$), 3.90 (s, 4H, $-OCH_2CH_2O-$), and 5.29 (m, 1H, $-CH=\overset{|}{C}-$); ^{13}C nmr δ134.9, 120.8, 113.0, 65.2, 65.1, 43.9, 41.4, 30.5, 26.9, 23.2, 23.0, 22.6, 21.5, 14.1; ir 1080-1200 (C-O) and 3010 cm^{-1} (HC=C-); ms M$^+$ 222.1617 (calcd. for $C_{14}H_{22}O_2$: 222.1620). <u>Anal.</u> Calcd. for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98; O, 14.40. Found: C, 75.99; H, 9.99; O, 14.30.

<u>5,8aβ-Dimethyl-3,4,4aα,7,8,8a-hexahydro-1[2H]-naphthalenone (**44**)</u>

Ketal olefin **43** (620 mg, 2.79 mmol) was dissolved in acetone (15 mL) (reagent grade) and <u>p</u>-toluenesulfonic acid (530 mg, 2.79 mmol) was added. The mixture was stirred at room temperature under an argon atmosphere for 16 h. Then the mixture was added with ice-cold saturated solution of sodium bicarbonate and extracted with dichloromethane (20 × 4 mL) and the extracts washed with saturated solution of sodium chloride. The combined extract was dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel (10% ethyl acetate/petroleum ether) gave a pure colorless oil of ketone **44** (500 mg; 100% yield): ^{1}H nmr δ1.06 (s, 3H, angular CH_3-), 1.66 (s, 3H, CH_3-C=), and 5.35 (m, 1H, -CH=C-); ir 1710 (C=O) and 3010 cm^{-1} (HC=C-); ms M$^+$ 178.1360 (calcd. for $C_{12}H_{18}O$: 178.1358).

5,8aβ-Dimethyl-2α-phenylseleneny1-3,4,4aα,7,8,8a-hexahydro-1[2H]-naphthalenone (**45**)

Diisopropylamine (0.3 mL, 2.14 mmol) (distilled over calcium hydride) was dissolved in dry THF (9 mL) and stirred at -78°C under an argon atmosphere. Methyllithium (1.29 mL, 1.3 M solution in *n*-hexane) was added dropwise *via* a syringe and mixture stirred for 10 min. A solution of ketone **44** (250 mg, 1.40 mmol) in THF (0.5 mL) was added slowly and continued stirring for 10 min. A solution of phenylselenenyl chloride (320 mg, 1.67 mmol) in THF (0.5 mL) was added dropwise and reaction stirred for 3 h at -78°C. Then ice-cold 1N aqueous hydrochloric acid solution (10 mL) was added and extracted with ether (20 × 4 mL). The extracts were washed with saturated solution of sodium chloride, and extracts combined, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to give a yellow oil of selenide **45** (410 mg; 88% yield) as a single isomer: ^1H nmr δ1.15 (s, 3H, angular CH_3-), 1.65 (s, 3H, $CH_3-\overset{|}{C}=$), 4.54 (dd, 1H, J = 12 Hz, J' = 6 Hz, $-\overset{|}{C}HSePh$), 5.34 (m, 1H, $-\overset{|}{C}H=\overset{|}{C}-$), 7.45 (m, 5H, aromatic protons); ir 1590 (C=C), 1710 (C=O), and 3040-3080 cm^{-1} (aromatic); ms M^++1 334.0852 (calcd. for $C_{18}H_{23}OSe$: 334.1349).

5,8aβ-Dimethyl-4aα,7,8,8a-tetrahydro-1[4H]-naphthalenone (**47**)

Selenide **45** (300 mg, 0.90 mmol) was dissolved in dry THF (10 mL) and solution cooled to 0°C. 30% hydrogen peroxide (0.26 mL) was added slowly followed by 0.73 mL of distilled water. The mixture was stirred for 5 h from 0° - 15°C. The mixture was then washed with saturated solution of sodium bicarbonate, extracted with ether (20 × 4 mL) and extracts washed with saturated sodium chloride solution. The extracts were dried, filtered, and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate/petroleum ether) afforded a dienone **47** as a light yellow oil (130 mg; 78% yield): ^1H nmr δ1.02 (s, 3H, angular CH_3-), 1.68 (s, 3H, $CH_3{-}\overset{|}{C}{=}$), 5.42 (m, 1H, $-\overset{|}{C}H{=}\overset{|}{C}-$), 5.94 (ddd, 1H, J = 11 Hz, J' = 3 Hz, J" = 1.5 Hz, vinylic proton H_a), 6.90 (ddd, 1H, J = 11 Hz, J' = 6 Hz, J" = 2 Hz, vinylic proton H_b); ir 1690 (C=O) and 3040 cm^{-1} (C=C); ms M^+ 176.1198 (calcd. for $C_{12}H_{16}O$: 176.1201).

2α,3α-Epoxy-5,8aβ-dimethyl-2,3,4aα,7,8,8a-hexahydro-1[4H]-naphthalenone (**48**)

To a solution of of dienone **47** (351 mg, 2.00 mmol) in ethanol (3 mL) was added with stirring, a solution of sodium hydroxide (30 mg) in water (0.1 mL). With stirring and cooling at 30-35°C was added 30% hydrogen peroxide (0.34 mL, 3.00 mmol) over a period of 2 min by a syringe. After an additional hour, the mixture was diluted with water and extracted with dichloromethane (10 × 4 mL). The combined extract was washed with saturated sodium chloride solution, dried, filtered, and concentrated. Purification of the crude product on silica gel flash column chromatography (5% ethyl acetate/petroleum ether) gave the epoxide **48** (339 mg; 89% yield). Single recrystallization from petroleum ether gave pure white crystals (m.p. 54-55°C): ^{1}H nmr δ0.96 (s, 3H, angular CH_3-), 1.66 (s, 3H, $\underline{C}H_3$-$\overset{|}{C}$=), 3.20 (d, 1H, J = 4 Hz, proton H_a), 3.56 (br s, 1H, proton H_b), and 5.40 (m, 1H, -CH=$\overset{|}{C}$-); ir 1270 (oxirane), 1720 (C=O) and 3020 cm^{-1} (-C=C-); ms M^+ 192.1153 (calcd. for $C_{12}H_{16}O_2$: 192.1150).

3α-Hydroxy-5,8aβ-dimethyl-3,4,4aα,7,8,8a-hexahydronaphthalene (49)

Hydrazine hydrate (0.48 mL, 9.77 mmol) was dissolved in distilled methanol (2 mL) and glacial acetic acid (0.02 mL, 0.38 mmol) was added and stirred under an argon atmosphere for 10 min. Epoxide (380 mg, 1.96 mmol) dissolved in methanol (5 mL) was added dropwise over a period of 1 h via a dropping funnel. The mixture was stirred for another 2.5 h at room temperature and then ice-cold water was added. The solution was washed with saturated solution of sodium bicarbonate, extracted with dichloromethane (20 × 4 mL) and extracts washed with saturated sodium chloride solution. The extracts were dried, filtered, and concentrated. The residue was subjected to flash column chromatography (20% ethyl acetate/petroleum ether) to give light yellow oil of allylic alcohol **49** (258 mg; 74% yield): ^{1}H nmr δ0.86 (s, 3H, angular CH_3-), 1.68 (s, 3H, $CH_3\text{-}\overset{|}{C}=$), 4.22 (br t, 1H, J = 4 Hz, $=C\underline{H}\text{-}OH$), 5.36 (m, 1H, $\underline{H}\overset{|}{C}=CCH_3$), 5.65 (ddd, 1H, J = 10 Hz, J' = 4 Hz, J" = 1.5 Hz, $H\overset{|}{C}=C\underline{H}\text{-}\overset{|}{C}HOH$), and 5.78 (dd, J = 10 Hz, J' = 1 Hz, $\underline{H}\overset{|}{C}=CH\overset{|}{C}HOH$); ir 1030 (C-O), 1650 (-C=C-), 3040 ($HC\text{-}\overset{|}{C}=\overset{|}{C}\text{-}$), and 3300-3400 cm^{-1} (-OH); ms M$^+$ 178.1355 (calcd. for $C_{12}H_{18}O$: 178.1358).

5,8aβ-Dimethyl-4aα,7,8,8a-tetrahy[illegible]ro-3[4H]-naphthalenone (50)

Allylic alcohol **49** (64.12 mg, 0.36 mmol) was dissolved in dichloromethane (4 mL) (freshly distilled over calcium hydride). Pyridinium dichromate (188 mg, 0.54 mmol) was added and mixture stirred at room temperature under an argon atmosphere for 4 h. Then the reaction mixture was filtered through a sintered glass funnel (4-8 μ) followed by washing thoroughly with dichloromethane, and filtrate concentrated. The residue was purified by a flash column chromatography (10% ethyl acetate in petroleum ether) to give a dienone **50** (56.36 mg; 89% yield) as a yellow oil: ^1H nmr δ1.06 (s, 3H, angular CH_3-), 1.65 (br s, 3H, $CH_3-\overset{|}{C}=$), 5.38 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$), 5.86 (dd, 1H, J = 10 Hz, J' = 1.5 Hz, α-vinylic proton), and 6.83 (d, 1H, J = 10 Hz, β-vinylic proton); ir 1675 (C=O) and 3020 cm^{-1} ($H\overset{|}{C}=\overset{|}{C}-$); ms M^+ 176.1198 (calcd. for $C_{12}H_{16}O$: 176.1201). Anal. Calcd. for $C_{12}H_{16}O$: C, 81.76; H, 9.16. Found: C, 81.38; H, 9.09.

3-Triethyl silyloxy-5,8aβ-dimethyl-1,4,4aα,7,8,8a-hexahydronaphthalene (51)

Dienone **50** (287 mg, 1.62 mmol) was dissolved in triethylsilane (10 mL) and stirred at room temperature for 10 min. tris-Triphenyl phosphine rhodium(I) chloride (Wilkinson's catalyst) was added in a catalytic amount. Mixture was stirred at room temperature under an argon atmosphere for 6 h and was concentrated *in vacuo*. The resulting residue was then subjected to column chromatography using 20% ethyl acetate in petroleum ether as an eluent to give a yellow oil of pure silyl enol-ether **51** (508 mg; 100% yield): ^{1}H nmr δ0.5-1 (complex, 15H, 3× CH$_3$CH$_2$-), 1.00 (s, 3H, angular CH$_3$-), 1.63 (s, 3H, CH$_3$-C=), 4.80 (br s, 1H, HC=C-OSi-), and 5.36 (br s, 1H, HC=C-); ir 1186-1208 (Si-OCH$_2$CH$_3$) and 1665 cm^{-1} (-C=C-OSi-); ms M$^+$ 292.2224 (calcd. for C$_{18}$H$_{32}$OSi: 292.2222).

5,8aβ-Dimethyl-1,2,4aα,7,8,8a-hexahydro-3[4H]-naphthalenone (52)[*]

Silylenol-ether **51** (500 mg, 1.71 mmol) was dissolved in dry THF (10 mL) and tetra-*n*-butylammonium fluoride (1 M solution in THF; 1.7 mL, 1.71 mmol) was added at 0°C. The mixture was stirred for 1 h at 0°C to room temperature

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[*] When the reaction was carried out under the same condition without isolation of the intermediate silyl enol-ether **51**, the ketone **52** was obtained in 89% yield over two steps.

under an argon atmosphere. The solution was concentrated and residue was purified by flash column chromatography using 10% ethyl acetate in petroleum ether as an eluent to afford the saturated ketone **52** (226 mg; 73% yield: ^{1}H nmr δ1.00 (s, 3H, angular CH_3-), 1.58 (s, 3H, $CH_3-\overset{|}{C}=$), and 5.40 (br s, 1H, $H\overset{|}{C}=\overset{|}{C}-$); ir 1710 (C=O) and 3040 cm^{-1} ($HC=\overset{|}{C}-$); ms M^+ 178.1356 (calcd. for $C_{12}H_{18}O$: 178.1358).

3[4]-(t-Butylthiocarbonyl cyanomethylene)-5,8aβ-dimethyl-1,2,4aα,7,8,8a-hexahydronaphthalene (**53**) and 3-(t-butylthiocarbonyl cyanomethyl)-5,8aβ-dimethyl-1,4,4aα,7,8,8a-hexahydronaphthalene (**54**)

S-t-Butyl cyanothiolacetate (458 mg, 2.92 mmol) and DABCO (330 mg, 2.95 mmol) were dissolved in freshly distilled THF (10 mL) and stirred under an argon atmosphere at room temperature for 10 min. Anhydrous sodium sulfate (622 mg, 4.38 mmol) was added followed by slow addition of a solution of ketone **52** (261 mg, 1.46 mmol) in THF (1 mL). The mixture was stirred at room temperature for 48 h. Ice-cold 1N aqueous hydrochloric acid solution was added and extracted with dichloromethane (20 × 4 mL). The extracts were washed with saturated solution of sodium chloride, dried, filtered, and concentrated. Flash column chromatography of the residue on silica gel (40% benzene in petroleum ether) afforded an isomeric mixture of the condensed product **53** (42.26 mg; 58% yield). The following spectral data were recorded on a regioisomeric mixture of **53**: ^{1}H nmr δ0.90 (both s, 3H, angular CH_3-), 1.52,1.54 (both s, 9H total, $-C(CH_3)_3$), and 5.38 (br s, 1H, $H\overset{|}{C}=\overset{|}{C}-$); ir 1375 ($-C(CH_3)_3$), 1670 (C=O), and 2240 cm^{-1} ($C\equiv N$); ms M$^+$ 317.1814 (calcd. for $C_{19}H_{27}NOS$: 317.1813).

Further elution with the same solvent gave a diastereomeric mixture (*ca.* 3:2) of **54** (10.89 mg; 15% yield): ^{1}H nmr δ0.78 (s, 3H, angular CH_3-), 1.50 (s, 9H, $-C(CH_3)_3$, for major isomer), 1.52 (s, 9H, $-C(CH_3)_3$, for minor isomer), 4.05 (br s, 1H, $-\overset{|}{C}\underline{H}CN$, for minor isomer), 4.75 (br s, 1H, $-\overset{|}{C}\underline{H}CN$, for major isomer), 5.38 (m, 1H, C-6 vinylic proton), and 5.90 (m, 1H, C-2 vinylic proton); ir 1375 ($-C(CH_3)_3$) and 1670 (C=O); ms M$^+$ 317.1813 (calcd. for $C_{19}H_{27}NOS$: 317.1813).

3-(*t*-Butylthiocarbonyl cyanomethyl)-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (55)

A. Using sodium borohydride as a reducing agent

A mixture of condensed products **53** and **54** (113 mg, 0.35 mmol) was dissolved in absolute ethanol (7 mL) and mixture stirred and cooled to 0°C. Sodium borohydride (3.30 mg, 0.09 mmol) was added and mixture stirred for 2 h at 0°C under an argon atmosphere. Afterwards, the mixture was washed with ice-cold saturated ammonium chloride solution, extracted with dichloromethane (10 × 3 mL) and the extracts washed with saturated sodium chloride solution. The extracts were combined, dried, filtered, and concentrated. Column chromatography (flash) of the crude product on silica gel (50% benzene in petroleum ether) afforded diastereomeric mixture of saturated cyanothiolesters **55** (83 mg; 74% yield) (the two major isomers being <u>ca.</u> 1:2 ratio from ^{1}H nmr integration). The following spectral data were recorded on the mixture. The following ^{1}H nmr was attributable for the major isomer: ^{1}H nmr δ0.80 (s, 3H, angular CH_3-), 1.52 (s, 9H, $-C(CH_3)_3$), 3.37,3.39 (both d, 1H, J = 8 Hz each, $-\overset{|}{C}HCN$), and 5.34 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$). The following ^{1}H nmr was attributable for the minor isomer: $-C(CH_3)_3$), 3.69,3.70 (both d, 1H each, J = 12 Hz each, $-\overset{|}{C}HCN$), and 5.33 (br s, 1H, $\underline{H}\overset{|}{C}=\overset{|}{C}-$); ir 1360-1380 ($-C(CH_3)_3$), 1678 (C=O), and 2240 cm^{-1} (C≡N); ms M$^+$ 319.1971 (calcd. for $C_{19}H_{29}NOS$: 319.1970).

B. Using lithium tri-t-butoxyaluminum hydride as a reducing agent

Isomeric mixture of condensed products **53** and **54** (98.72 mg, 0.31 mmol) was dissolved in dry THF (5 mL) and cooled to 0°C with stirring. Lithium tri-t-butoxyaluminum hydride (119 mg, 0.47 mmol) was added and the mixture was stirred under an argon atmosphere for 3.5 h at 0°C. The mixture was then quenched with ice-cold 1N aqueous hydrochloric acid solution followed by extraction with dichloromethane (10 × 3 mL). The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The ^{1}H nmr of the crude product was found to be identical to that previously reported in method A (vide supra) as a diastereomeric mixture (ca. 2:3 ratio according to ^{1}H nmr integration). The yield of this reaction was calculated as an overall yield after the subsequent reduction with sodium borohydride (vide infra).

3-(1-Cyano-2-hydroxyethyl)-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (56)

A. By reduction of compound 55*

Compound 55 (185 mg, 0.58 mmol) was dissolved in absolute ethanol (7 mL) and cooled to 0°C with stirring. Sodium borohydride (90 mg, 2.43 mmol) was added and the mixture stirred at room temperature for 10 h under an argon atmosphere. Afterwards, ice-cold water was added and the mixture washed with aqueous saturated solution of ammonium chloride followed by extraction with dichloromethane (20 × 3 mL). The extracts were washed with sodium chloride solution, dried, filtered, and concentrated. The residue was chromatographed on silica gel (50% ethyl acetate in petroleum ether) to give a colorless oil of alcohol **56** (119 mg; 88% yield or 96% yield based on recovered starting material). The following spectral data were recorded on the mixture of diastereomers. The following ^{1}H nmr was attributable for the major isomer: ^{1}H nmr δ0.80 (s, 3H, angular CH_3-), 1.60 (s, 3H, $CH_3-\overset{|}{C}=$), 2.72 (dt, 1H, J = 7 Hz, J' = 6 Hz,

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*Compound 55 obtained by method B gave 81% yield over two steps, of the alcohol **56**.

$-\overset{|}{\mathrm{C}}\mathrm{HCN}$), 3.90 (m, 2H, $-\mathrm{C\underline{H_2}}-\mathrm{OH}$), and 5.36 (m, 1H, $\mathrm{H}\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}-$); the following ^{1}H nmr was attributable for the minor isomer: ^{1}H nmr δ0.87 (s, 3H, angular $\mathrm{CH_3}-$), 1.66 (s, 3H, $\mathrm{CH_3}-\overset{|}{\mathrm{C}}{=}$), 3.02 (m, 1H, $-\overset{|}{\mathrm{C}}\mathrm{HCN}$), 3.90 (m, 2H, $-\mathrm{C\underline{H_2}OH}$), and 5.36 (m, 1H, $\mathrm{H}\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}-$); ir 1060 (C-O), 2260 (C≡N), and 3400-3500 cm^{-1} (-OH); ms M$^+$ 233.1778 (calcd. for $\mathrm{C_{15}H_{23}NO}$: 233.1780).

B. <u>Direct reduction from mixture of **53** and **54** at -40°C to room temperature</u>

Regioisomeric mixture of condensed products **53** and **54** (124 mg, 0.39 mmol) was dissolved in ethanol (7 mL) and cooled to -40°C with stirring for 10 min. Sodium borohydride (69 mg, 1.82 mmol) was added and mixture stirred for 4 h at 40°C under an argon atmosphere. Temperature was increased to room temperature and stirring continued for another 24 h. Isolation and purification processes were performed in the same manner as mentioned in method A, to give a pure colorless oil of alcohol **56** as a mixture of diastereomers (83.17 mg; 91% yield). Spectral data of all respects were identical with those already reported in method A (<u>vide supra</u>).

C. Direct reduction from mixture of 53 and 54 at -78°C to room temperature

Condensed products **53** and **54** (7.13 mg, 0.02 mmol) was dissolved in absolute ethanol (2 mL) and stirred at -78°C under an argon atmosphere for 5 min. Sodium borohydride (3.34 mg, 0.09 mmol) was added and mixture stirred at -78°C for 1.5 h. Temperature was increased to room temperature and stirring continued for another 24 h. Isolation and purification processes were done in the same manner as mentioned in method A, to give a colorless oil of a diastereomeric mixture of alcohols **56** (3.99 mg; 76% yield over two steps). The ^{1}H nmr spectrum was found to be identical to that previously reported in method A (*vide supra*).

3β-(1-Cyanoethenyl)-5,8aβ-dimethyl-1,2,3,4,4aα,8,8a-octahydronaphthalene (57) and 3α-(1-cyanoethenyl)-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (58)

Diastereomeric mixture of alcohols **56** (41.97 mg, 0.18 mmol) was dissolved in dry ether (5 mL) and stirred for 5 min. Dicyclohexylcarbodiimide (74 mg, 0.36 mmol) and a catalytic amount of copper(I) chloride were added. The mixture was heated at reflux (50°C) under an argon atmosphere for 8.5 h. It was then brought to a room temperature, diluted with ether, filtered through a sintered glass funnel (4-8 μ) and filtrate concentrated. The residue was purified by flash column chromatography on silica gel (40% petroleum ether in benzene) to give a clear colorless oil of a mixture* of **57** and **58** (37.47 mg; 94% yield) in <u>ca.</u> 2:1 ratio according to ^{1}H nmr integration. This mixture was subjected to separation by a Chromatotron using 5% ether in petroleum ether as an eluent to give **57**, a β-isomer (11.22 mg) and **58**, an α-isomer (<u>ca.</u> 7 mg) and a mixture of **57** and **58** (<u>ca.</u> 10 mg). The following spectral data were attributed to the β-isomer. ^{1}H nmr δ0.82 (s, 3H, angular $\mathrm{CH_3}$-), 1.62 (br s, 3H, $\mathrm{CH_3{-}\overset{|}{C}{=}}$), 2.28 (m, 1H, C-7 axial proton), 5.36 (m, 1H, $\mathrm{H\overset{|}{C}{=}\overset{|}{C}{-}}$), 5.74 (dd, 1H, J = 2 Hz, J' = 1 Hz, $\mathrm{-\overset{|}{C}{=}C\underline{H}H}$), and 5.82 (br s, 1H, $J_{w_{1/2}}$ = 2 Hz, $\mathrm{-\overset{|}{C}{=}CH\underline{H}}$); ir ($\mathrm{CHCl_3}$) 930 (olefinic C-H), 1620 (C=C), and 2210 cm^{-1} (C≡N); ms M$^+$ 215.1[illegible]6 (calcd. for $\mathrm{C_{15}H_{21}N}$: 215.1674). The following spectral data were attributed to the α-isomer: ^{1}H nmr δ0.87 (s, 3H, angular $\mathrm{CH_3}$-), 1.66 (br s, 3H, $\mathrm{CH_3{-}\overset{|}{C}{=}}$), 2.72 (m, 1H, C-7 equatorial proton), 5.34 (m, 1H, $\mathrm{H\overset{|}{C}{=}\overset{|}{C}{-}}$), 5.85 (d, 1H, J = 2 Hz, $\mathrm{-\overset{|}{C}{=}C\underline{H}H}$), and 6.07 (d, 1H, J = 2 Hz,

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*Epimeric mixture at C-7 (according to eudesmane skeleton numbering).

$-\overset{|}{C}=CH\underline{H}$); ir ($CHCl_3$) 930 (olefinic C-H), 1620 (C=C), and 2210 cm^{-1} (C≡N); ms M^+ 215.1663 (calcd. for $C_{15}H_{21}N$: 215.1674).

(±)α-Costal (**34**)

Cyano olefin **57** (10 mg, 0.05 mmol) was dissolved in dry toluene (0.5 mL) (distilled over calcium hydride) and cooled to -78°C with stirring under an argon atmosphere. After 5 min diisobutylaluminum hydride (25% by wt in toluene) (0.05 mL, 0.07 mmol) was added slowly via a syringe. After the mixture had been stirred for 3 h at -78°C, it was washed with dilute aqueous solution of oxalic acid, extracted with ether (2 × 2 mL), and extracts dried, filtered, and concentrated. The resulting crude product was subjected to rapid column chromatography (40% petroleum ether in benzene) to give racemic α-costal (**34**) (5.47 mg; 54% yield): ^1H nmr ($CDCl_3$) δ0.84 (s, 3H, angular CH_3-), 1.60 (s, 3H, $CH_3-\overset{|}{C}=$), 2.56 (m, 1H, $-\overset{|}{C}H-\overset{|}{C}=$), 5.32 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$), 5.90 (br s, 1H, $J_{w_{1/2}}$ = 1.5 Hz, $-C=C\underline{H}H$); 6.30 (br s, 1H, $J_{w_{1/2}}$ = 1.5 Hz, $-\overset{|}{C}=CH\underline{H}$), and 9.54 (s, 1H, -CHO); ^1H nmr (CCl_4) δ0.83 (s, 3H, angular $-CH_3$), 1.58 (s, 3H, $CH_3-\overset{|}{C}=$), 2.53 (m, 1H, $-\overset{|}{C}H-\overset{|}{C}=$), 5.28 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$), 5.90 (br s, 1H, $J_{w_{1/2}}$ = 1.5 Hz, $-\overset{|}{C}=C\underline{H}H$), 6.21 (br s, 1H, $J_{w_{1/2}}$ = 1.5 Hz, $-\overset{|}{C}=CH\underline{H}$), and 9.52 (s, 1H, -CHO);

^{13}C nmr δ194.6, 155.4, 134.7, 132.8, 121.2, 46.9, 40.2, 37.9, 37.2, 32.4, 29.7, 29.0, 27.0, 23.0, 21.1; ir ($CHCl_3$) 940 (olefinic C-H), 1620 (C=C), 1694 (CHO) and 2700 cm^{-1} (aldehyde C-H); ms M^+ 218.1671 (calcd. for $C_{15}H_{22}O$: 218.1671).

(±) Epi-α-costal (59)

Cyano olefin **58** (5 mg, 0.02 mmol) was dissolved in dry toluene (0.5 mL) and solution cooled to -78°C with stirring under an argon atmosphere. Diisobutylaluminum hydride (5% by wt in toluene) (0.15 mL, 0.05 mmol) was added slowly *via* a syringe. The mixture was stirred for 3 h at -78°C, and washed with dilute aqueous solution of oxalic acid, extracted with ether (2 × 2 mL) and extracts dried, filtered, and concentrated. The resulting crude product was subjected to rapid column chromatography (40% petroleum ether in benzene) to give racemic epi-α-costal **59** (2.45 mg; 48% yield): ^1H nmr δ0.85 (s, 3H, angular $-CH_3$), 1.54 (br s, 3H, $CH_3-\overset{|}{C}=$), 3.04 (m, 1H, $-\overset{|}{C}H-\overset{|}{C}=$), 5.34 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$), 6.11 (s, 1H, $-\overset{|}{C}=C\underline{H}H$), 6.48 (d, 1H, J = 1.5 Hz, $-\overset{|}{C}=CH\underline{H}$), and 9.48 (s, 1H, -CHO); ir ($CHCl_3$) 800 (C=C), 1697 (CHO), and 2852 cm^{-1} (aldehyde C-H); ms M^+ 218.1672 (calcd. for $C_{15}H_{22}O$: 218.1671).

3β-(t-Butylthiocarbonyl cyanomethyl)-5,8aβ-dimethyl-3,4,4aα,7,8,8a-hexahydronaphthalene (60) and 3β-(t-butylthio acrylonitriloxy)-4,8aβ-dimethyl3,4,4aα,7,8,8a-hexahydronaphthalene (61)

Triphenylphosphine (110 mg, 0.42 mmol) was dissolved in dry THF (3 mL) and stirred under an argon atmosphere at -15°C for 5 min. Diethyl azodicarboxylate (0.07 mL, 0.42 mmol) was added slowly and cooled to -30°C while stirring. A solution of allylic alcohol **49** (5[illegible]8 mmol) in THF (0.5 mL) was add[illegible]y by a syringe followed by addition of a solution of S-t-butyl cyanothiolacetate (88 mg, 0.5[illegible]l) in THF (0.5 mL). The mixture was stirred for 3.5 h at -35°C under an argon atmosphere. Afterwards, ice-cold water was added followed by washing with 1N aqueous hydrochloric acid solution and extracted with dichloromethane (15 × 4 m[illegible] The extracts were washed with saturated sodium chloride solution, combined, dried, filtered, and concentrated. The crude product was subjected to flash column chromatography on silica gel (40% benzene in petroleum ether) to give an isomeric mixture of compounds **60** (33.86 mg; 36% yield) and **61** (16.17 mg; 18% yield) which were inseparable* by column chromatography. The following spectral data were attributed for compound **60** (a 1:1 diastereomeric mixture) after signals for **61** had been subtracted: ^1H nmr δ0.95,0.98 (both s, 3H each, angular $-CH_3$ for two isomers), 1.52 (s, 9H, $-C(CH_3)_3$, 1.66 (br s, 3H, $CH_3-\overset{|}{C}=$), 3.50 (d, 1/2× 1H, J = 6 Hz, $-\overset{|}{C}HCN$, from one isomer), 3.58 (d, 1/2× 1H, J = 6 Hz, $-\overset{|}{C}HCN$, from another isomer), and 5.34 (m, 1H, $HC=\overset{|}{C}-$); ir 1370 ($-C(CH_3)_3$), 1680 (C=O), and 2240 cm^{-1} (C≡N; ms M^+ 317.1819 (calcd. for $C_{19}H_{27}NOS$: 317.1813). The following spectral data were assigned for compound **61**: ^1H nmr δ1.01 (s, 3H, angular CH_3-), 1.43 (s, 9H, $-C(CH_3)_3$), 1.66 (br s, 3H, $CH_3-\overset{|}{C}=$), 5.00 (s, 1H, $NC-\overset{|}{C}H=\overset{|}{C}-$), 5.4-5.8 (complex, 4H, H_a, H_b, H_c, H_d); ir 2210 cm^{-1} (C≡N); ms M^+ 317.1806 (calcd. for $C_{19}H_{27}NOS$: 317.1813).

3β-(1-Cyano-2-hydroxyethyl)-5,8aβ-dimethyl-3,4,4aα,7,8,8a-hexahydronaphthalene (62)

Isomeric mixture of compounds **60** and **61** (45.52 mg, 0.14 mmol) was dissolved in absolute ethanol (5 mL) and cooled to 0°C with stirring. Sodium borohydride (21 mg, 0.55 mmol) was added and mixture continued stirring for 30 h at room temperature. The mixture was then washed with

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*Separated after subsequent reduction step with sodium borohydride in which **60** was reduced to **62**, and **61** remained intact.

saturated ammonium chloride solution, extracted with dichloromethane (5 × 3 mL) and extracts washed with saturated solution of sodium chloride. The extracts were combined, dried, filtered, and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate in petroleum ether) to give compound **61** (vide supra) and the alcohol **62** (16.92 mg; 78% yield based on the amount of compound **60**). The following spectral data were recorded on a mixture of diastereomers (ca. 1:1 ratio from ^1H nmr integration): ^1H nmr δ0.93, 0.96 (both s, 3H each, angular CH_3-), 1.66 (br s, 3H, CH_3-C[illegible] 2.7-2.9 (complex, 2H, -$\overset{|}{C}\underline{H}$-$\overset{|}{C}$HCN and -$\overset{|}{C}$H-$\overset{|}{C}\underline{H}$CN), 3.90 (br s, 2H, -$C\underline{H_2}$-OH), 5.3-5.8 (complex, 4H, H_a, H_b, H_c, H_d); ir 1060 (C-O), 2260 (C≡N), and 3400-3500 cm^{-1} (-OH); ms M^+ 231.1617 (calcd. for $C_{15}H_{21}NO$: 231.1623).

3-(t-Butylthiocarbonyl cyanomethyl)-5,8aβ-dimethyl-3,4,4aα,7,8,8a-hexahydro-1[2H] naphthalenone (68)

To a solution of S-t-butyl cyanothiolacetate (160 mg, 1.01 mmol) in distilled benzene (7 mL) was added chlorotrimethylsilane (0.11 mL, 0.92 mmol) and cooled to ~5°C with stirring. Sodium hydride (50% dispersion in oil; 72 mg, 1.52 mmol) was added, followed by, after 5 min stirring, dropwise addition of a solution of dienone **47** (121 mg, 0.68 mmol) in dry benzene (0.5 mL). The mixture was heated at reflux for 16 h under an argon atmosphere. It was then cooled to room temperature and 1N aqueous hydrochloric acid solution was added, extracted with dichloromethane (10 × 3 mL) and extracts concentrated. The residue was dissolved in methanol (20 mL), treated with aqueous potassium fluoride solution (0.5 g/10 mL) for 10 min followed by acidification (1N HCl), and extracted with dichloromethane (20 × 4 mL). The extracts were dried, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel* (10% ethyl acetate/skelly B) to give a diastereomeric mixture of 1,4-adduct **68** (136 mg; 75% yield based on recovered dienone **47**) in <u>ca.</u> 2:2:1:1 ratio from ^1H nmr integration. The following spectral data were recorded on the mixture. The following ^1H nmr was attributable for the two major isomers: ^1H nmr δ1.08 (s, 3H, angular CH_3-, from one isomer), 1.12 (s, 3H, angular CH_3-, from another

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*After column chromatography the product **68** was still contaminated with unreacted thiolester due to the same R_f value. Thus, the contaminated product was further purified by molecular distillation using Kugelrohr apparatus (100°C/1.5 torr) for 2 h to distill off the thiolester.

isomer), 1.54 (s, 9H, $-C(CH_3)_3$, from one isomer), 1.52 (s, 9H, $-C(CH_3)_3$, from another isomer), 1.68 (br s, 3H, $CH_3-C=$, overlapping for all four isomers), 3.44 (d, 2/4× 1H, J = 5 Hz, -CHCN, from one isomer), 3.53 (d, 2/4× 1H, J = 5 Hz, -CHCN, from another isomer), 5.42 (m, 1H, HC=C-, overlapping for all four isomers). The following ^1H nmr was attributable for the two minor isomers: ^1H nmr δ1.20 (s, 3H, angular CH_3-, from one isomer), 1.28 (s, 3H, angular CH_3-, from another isomer), 1.56* (s, 9H, $-C(CH_3)_3$), 3.46 (d, 1/4× 1H, J = 5 Hz, -CHCN, from one isomer), 3.64 (d, 1/4× 1H, J = 5 Hz, -CHCN, from another isomer); ir ($CHCl_3$) 1370 ($-C(CH_3)_3$), 1679 (thiolester C=O), 1710 (ketone C=O), and 2220 cm^{-1} (C≡N); ms M^+ 333.1765 (calcd. for $C_{19}H_{27}NO_2S$: 333.1762).

3-(t-Butylthiocarbonyl cyanomethyl)-1-hydroxy-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (69)

A diastereomeric mixture of Michael adduct **68** (41.34 mg, 0.12 mmol) was dissolved in absolute ethanol (4 mL)

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*Another singlet attributable for t-butyl group of other minor isomer was presumably overlapping with singlet from major isomer.

and cooled to 0°C with stirring. Sodium borohydride (10 mg, 0.26 mmol) was added and mixture stirred for 1.5 h at 0°C. Saturated aqueous ammonium chloride solution was added and the resulting mixture extracted with dichloromethane (5 × 3 mL). The combined extract was dried, filtered, and concentrated. Flash column chromatography of the crude product on silica gel (40% ethyl acetate/petroleum ether) gave the mixture of alcohols **69** (30 mg; 75% yield). The following spectral data were recorded on the mixture: ^{1}H nmr δ0.84 (br s, 3H, $J_{w1/2}$ = 4 Hz, angular CH_3-), 1.51 (br s, 9H, $-C(CH_3)_3$), 1.62 (br s, 3H, $CH_3-C=$), 3.4-3.6 (m, 2H, -CHCN and -C<u>H</u>OH), and 5.40 (m, 1H, HC=C-); ir 1370 (-C[illegible]), 1680 (C=O), 2250 (C≡N), and 3500-3600 cm^{-1} (-OH); ms M$^+$ 335.1919 (calcd. for $C_{19}H_{29}NO_2S$: 335.1919).

3-Cyanomethyl-1-hydroxy-5,8aβ-dimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (71)

Mixture of alcohols **69** (74.35 mg, 0.22 mmol) was dissolved in dry chloroform (4 mL) (distilled from calcium hydride) and cooled to 0°C under an argon atmosphere. Methanesulfonyl chloride (0.05 mL, 0.66 mmol) was added slowly by a syringe followed by addition of triethylamine (0.15 mL, 1.10 mmol) and mixture stirred for 6 h at room temperature. The mixture was quenched with ice-cold 1N aqueous hydrochloric acid solution followed by washing the resulting solution with saturated sodium bicarbonate solution. Extracts, after extraction with dichlorometnane (8 × 4 mL), were combined, dried, filtered, and concentrated. This crude mesylate **70** (134 mg) showed satisfactory ir and ^1H nmr as follows: ^1H nmr $\delta 0.81$ (br s, 3H, angular CH_3-), 1.49 (s, 9H, $-C(CH_3)_3$), 1.58 (br s, 3H, $CH_3-\overset{|}{C}=$), 3.00 (s, 3H, CH_3-SO_3-), 3.4-3.6 (complex, 2H, $-\overset{|}{C}HCN$ and $-\overset{|}{C}\underline{H}OH$), and 5.33 (m, 1H, $H\overset{|}{C}=\overset{|}{C}-$); ir 1185, 1360 (O=S=O), 1680 (C=O), and 2260 cm^{-1} (C≡N).

The crude mesylate was dissolved in N,N-dimethylformamide (7 mL) (distilled over phosphorus pentoxide). Sodium iodide (480 mg, 3.20 mmol) and zinc dust (420 mg, 6.40 mmol) were added. The mixture was heated at reflux (~160°C) for 7 h under an argon atmosphere. It was then cooled to room temperature and filtered through a sintered glass funnel by washing with dichloromethane. The filtrate was subsequently washed with water, extracted with dichloromethane (5 × 4 mL) and extracts washed with saturated sodium chloride solution. The extracts were dried, filtered, and concentrated. The crude product was purified by flash column chromatography (30% ethyl acetate in petroleum ether) to afford diastereomeric mixture of alcohols 71 (6 mg; 14% yield from 69). The following spectral data were recorded on the mixture: ^{1}H nmr δ0.80, 0.82 (both s, 3H each, angular CH_3-), 1.64 (br s, 3H, $CH_3-\overset{|}{C}=$), 2.38 (bs d, 2H, J = 6 Hz, $-CH_2CN$), 3.39 (dd, 1H, J = 11 Hz, J' = 4 Hz, $-\overset{|}{C}\underline{H}OH$), and 5.38 (m, 1H, $HC=\overset{|}{C}-$); ir 2260 (C≡N) and 3400-3500 cm^{-1} (-OH); ms M^+ 219.1621 (calcd. for $C_{14}H_{21}NO$: 219.1623).

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