AN ABSTRACT OF THE THESIS OF

Lalith Ratnasiri Jayasinghe for the degree of Doctor of Philosophy in Chemistry presented on May 2, 1988.

Title: Approaches to the Synthesis of the Macrolactone Pyrrolizidine Alkaloids (-)-Integerrimine and (+)-Usaramine.

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Abstract approved: _____
James D. White

A formal total synthesis of the macrolactone pyrolizidine alkaloid (-)-integerrimine (**2**), from R-(+)-citronellal (**93**) is described. Aldehyde **93** was converted to exo methylene derivative **94** which was reduced to allylic alcohol **95**. The epoxides **96** and **98**, obtained in a ratio of 3:1 respectively by Sharpless epoxidation of **95** with diisopropyl (-)-tartrate, were separated as their 3,5-dinitrobenzoates **97** and **99** . Diol **100**, derived from hydride opening of the major epoxide **97**, was protected as the bis-3,5-dinitrobenzoate **101**, which was oxidatively cleaved at the isopropylidene terminus. Methanolysis of the dinitrobenzoates and acid catalyzed lactonization provided δ-lactone **102**, the structure of which was confirmed by X-ray crystallographic analysis. Oxidation of the primary alcohol of **102**, followed by introduction of the E-ethylidene group, furnished **31** which has been previously converted to (-)-**2** .

The Sharpless epoxidation of **95** employing (+)-tartrate furnished **98** and **96** in 96:4 ratio respectively. Epoxide **98** was converted to **102** and hence to **31**. Epoxide **98** was also protected as its silyl ether **109** and the olefin was oxidatively cleaved. The resulting carboxylic acid was converted to **110**, acid catalyzed opening of which was anchimerically assisted by the ester function to give δ-lactone **112**.

The primary alcohol of **112** was reduced to a methyl group via iodide **113** and removal of the silyl blocking group from **114** then yielded **102**.

An approach to the chiral synthesis of (+)-usaramine (**5**) began from epoxide **98** . The diol **121**, derived from opening of **98** with pivalic acid, was protected as the acetonide **122** and the pivalate ester was reduced to give **123**. Alcohol **123** was oxidized to carboxylic acid **124** which was converted to methyl ester **125**. The latter provided **120**, via acid **126**, by truncation of the isopropylidene group. Since introduction of the E-ethylidene substituent could not be accomplished on **120**, δ-lactone **137** was used as the substrate for the aldol reaction with acetaldehyde. This lactone was prepared from **126** by cleavage of the acetonide, selective protection of the primary hydroxyl of the derived diol as **136**, and subsequent lactonization with Mukaiyama's reagent. Introduction of the ethylidene group and deprotection of **138** provided **139**. The first chiral synthesis of (-)-**140**, the dimethyl ester of naturally occurring (+)-retronecic acid (**117**), was achieved by methanolysis of **139**.

The ester **130** was prepared by titanate-mediated transesterification of **125** with 2-(trimethylsilyl)ethanol and subsequent oxidative cleavage of the olefin. This carboxyl terminus of **130** was coupled with the retronecine derivative **26** via anhydride **150** to yield **143**. A nucleophilic macrolactonization protocol was attempted on **151**, which was obtained by selective desilylation of **143**, but this unexpectedly provided **153** instead of the macrolactone **149**. Further treatment of **153** with excess fluoride at elevated temperature yielded the macrolactone **149**, which contains the carbon skeleton and stereochemistry of (+)-usaramine (**5**) but lacks the ethylidene side chain.

Approaches to the Synthesis of the Macrolactone Pyrrolizidine Alkaloids (-)-Integerrimine and (+)-Usaramine

by

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Date thesis is presented May 2, 1988

Typed by Jeanne Reisner for Lalith Ratnasiri Jayasinghe

To the memory of my parents

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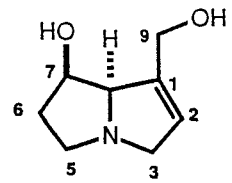
APPROACHES TO THE SYNTHESIS OF THE MACROLACTONE PYRROLIZIDINE ALKALODS (-)-INTEGERRIMINE AND (+)-USARAMINE

INTRODUCTION

Pyrrolizidine alkaloids are found in a wide variety of plant species that include Senecio, Crotalaria, Heliotropium, Amsinckia, Erechtites, Trichodesma and Cocalia.[1,2] Many of these alkaloids have been shown to be hepatotoxic, carcinogenic and mutagenic.[3] Others have shown antitumor activity,[1] but their hepatotoxicity would seem to present an obstacle to their therapeutic usefulness. Hepatotoxic effects in cattle and horses from ingestion of plants containing pyrrolizidine alkaloids have caused a significant economic loss to the livestock industry in many parts of the world.[1,4,5] Since these alkaloids can pass through the food chain they have also become an emerging public health problem.[6,7]

Pyrrolizidine alkaloids frequently occur naturally as macrocyclic dilactones, in which a pyrrolizidine diol (necine base) is esterified with a diacid (necic acid) to produce eleven-, twelve-, thirteen- or fourteen-membered rings.[1,2] Retronecine (**1**) is the pyrrolizidine moiety of many naturally occurring alkaloids. Prominent among



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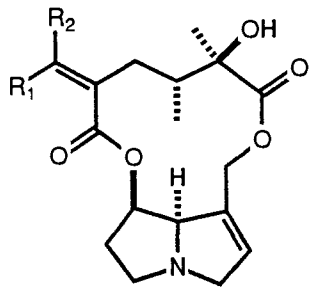
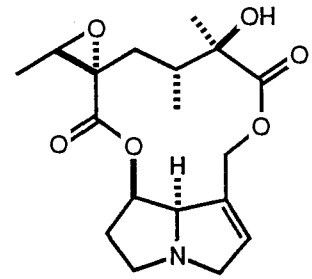
these natural compounds is a set of twelve-membered macrolactones (figure 1) that includes integerrimine (**2**),[8] senecionine (**3**),[9] jacobine (**4**),[10,11] usaramine (**5**),[12] retrorsine (**6**)[9] and yamataimine (**7**).[13]



2 : R_1= H, R_2=CH_3

3: R_1= CH_3, R_2= H



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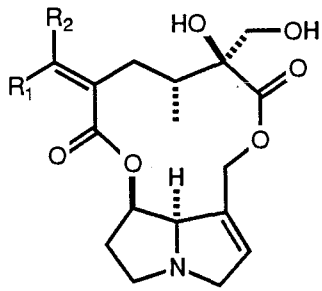

5 : R_1=H, R_2=CH_3

6 : R_1=CH_3, R_2=H

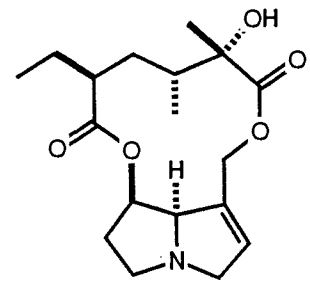

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Figure 1. Twelve-membered macrolactone pyrrolizidine alkaloids

An important structural feature required for toxicity of these alkaloids is the presence of a 1,2 double bond in the pyrrolizidine ring. Evidence has shown[1,14] that the toxic metabolites are not the alkaloids themselves but are pyrrolic derivatives formed by dehydrogenation of the pyrrolizidine moiety. Metabolic activation of pyrrolizidine alkaloids in animals occurs chiefly in the liver, and thus toxic actions in other organs are probably due to metabolites originating in the liver.[1] The toxicity of these pyrrolic derivatives is associated with their reactivity as alkylating agents. As shown in figure 2, donation of the lone pair of electrons on the pyrrolic nitrogen can force elimination of the ester functionality at C-7 and C-9, generating highly electrophilic iminium species. These iminium ions readily undergo nucleophilic attack at C-7 and C-9. It is believed that these two centers provide sites for biological alkylation and thus serve to cross-link biomolecules such as nucleic acids.[1]

The intriguing stuctures and wide range of biological activities associated with the macrocyclic pyrrolizidine alkaloids have attracted the close attention of synthetic organic chemists in recent years. Although the synthesis of retronecine (**1**) has been widely studied, [15-17] only a few reports have so far been published on the necic acids and on the total synthesis of the alkaloids themselves.[18-26]

The first synthesis of a macrocyclic pyrrolizidine alkaloid was achieved by Robins and Sakdarat in 1980.[18] They constructed an unnatural eleven-membered macrocyclic dilactone **11** from (+)-retronecine (**1**) and 3,3-dimethylglutaric anhydride (**8**), as shown in scheme 1. Treatment of 3,3-dimethylglutaric anhydride (**8**) with (+)-retronecine (**1**) in chloroform gave a mixture of C-9 and C-7 monoesters of retronecine (**9** and **10**) in 2:1 ratio. Macrolactonization was achieved by the

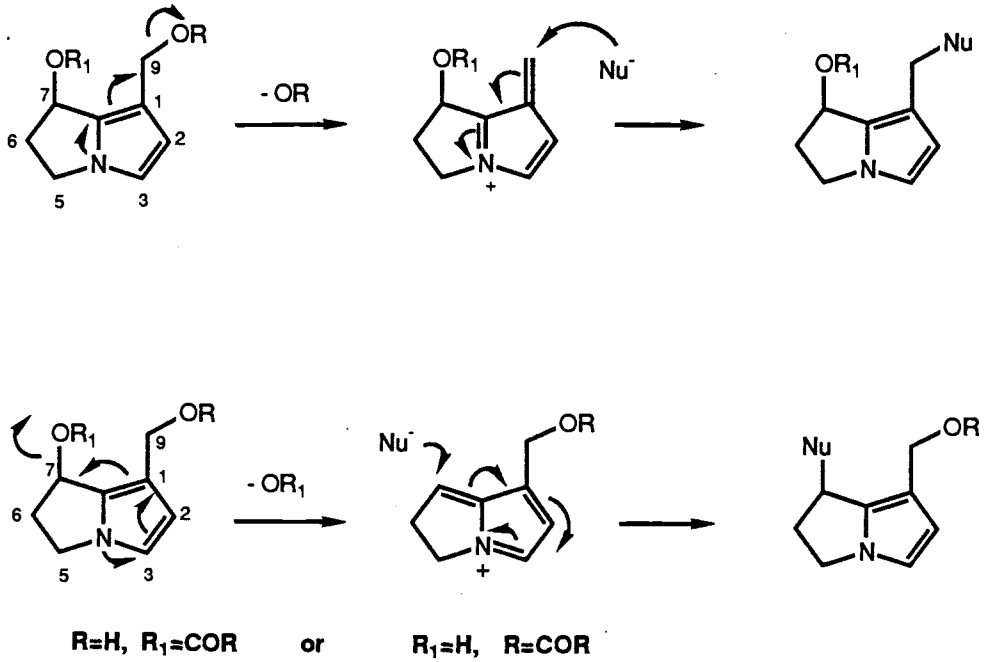
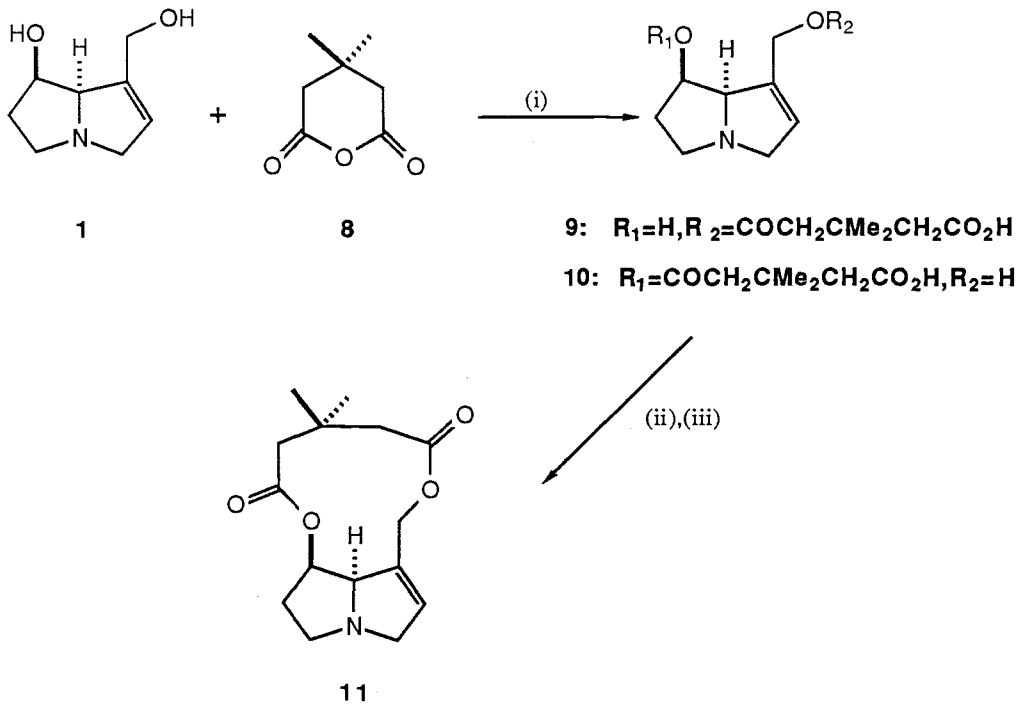


Figure 2. Mechanism of bialkylation of pyrrolic derivatives of pyrrolizidine alkaloids.



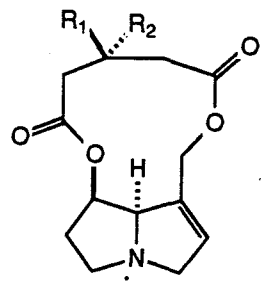
(i) $CHCl_3$, rt, 24h; (ii) 2,2'-dithiopyridine, Ph_3P; (iii) DMF, reflux, 20h

SCHEME 1

Corey-Nicolaou double activation method[27] using pyridine-2-thiol esters to yield the pyrrolizidine alkaloid **11** . Later, Robins et al[19,20] synthesized a natural pyrrolizidine alkaloid, (+)-dicrotaline (**12**) and its C-13 epimer **13** , employing the same strategy.

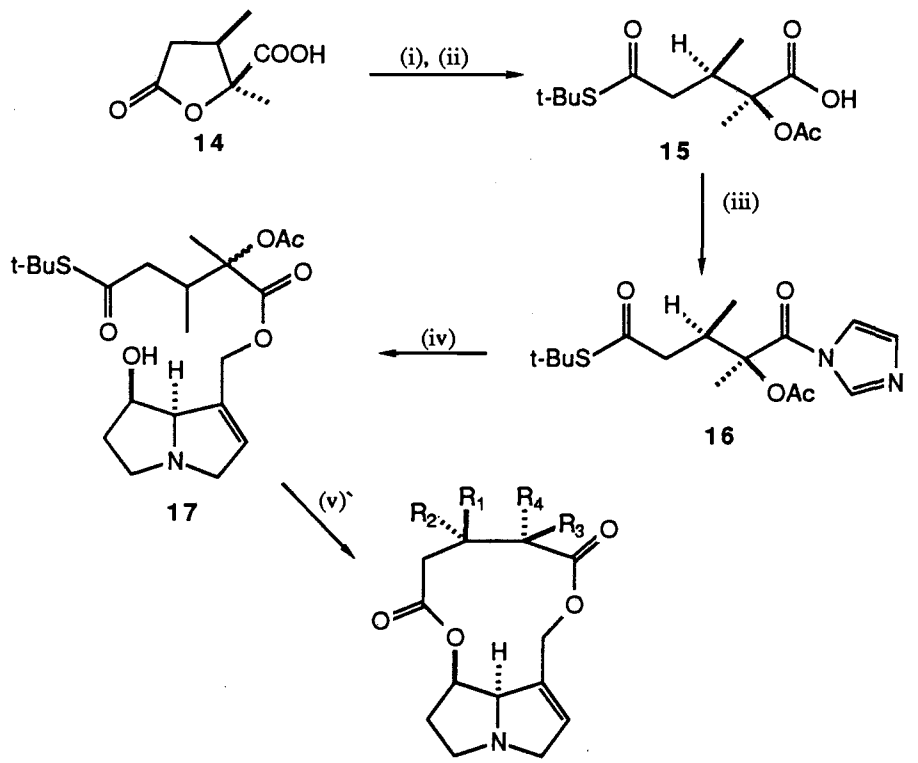
Huang and Meinwald[21] reported a synthesis of an O-acetyl derivative of the macrolactone pyrrolizidine alkaloid crobarbatine and its diastereomer (**18** and **19**), using copper(I) trifluoromethanesulfonate-benzene complex and t-butylthioester **17** in the crucial macrolactonization step (scheme 2). The racemic valerolactone **14** was treated with dimethylaluminum tert-butylsulfide and then with acetic anhydride to give α-acetoxy acid **15**, which was converted to imidazolide **16** with N,N'-carbonyldi-

imidazole. Selective esterification at the allylic hydroxyl group of retronecine (**1**) took place when imidazolide **16** was treated with (+)-(**1**) in the presence of catalytic sodium hydride, and yielded tert-butylthioester **17** . Finally, the macrolactonization using copper(I) trifluoromethanesulfonate-benzene complex afforded **18** and **19** . Unfortunately,attempts at conversion of these acetates to the free alcohols were unsuccessful, and thus comparison of synthetic material with natural crobarbatine was not possible.



12: R_1= OH, R_2= Me
13: R_1= Me, R_2=OH

Vedejs et al [22] used an interesting nucleophilic macrolactonization reaction in their synthesis of (±)-crispatine (**22**) and (±)-fulvine (**23**). The cyclization step involved mesylate displacement by carboxylate ion, which was generated in situ via the desilylation of a trimethylsilylethyl ester **20** (scheme 3). Removal of the methoxymethyl ether from the macrolactone **21** afforded (±)-crispatine (**22**). An analogous sequence of reactions was used to prepare (±)-fulvine (**23**), and Vedejs

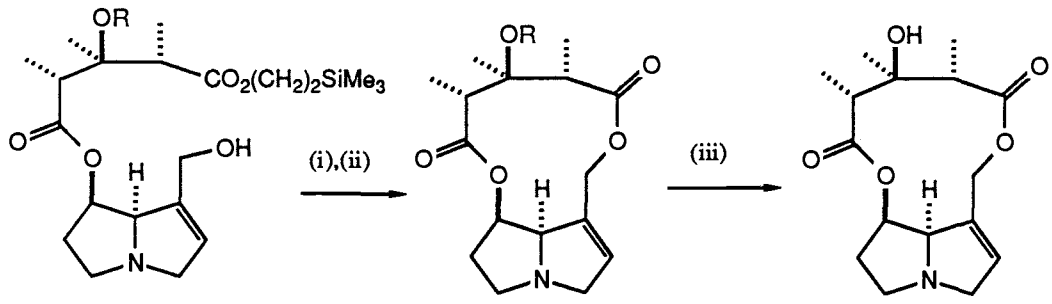


(i) Me_3Al, CH_2Cl_2; Me_2AlS^tBu, CH_2Cl_2; (ii) Ac_2O, Et_3N, DMAP;(iii) N,N'-carbonyldiimidazole, THF; (iv) Retronecine(**1**),NaH(cat), THF; (v) Copper(I) trifluoromethanesulfonate-benzene complex, toluene.

SCHEME 2

also employed this nucleophilic macrolactonization methodology in his recent synthesis of the eleven-membered pyrrolizidine alkaloid, monocrotaline (**24**).[23]

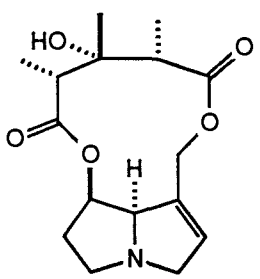
Although over sixty twelve-membered macrolactone pyrrolizidine alkaloids have been found in nature, only integerrimine (**2**) has so far been synthesized. The



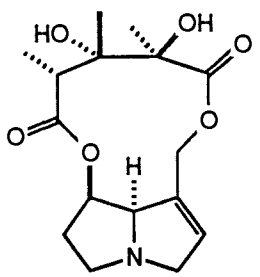
(i) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (ii) Bu_4NF, CH_3CN; (iii) $BF_3.Et_2O$-C_2H_5SH.

SCHEME 3

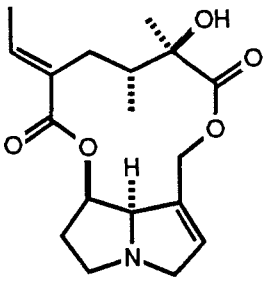
first total synthesis of integerrimine was achieved by Narasaka et al[24] using a new esterification reaction, in which a methylthiomethyl group served as an activatable protecting group for the carboxylic acid. The target molecule (**2**) was constructed by coupling a protected form of integerrinecic acid **25** with 9-tert-butyldimethyl-siloxyretronecine (**26**) via the anhydride **27** (scheme 4). The racemic anhydride **27** was synthesized by the method shown in scheme 5.



23: FULVINE



24: MONOCROTALINE



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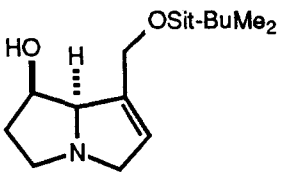

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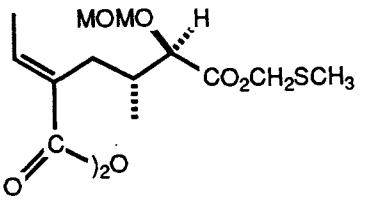

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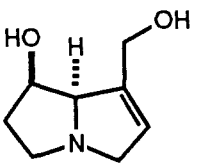

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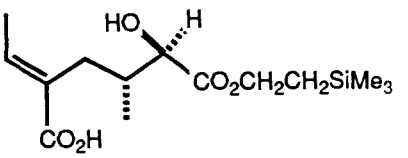

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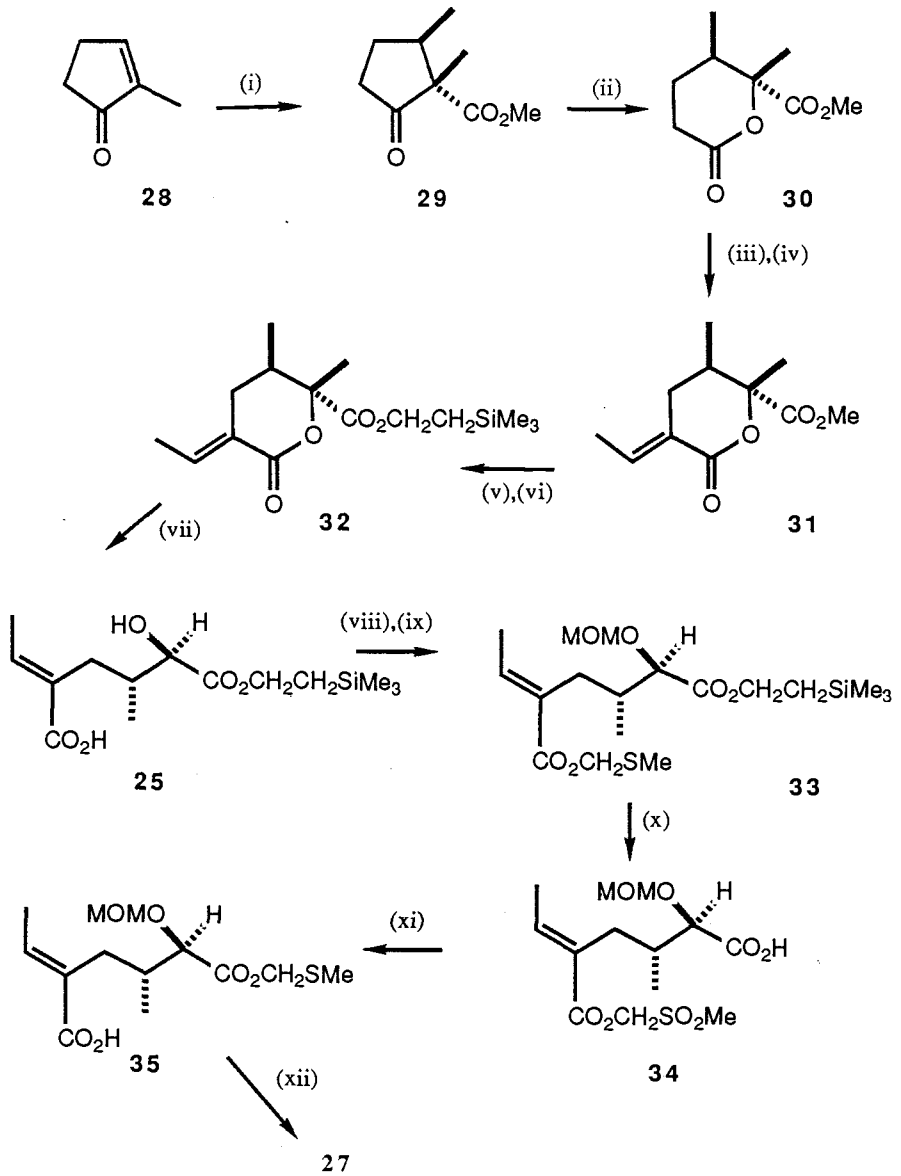
SCHEME 4

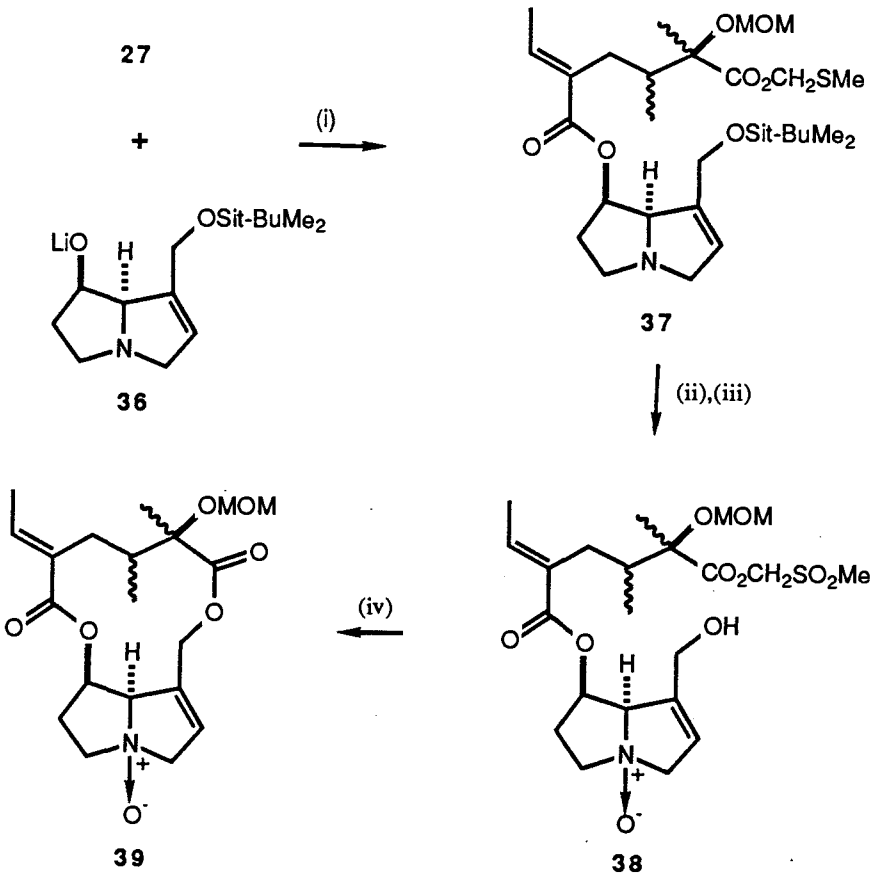
2-Methyl-2-cyclopentenone (**28**) was treated with lithium dimethylcuprate and the resulting enolate was quenched with carbon dioxide. The acid obtained was esterified with diazomethane to afford the methyl ester **29** . After Baeyer-Villiger oxidation of **29** to lactone **30**, the enolate was treated with acetaldehyde. Elimination of the β-hydroxy lactone with Mukaiyama's reagent[28] gave the ethylidene pentanolide **31** with an E: Z-isomer ratio of 6:1. The E ester **31** was separated by chromatography and was converted to trimethylsilylethyl ester **32** via the lactone acid. Selective ring opening of **32** with lithium hydroxide in the presence of hydrogen peroxide[29] afforded the integerrinecic acid derivative **25**. The acid was successively protected as its methylthiomethyl (MTM) ester and as the methoxymethyl (MOM) ether to furnish **33**. Removal of the trimethylsilylethyl group, followed by oxidation of the MTM ester, yielded sulfone **34**. Finally, the tertiary carboxylic acid was protected as its MTM ester, and the methanesulfonylmethyl ester was selectively hydrolyzed with sodium hydroxide to give carboxylic acid **35**. The latter was converted to the anhydride **27** in preparation for coupling with 9-tert-butyldimethylsiloxyretronecine (**26**).

Retronecine (**1**), which was synthesized by a modification of Geissman's route,[15] was selectively protected at the C_9 hydroxyl group as its tert-butyldimethylsilyl (TBDMS) ether **26**. The lithium alkoxide **36** was treated with the anhydride **27** in the presence of catalytic dimethylaminopyridine (DMAP) to yield the ester **37** (scheme 6) as a mixture of two inseparable diastereomers. After removal of the TBDMS group from **37**, the MTM ester was converted to the more reactive



(i) Me_2CuLi, 0°C, Et_2O; CO_2, -78°C; CH_2N_2; (ii) MCPBA, CH_2Cl_2 Li_2CO_3; (iii) LDA, CH_3CHO; (iv) 2-Fluoro-1-methylpyridinium p-toluenesulfonate, Et_3N; (v) LiOH , THF, H_2O; (vi) 2-Chloro-1-methylpyridinium iodide, $Me_3Si(CH_2)_2OH$, Et_3N; (vii) LiOH, H_2O_2, THF, H_2O; (viii) CH_3SCH_2Cl, NaI, $(i\text{-}Pr)_2NEt$; (ix) CH_3OCH_2Cl,NaI, $(i\text{-}Pr)_2NEt$; (x) Bu_4NF; H_2O_2, $(NH_4)_6Mo_7O_{24}$(cat); (xi) CH_3SCH_2Cl, NaI, $(i\text{-}Pr)_2NEt$; 1N NaOH(1eq); (xii) 2-Chloro-1-methyl-pyridinium iodide, Et_3N.

SCHEME 5

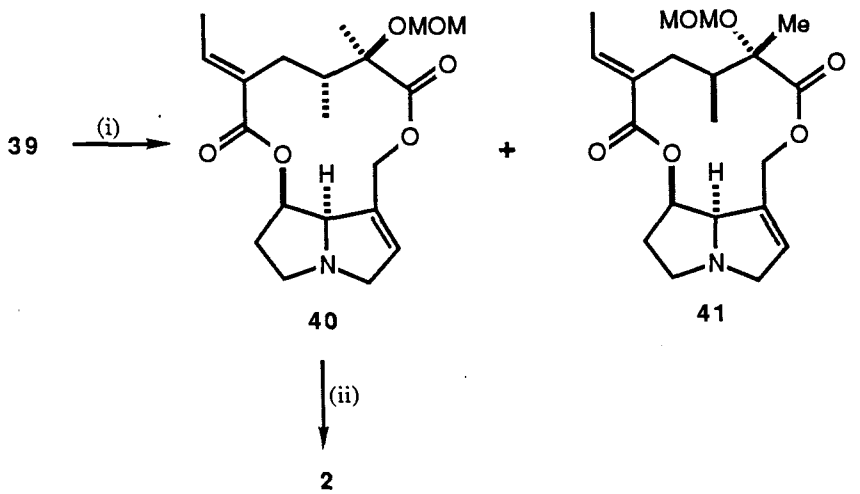


(i) DMAP(cat),THF; (ii) NH_4F,MeOH/H_2O, 60°C; (iii) H_2O_2,$(NH_4)_6Mo_7O_{24}$(cat)
(iv) n-BuLi,THF, -78°C.

SCHEME 6

methylsulfonylmethyl ester **38** with hydrogen peroxide and a molybdenum(VI) catalyst. Macrolactonization was achieved by treating **38** with an equimolar amount of n-butyllithium in tetrahydrofuran to yield the bislactone **39**. After reduction of the N-oxide the diastereomers were separated by preparative thin layer chromatography, affording the desired macrolactone **40** along with **41** in a 1:2 ratio (scheme 7). Acid catalyzed deprotection of the tertiary alcohol in **40** afforded the target integerrimine (2).

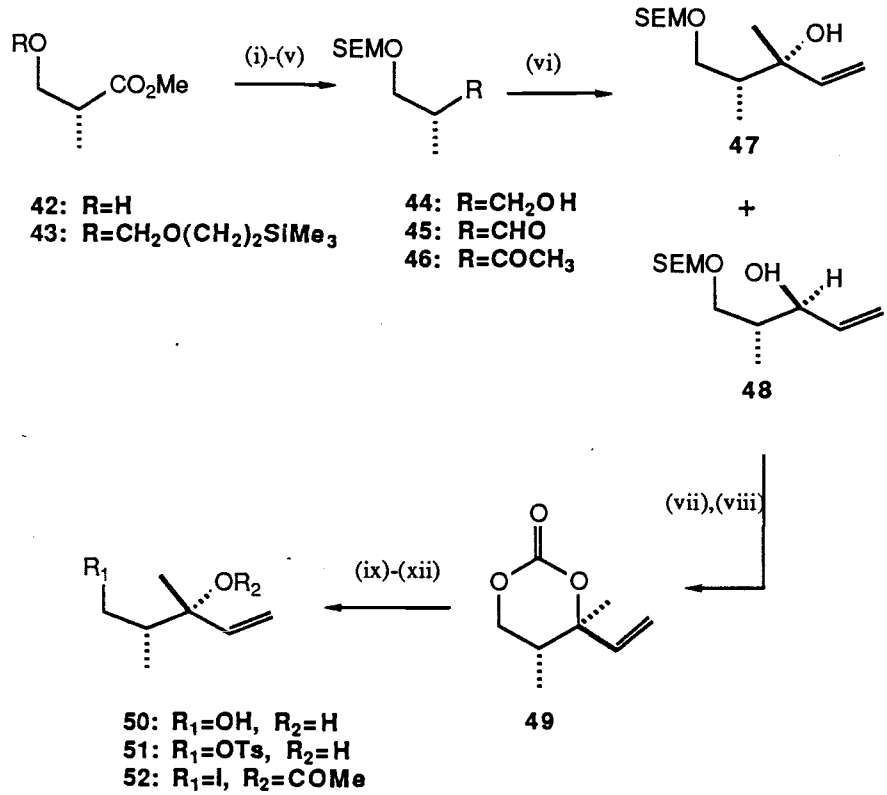
More recently, both White[25]and Yamada[26] reported two elegant, chiral syntheses of integerrimine (**2**). In White's synthesis, optically pure integerrinecic acid derivative **59** was obtained starting from readily available R-(-)-3-hydroxy-2-methyl propionate (**42**) via iodo acetate **52** (scheme 8). Protection of the hydroxyl functionality of **42** as its trimethylsilylethoxymethyl(SEM) ether **43**, followed by reduction with lithium aluminum hydride, yielded the alcohol **44** which was oxidized to the aldehyde **45**. Consecutive treatment of **46** with methylmagnesium bromide and Swern oxidation conditions afforded **46** which, in a chelation controlled Grignard reaction with vinylmagnesium bromide, provided a 4:1 mixture of the desired alcohol **48** and its diastereomer **47**. These were separated as their cyclic carbonates by high-pressure liquid chromatography and the major carbonate **49** was hydrolyzed to **50**. This diol was taken to iodo acetate **52** via the primary tosylate **51**.



(i) Zn, 2N H_2SO_4, DME, rt; (ii) 2N H_2SO_4, DME, 40°C.

SCHEME 7

Exposure of **52** to lithium diisopropylamide and subsequent treatment of enolate **53** with acetaldehyde yielded the β-hydroxy lactone **54** (scheme 9). Acetylation of **54** then gave **55**. Oxidative cleavage of the vinyl substituent and elimination of the acetoxy group cleanly furnished E-isomer **56**, which was converted to the trimethylsilylethyl ester **57**. δ-Lactone **57** was hydrolyzed to

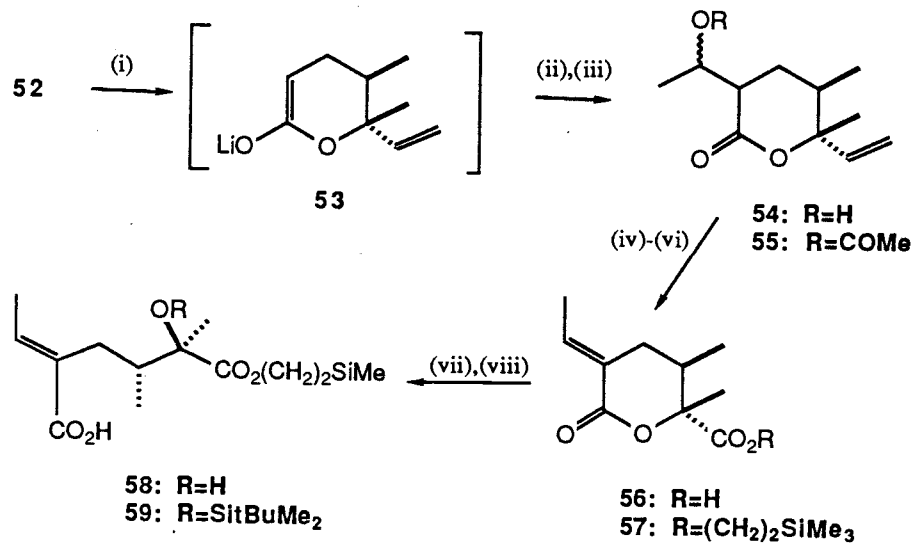


(i) SEMCl , i-Pr_2NEt, CH_2Cl_2, rt ; (ii) $LiAlH_4$, Et_2O, rt, ; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C ; Et_3N ; (iv) MeMgBr, Et_2O; (v) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N; (vi) CH_2=CHMgBr, THF, -78°C, (vii) Bu_4NF, HMPA, 100°C;(viii) N,N'-carbonyldiimidazole, toluene, 90°C, (ix) MeONa, MeOH, rt; (x) TsCl, pyridine, rt ; (xi) NaI, 2-butanone, reflux; (xii) Ac_2O, DMAP, CH_2Cl_2, 0°C.

SCHEME 8

hydroxy acid **58** by the method of Narasaka,[24] and the tertiary alcohol was protected as its tert-butyldimethylsilyl ether **59**.

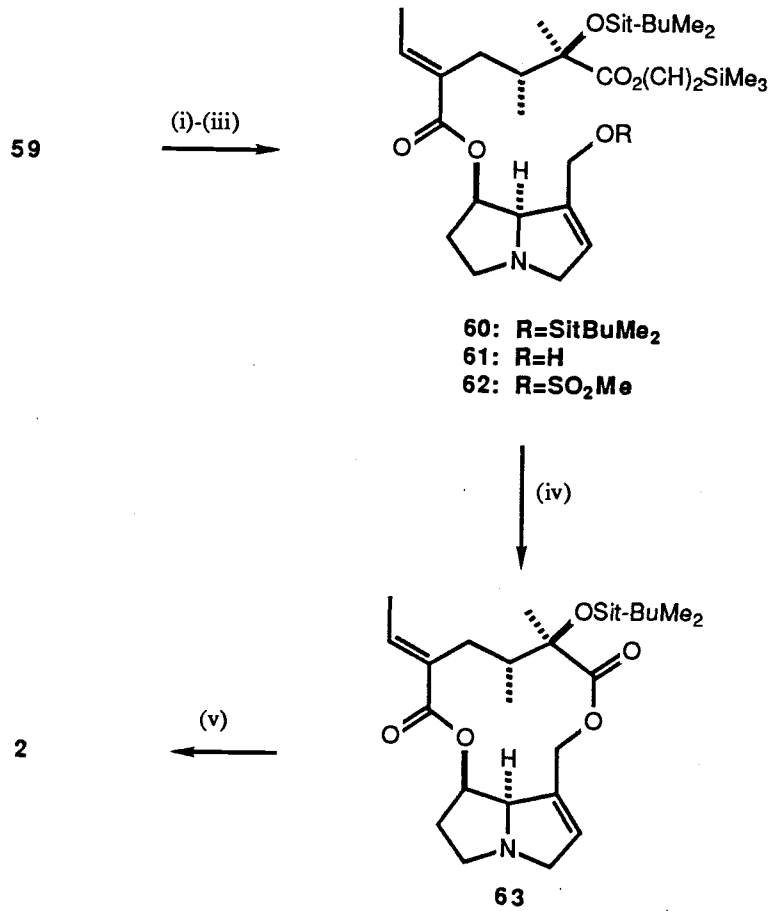
(+)-Retronecine (**1**) was obtained by basic hydrolysis of monocrotaline[30] and the primary hydroxyl group was selectively protected as the tert-butyl dimethylsilyl ether to give **26** . The carboxyl group of **59** was activated as its acyl phosphate,[22,23] and was treated with lithium alkoxide **36** to yield the diester **60**(scheme 10). The primary silyl ether was removed selectively from **60** to provide **61.** Conversion of **61** to macrolactone **63** was achieved via mesylate **62** using the nucleophilic macrolactonization procedure described previously by Vedejs.[22,23] Finally, treatment of silyl ether **63** with hydrogen fluoride afforded (-)-integerrimine (**2**).



(i) 3.5 eq. LDA, THF -78°C; (ii) CH_3CHO, -78°C; (iii) Ac_2O, Et_3N, DMAP(cat); (iv) $RuCl_3.3H_2O$(cat), $NaIO_4$, $CH_3CN/CCl_4/H_2O$; (v) DBU, CH_2Cl_2; (vi) $Me_3Si(CH_2)_2OH$, 2-chloro-1-methylpyridinium iodide, Et_3N; (vii) 1.2eq. LiOH, H_2O_2, THF/H_2O; (viii) 2,6-lutidine, t-$BuMe_2SiOSO_2CF_3$, CH_2Cl_2.

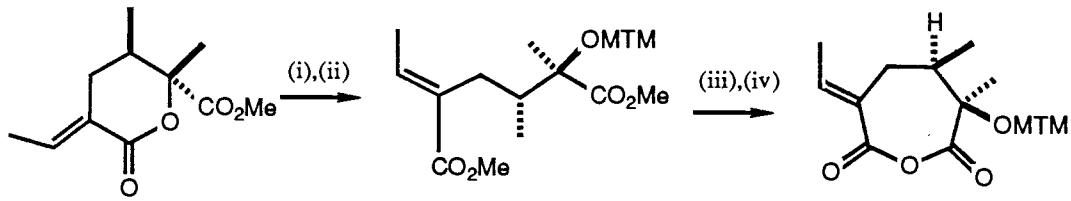
SCHEME 9

Yamada,[26] using a quite different macrolactonization strategy, employed the cyclic anhydride **65** (scheme 11) of integerrinecic acid and stannoxane **66** in a novel coupling reaction to obtain selectively the monoester **67** (scheme 12). In this synthesis, lactone ester **31**, which was also an intermediate in Narasaka's route,[24]



(i) $(EtO)_2POCl$, Et_3N, THF; **36**, DMAP(cat); (ii) NH_4F, $MeOH/H_2O$, 60°C; (iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; (iv) Bu_4NF, CH_3CN, rt; (v) aq. HF/CH_3CN (1:1), rt.

SCHEME 10



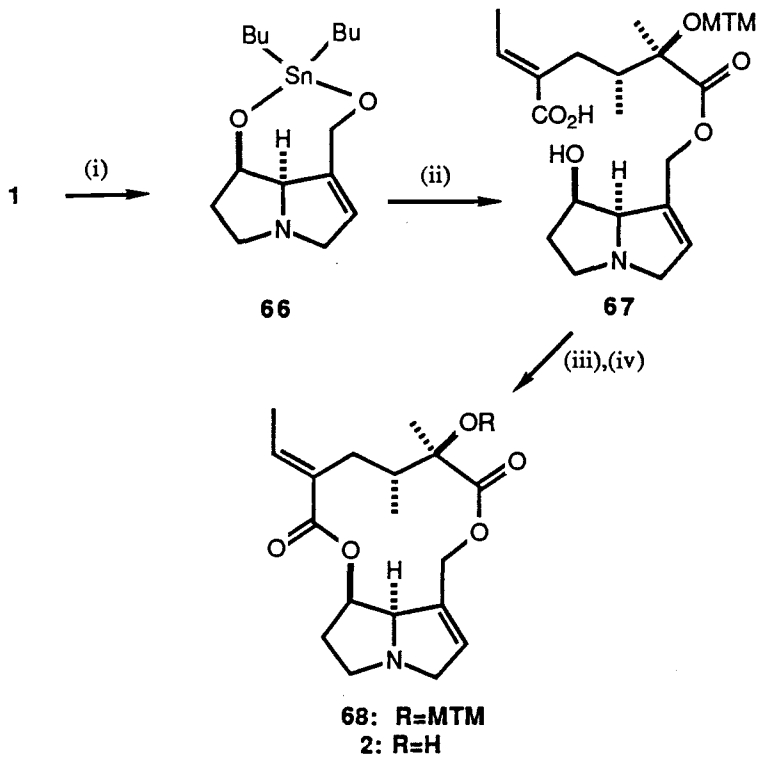
31 64 65

(i) NaOMe, MeOH, rt; (ii) DMSO-Ac_2O, 40°C; (iii) KOH/MeOH, reflux, 1h; (iv) DCC, CH_2Cl_2.

SCHEME 11

was opened by methanolysis and the tertiary alcohol was protected as its methylthiomethyl(MTM) ether **64**.[31] Saponification of **64** to the diacid and subsequent treatment with dicyclohexylcarbodiimide(DCC) afforded the cyclic anhydride **65**.

Retronecine (**1**), which was synthesized in optically pure form,[16] was treated with dibutyltin oxide[32] in benzene and the resulting cyclic stannoxane (**66**) (scheme 12) was reacted with anhydride **65** to yield **67**. Macrolactonization was achieved by the method of Yamaguchi,[33] utilizing 2,4,6-trichlorobenzoyl chloride, and gave **68** in 75% yield. Deprotection of the MTM group with triphenylcarbonium tetraflouroborate[34] furnished (-)-integerrimine (**2**). It is noteworthy that, in this regioselective elaboration of the unsymmetrical dilactone, no protecting groups were used to distinguish the two carboxyl groups in the necic acid nor the two hydroxyl groups in retronecine (**1**).

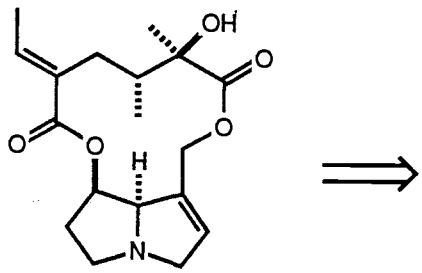


(i) $(n\text{-}Bu)_2SnO$, C_6H_6, reflux; (ii) **65**, 0°C to rt, C_6H_6, 3h; (iii) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, reflux, 1.5h; (iv) Triphenylcarbonium tetrafluoroborate, CH_2Cl_2, rt, 1.5h.

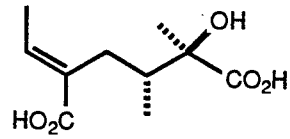
SCHEME 12

FORMAL TOTAL SYNTHESIS OF (-)-INTEGERRIMINE

Several aspects of the previous synthesis of integerrimine (**2**) by White and Ohira[25] were taken into consideration in designing a new and improved strategy. Specifically, the mixture **47/48** obtained from the Grignard reaction of **46** (scheme 8) was a significant obstacle, since the need for high-pressure liquid chromatographic separation of the mixture **47/48** at an early stage in the sequence presented a serious logistical problem. In addition, this approach could not be readily modified to accommodate other pyrrolizidine alkaloids, such as usaramine (**5**). Thus, our goal was to design a more flexible strategy for synthesis of **69** that would avoid these drawbacks and, prospectively, would afford entry to the family of necic acids that bear a 3R methyl substituent (Figure 1.)

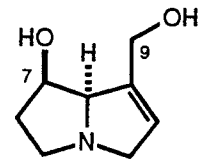


2: INTEGERRIMINE



69

+



1

We envisioned from the outset a strategy for assembling the dilactone (-)-integerrimine (**2**) that combined the natural diol (+)-retronecine (**1**) with a derivative of (+)-integerrinecic acid (**69**). (+)-Retronecine (**1**) can be obtained by basic hydrolysis of monocrotaline[30] and, thus our initial objective was to accomplish a chiral synthesis of (+)-integerrinecic acid (**69**).

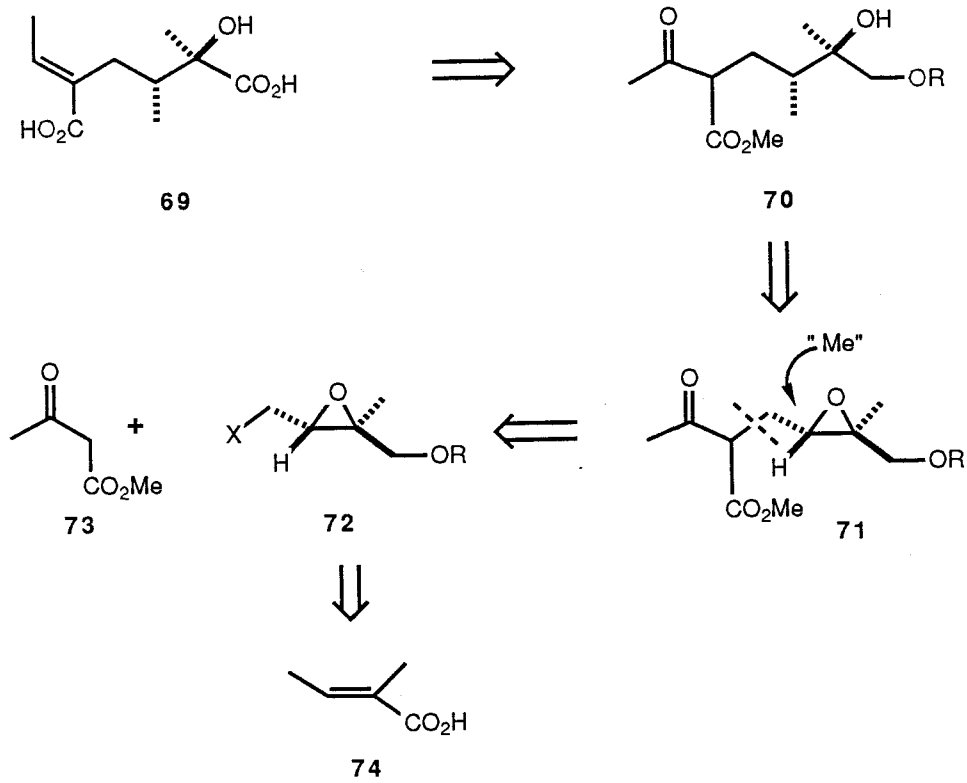
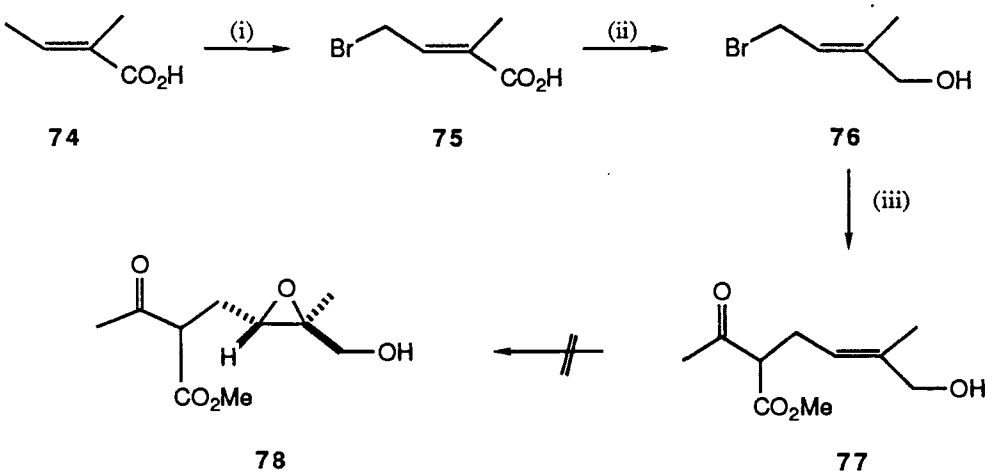


Figure 3. Retrosynthetic analysis of (+)-integerrinecic acid.

It was postulated that both chiral centers in the final target molecule could be introduced by a Sharpless epoxidation of an appropriate allylic alcohol, which should be easily obtained from a commercial starting material. Regio- and stereo-controlled opening of the epoxide by lithium dimethylcuprate would provide the two stereogenic centers with the desired configurations. A retrosynthetic plan for the synthesis of **69**, based on this strategy, is outlined in figure 3. The dicarboxylic acid **69** was to be obtained from β-keto ester **70**, and the latter could, in principle, be acquired by opening of the epoxide **71** with lithium dimethylcuprate. It was anticipated that synthesis of the epoxide **71** could be accomplished through an alkylation of methyl acetoacetate (**73**) with epoxide derivative **72**, which is available from tiglic acid (**74**)

69 are introduced early in the sequence by a single operation.

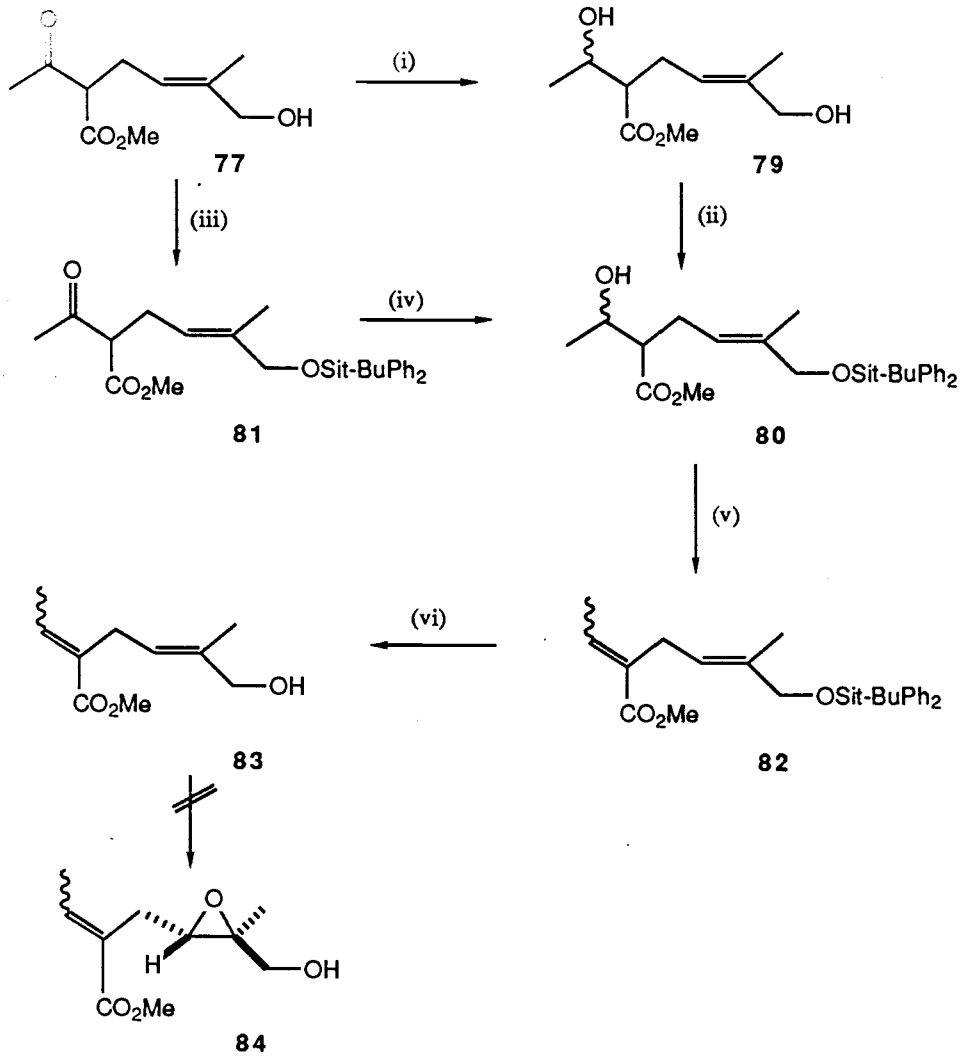
Bromination of tiglic acid (**74**) was carried out with N-bromosuccinimide by a known procedure[35] and γ-bromotiglic acid (**75**) was reduced via the mixed anhydride[36] to allylic alcohol **76** (scheme 13). Treatment of **76** with methyl acetoacetate (**73**) and sodium hydride provided the alkylated product **77** in 60% yield. It was expected that asymmetric epoxidation of **77** with tert-butylhydroperoxide, titanium(IV) isopropoxide, and diisopropyl (+)-tartrate[37] would afford **78** but, surprisingly, mainly starting material was recovered. This unexpected difficulty, perhaps associated with complexation of titanium(IV) with the β-keto ester funtionality, led us to examine an alternative route to **69**.



74 **75** **76** **78** **77**

(i) CCl_4 , N-bromosuccinimide, hυ, 2h, reflux (10%); (ii) NaH, THF, ethyl chloroformate, -20°C to 0°C; $NaBH_4$, -20°C to 0°C (91% crude); (iii) Methyl acetoacetate(2eq.), NaH, THF, rt (73%).

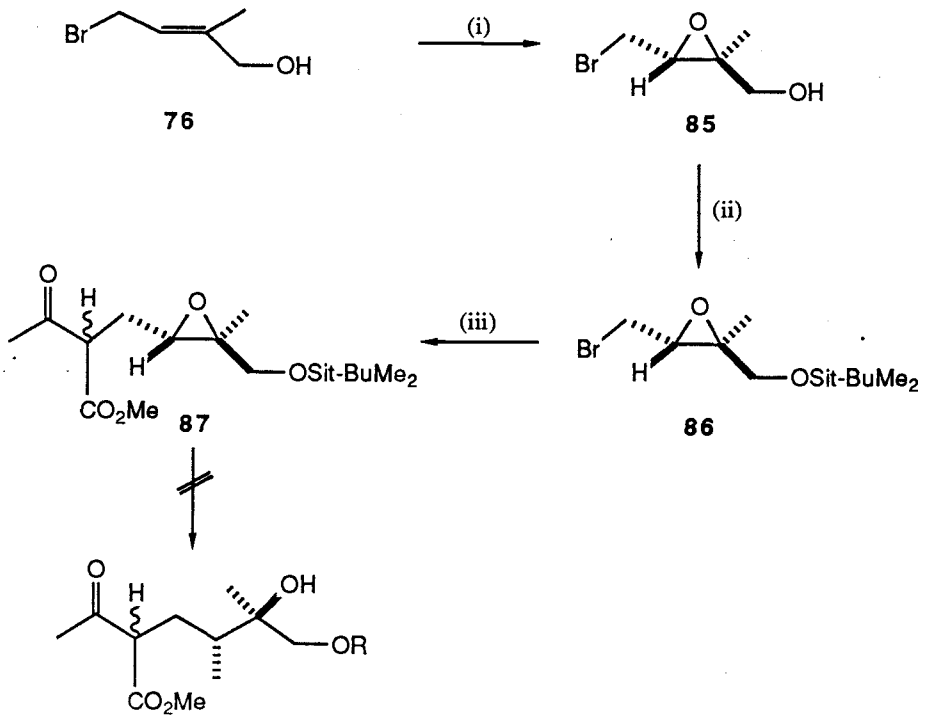
SCHEME 13



(i) $NaBH_4$, MeOH, 0°C (80%); (ii) t-$BuPh_2SiCl$, DMF, imidazole (82%); (iii) t-$BuPh_2SiCl$, DMF, imidazole (93%); (iv) $NaBH_4$, MeOH, 0°C (80%); (v) CH_3SO_2Cl, Et_3N, CH_2Cl_2; DBU (74%); (vi) Bu_4NF, THF (85%).

SCHEME 14

The difficulty associated with Sharpless epoxidation of **77** suggested that allylic alcohol **83** was probably a better substrate for this process. The synthesis of **83** is shown in scheme 14. β-Keto ester **77** was reduced to hydroxy ester **79** and the allylic hydroxyl group was selectively protected as the tert-butyldiphenylsilyl (TBDPS) ether **80** in an overall 66% yield from **77** (scheme 14). The transformation of **77** to **80** could also be carried out in 74% overall yield by first converting **77** to its TBDPS ether **81** and then reducing the keto group. Treatment of β-hydroxy ester **80** with methanesulfonyl chloride, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the α,β-unsaturated ester **82** as an inseparable mixture of E:Z isomers in the ratio 3:1 respectively.

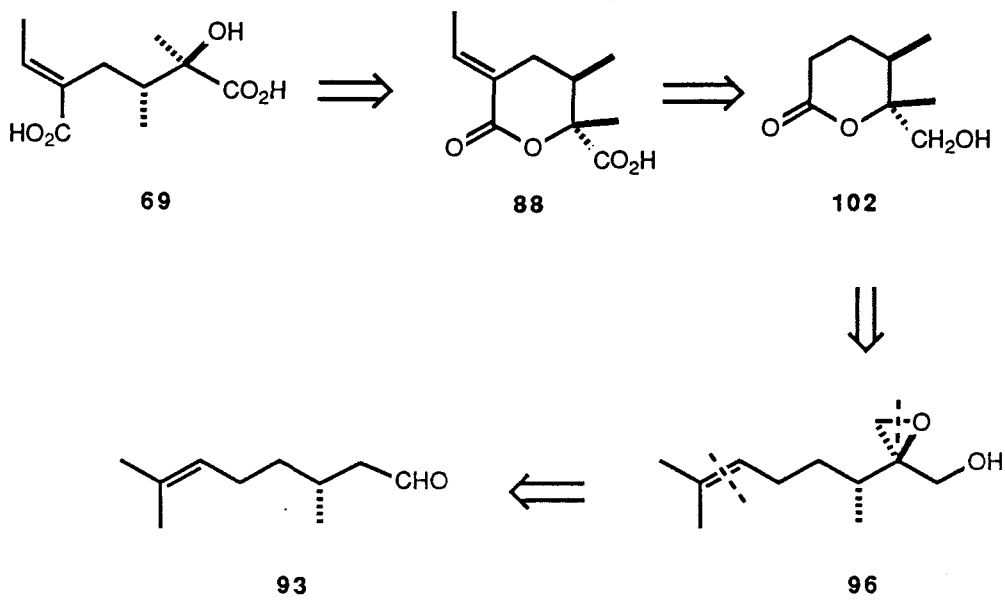


(i) t-Butylhydroperoxide, (+)-DIPT, $Ti(^iOPr)_4$, CH_2Cl_2, -20°C (80%); (ii) t-$BuMe_2SiCl$, DMF, imidazole (68%); (iii) Methyl acetoacetate, NaH, DMF, 45°C (36%).

SCHEME 15

Cleavage of the silyl ether of **82** with tetrabutylammonium fluoride gave allylic alcohol **83** in 85% yield. With the objective of preparing epoxide **84**, **83** was subjected to the same asymmetric epoxidation conditions[37] that were employed with **77** but, again, only starting material was recovered. This chemical inertness of **83** toward Sharpless epoxidation conditions is thought to be due to competing complexation of titanium(IV) with α,β-unsaturated ester in this case.

In view of the difficulty experienced in attempts to epoxidize **77** and **83**, it was decided to effect the asymmetric epoxidation at an earlier stage in the sequence.We were gratified to find that allylic alcohol **76** could be successfully converted to epoxide **85** under the Sharpless asymmetric epoxidation conditions in 80% yield (scheme 15). The hydroxyl function of **85** was protected as its tert-butyldimethylsilyl (TBDMS) ether **86**, and this compound was treated with the sodium enolate of methyl acetoacetate (**73**) to yield the desired alkylation product **87**.



69 **88** **102**

96 **93**

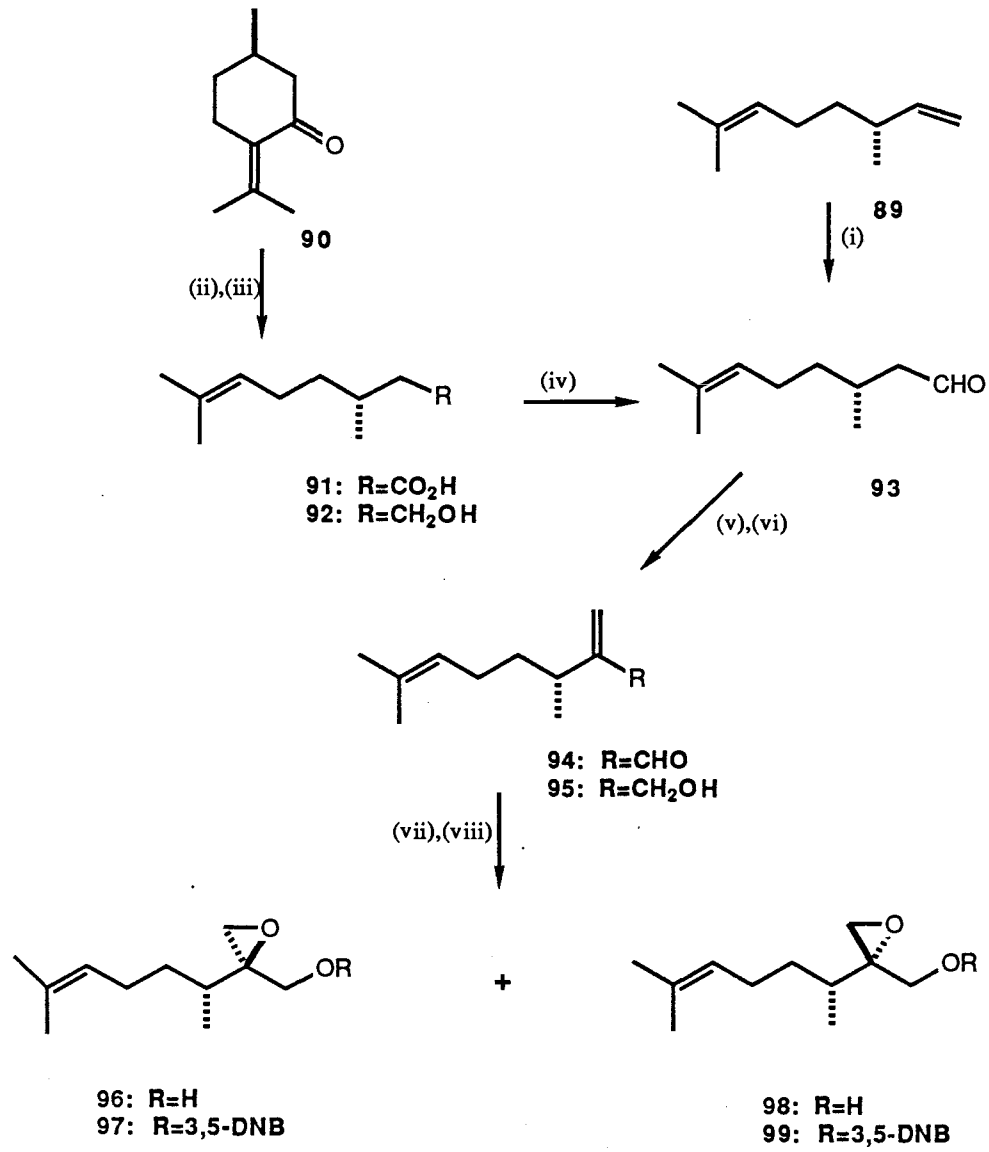
SCHEME 16

The stage was now set for opening of the epoxide to yield **70**. Unfortunately, the trisubstituted epoxide **87** proved to be inert toward lithium dimethylcuprate under a variety of conditions,[38] a result that we attribute to steric hindrance.

In light of these results, it became clear that a different strategy was required to introduce the 3R methyl group into (+)-integerrinecic acid (**69**). An attractive possibility was to start with a compound in which the R methyl substituent was already in place. With this in mind a second approach to the synthesis of **69** was initiated from R-(+)-citronallal. As shown in scheme 16, introduction of the second stereogenic center via epoxide **96** and oxidative cleavage of the trisubstituted olefin would lead to **102**. This lactone could easily be elaborated to (+)-integerrinecic acid lactone (**88**) and then to (+)- integerrinecic acid (**69**) itself.

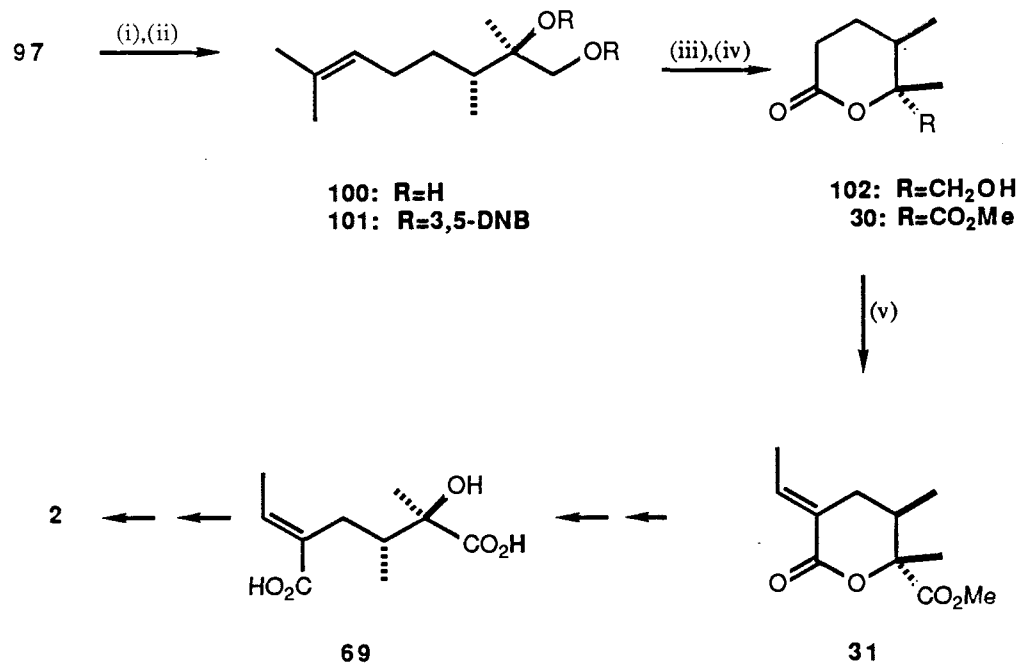
Initially, R-(+)-citronellal (**93**) was obtained by hydroboration, followed by oxidation, of commercially available R-(-)-β-citronellene (**89**) (scheme 17). However the optical purity of **89,** purchased from Fluka, was substantially lower than specification and consequently, the optical purity of **93** obtained by this means was only 73%. Since this was unsatisfactory for our work, optically pure **93** was prepared by a known procedure[39] from R-(+)-pulegone (**90**) via R-(+)-citronellic acid (**91**). Thus , **90** was saturated with hydrogen chloride at -5°C, and the chloro compound obtained was hydrolyzed with sodium hydroxide to provide R-(+)-citronellic acid (**91**). Lithium aluminum hydride reduction of **91**, followed by oxidation, yielded (+)-**93**. This reaction sequence provided easy access to optically pure **93** on a large scale.

The lithium enolate of **93** was alkylated with N,N-dimethylmethylene ammonium iodide, the resulting tertiary amine was quaternized with methyl iodide, and the methiodide was then treated with sodium bicarbonate to provide the exomethylene derivative **94**.[40] Selective 1,2-reduction of the α,β-unsaturated



(i) 9-BBN, THF, 0°C to rt; NaOH, H_2O_2; pyridinium chlorochromate, CH_2Cl_2(42%); (ii) HCl (gas), -5°C; NaOH, rt (53%); (iii) $LiAlH_4$, Et_2O, reflux (97%); (iv) Pyridinuim chlorochromate, CH_2Cl_2(70%) ; (v) $CH_2=N^+Me_2I^-$, LDA, THF; MeI, MeOH; $NaHCO_3$(aq), CH_2Cl_2 (78%); (vi) $NaBH_4$, $CeCl_3.6H_2O$, MeOH (95%); (vii) Cumene hydroperoxide, (-)-DIPT(cat), $Ti(^iOPr)_4$(cat) (69%); (viii) 3,5-Dinitrobenzoyl chloride, pyridine, DMAP (87%).

SCHEME 17



(i) $LiAlH_4$, THF, (82%) ; (ii) 3,5-Dinitrobenzoyl chloride, DMAP, pyridine (87%); (iii) $RuCl_3.3H_2O$ (cat), $NaIO_4$; K_2CO_3, MeOH; 5%HCl, $CHCl_3$ (55%); (iv) $RuCl_3.3H_2O$(cat), H_5IO_6; CH_2N_2 (53%); (v) CH_3CHO, LDA, HMPA; Ac_2O, Et_3N; DBU (50%).

SCHEME 18

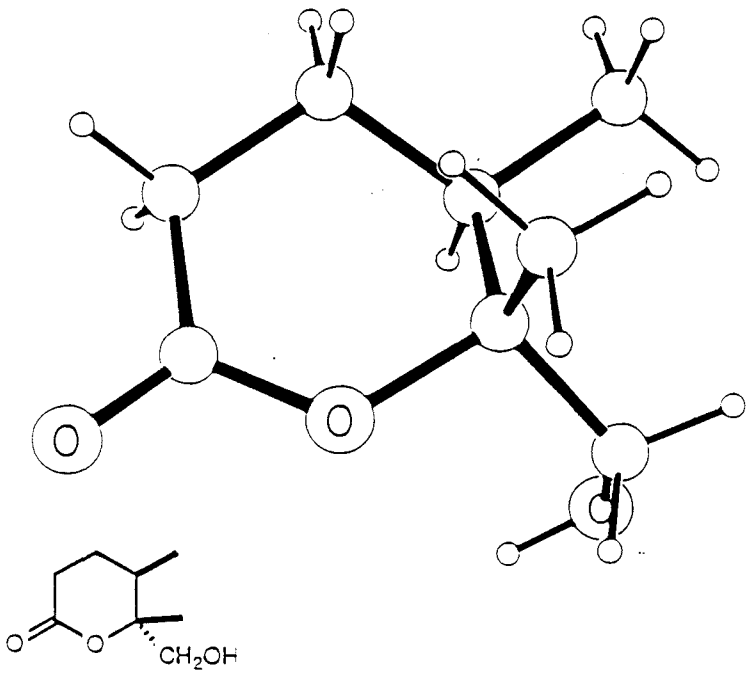
aldehyde **94** employing sodium borohydride in the presence of cerium chloride[41] gave allylic alcohol **95** in 95% yield. At this stage, the new version of the Sharpless epoxidation,[42] using catalytic titanium(IV) isopropoxide and diisopropyl (-)-tartrate was employed. This procedure was more economical and provided better yields than the earlier procedure (scheme 15). It was expected that this epoxidation of **95** would afford **96** but, in fact, a 3:1 mixture of diastereomers **96** and **98** was obtained. The major epoxide was tentatively assigned structure **96**. A probable

explanation for this result is that the asymmetric center adjacent to the double bond of **95**, which renders the two faces of the olefin diastereotopic, exerts a steric bias on the transition state of the epoxidation. In this argument, π–facial selectivity would be determined both by the tartrate and by the preexisting stereogenicity in **95**. Specifically, the configuration at C-3 of **95** would oppose the re face epoxidation directed by (-)-tartrate, giving rise to a stereochemical mismatch. This postulate was supported by the epoxidation of **95** with the enantiomeric diisopropyl (+)-tartrate, which provided **98** and **96** in a 96:4 ratio respectively (scheme 19). This tartrate directs epoxidation to the opposite (si) face of the olefin, with concert with steric bias generated by the preexisting stereogenic center. Thus, asymmetric induction is enhanced in this matched situation, resulting in the highly stereoselective epoxidation, observed.

The epoxy alcohols **96** and **98** were converted to their 3,5-dinitrobenzoates (3,5-DNB) **97** and **99**, which were separated by flash column chromatography and fractional crystallization. Reduction of **97** with lithium aluminum hydride afforded diol **100** in 82% yield. Before oxidative cleavage of the olefin in **100** with ruthenium(IV) was attempted it was necessary to protect the diol and, to this end, **100** was treated with 3,5-dinitrobenzoyl chloride to give the bis-3,5-DNB derivative **101** in 87% yield (scheme 18). Oxidative cleavage[43] of the isopropylidene group of **101** with ruthenium(IV), followed by methanolysis of the 3,5-dinitrobenzoates, and acid catalyzed lactonization, provided **102** in an overall 55% yield from **101**. The structure of **102** was confirmed by a single crystal X-ray crystallographic analysis (figure 4). Oxidation of **102** with catalytic ruthenium(III) chloride[44] and subsequent treatment of the resulting carboxylic acid with diazomethane gave methyl ester **30**, which displayed optical rotation, ^{1}H NMR, IR, and mass spectral data that were

identical to those reported.[24-26]

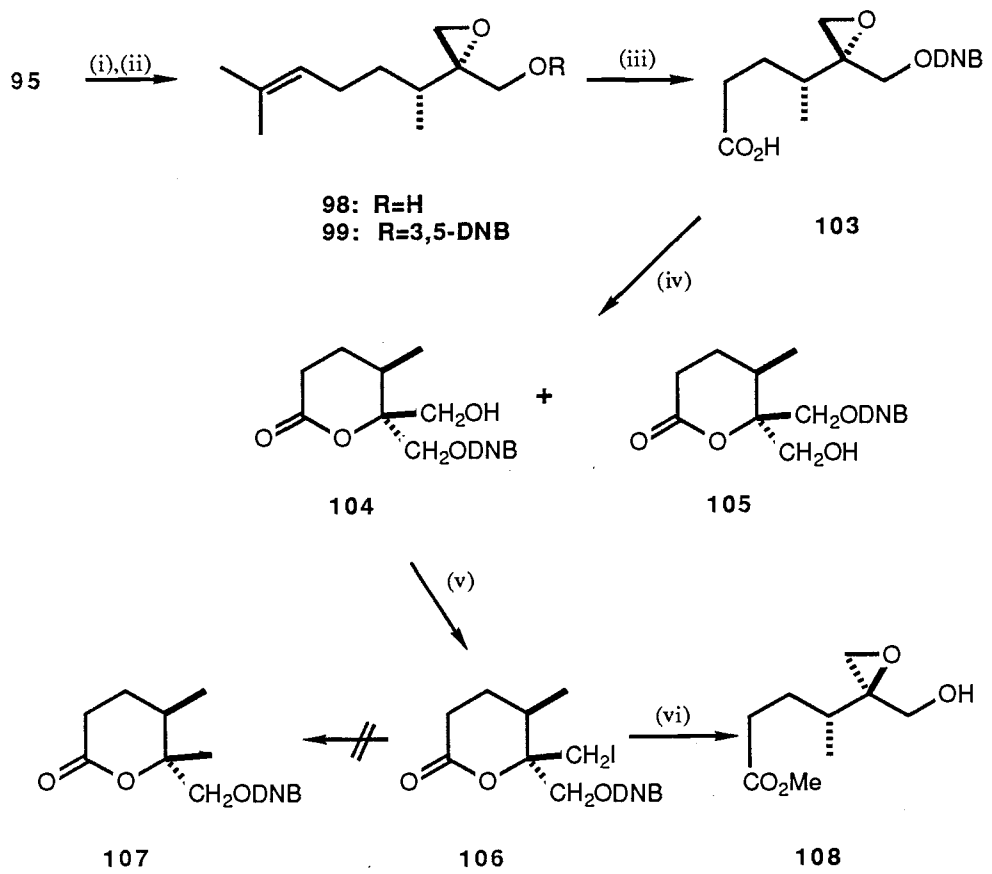
Introduction of the E ethylidene substituent via aldol condensation of **30** and elimination of the derived β-acetoxy lactone followed the route described previously.[24-26] Thus, the lithium enolate of **30** was treated with acetaldehyde and the resulting β-hydroxy lactone underwent elimination via the acetate with 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) to afford **31**. The lactone **31** was found to be identical in all respects to the substance prepared earlier.[24,26,45] Since conversion of **31** to (+)-integerrinecic acid **69** and to (-)-integerrimine (**2**) has already been accomplished,[24-26] this work constitutes a formal, enantioselective synthesis of (-)-integerrimine.



102

Figure 4. ORTEP diagram of **102**

The high stereoselectivity observed in the epoxidation of **95** with diisopropyl (+)-tartrate suggested that, if a means could be found for converting epoxide **98** to **31**, the synthesis of (+)-integerrinecic acid (**69**) could be made substantially more efficient. To obtain the stereochemistry of **31** however, the



(i) Cumene hydroperoxide, (+)-DIPT(cat), $Ti(^iOPr)_4$(cat) (81%); (ii) 3,5-Dinitrobenzoyl chloride, pyridine, DMAP (87%); (iii) $RuCl_3.3H_2O$ (cat), $NaIO_4$; (iv) Camphorsulfonic acid (cat), THF, reflux (44% from **99**); (v) Ph_3P, I_2, imidazole, C_6H_6(82%); (vi) K_2CO_3 (cat), MeOH (79%).

SCHEME 19

epoxide **98** must be opened at the quaternary center with inversion. We foresaw that this might be accomplished via an intermediate such as **103**, in which an acid catalyzed opening of the epoxide anchimerically assisted by the carboxyl group would lead to a δ-lactone. Two variations departing from **95** and employing this strategy are shown in schemes 19 and 20.

After protection of **98** as its 3,5-dinitrobenzoate (3,5-DNB) **99**, the olefin was oxidatively cleaved[43] to afford epoxy acid **103** (scheme 19). Exposure of this epoxide to catalytic camphorsulfonic acid gave two diastereomeric lactones in a 4:1 ratio. The major isomer was separated by flash column chromatography and the product was tentatively assigned the structure **104**. Confirmatory evidence for this assignment was obtained from subsequent transformations. Possible mechanisms for the epoxide opening are shown in figure 5. In pathway a the protonated epoxide would undergo anchimerically assisted opening with inversion of configuration at the quaternary center to afford the major lactone **104**. The minor isomer **105** would be obtained by path b, in which opening of the epoxide to a carbocation is followed in a SN_1 process by lactonization. This would presumably result in both configurations at the quaternary center.

The major lactone **104** was converted to iodide **106** with triphenylphosphine, iodine and imidazole[46] in 82% yield. However, treatment of **106** with tributyltin hydride did not provide **107** as expected, but led to decomposition of the starting material. Attempted removal of the 3,5-DNB group of **106** with catalytic potassium carbonate in methanol gave the epoxy ester **108**. The latter results not only from methanolysis of the 3,5-DNB ester but also from opening of the lactone and subsequent displacement of iodide by the derived alkoxide to form the epoxide.

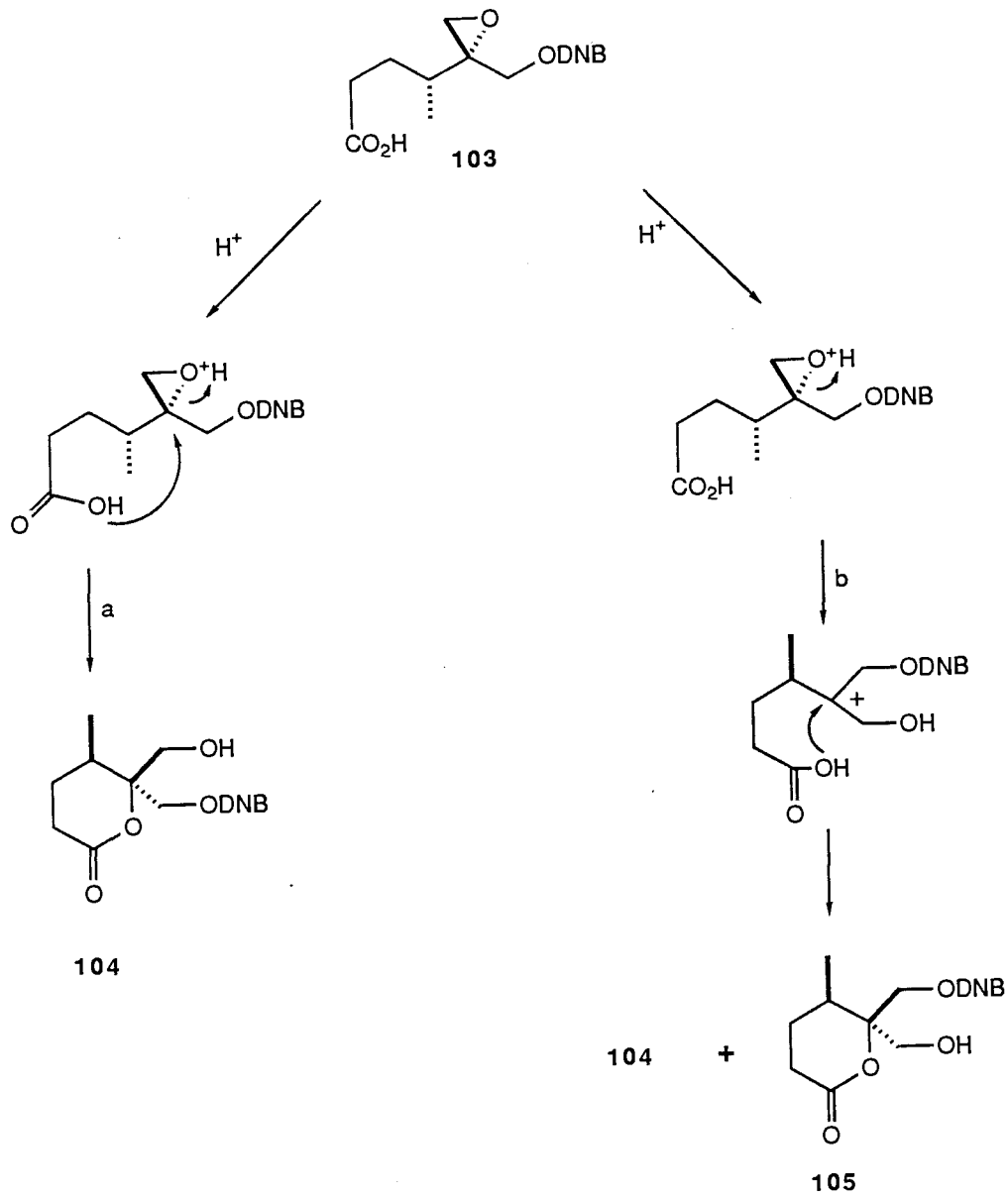
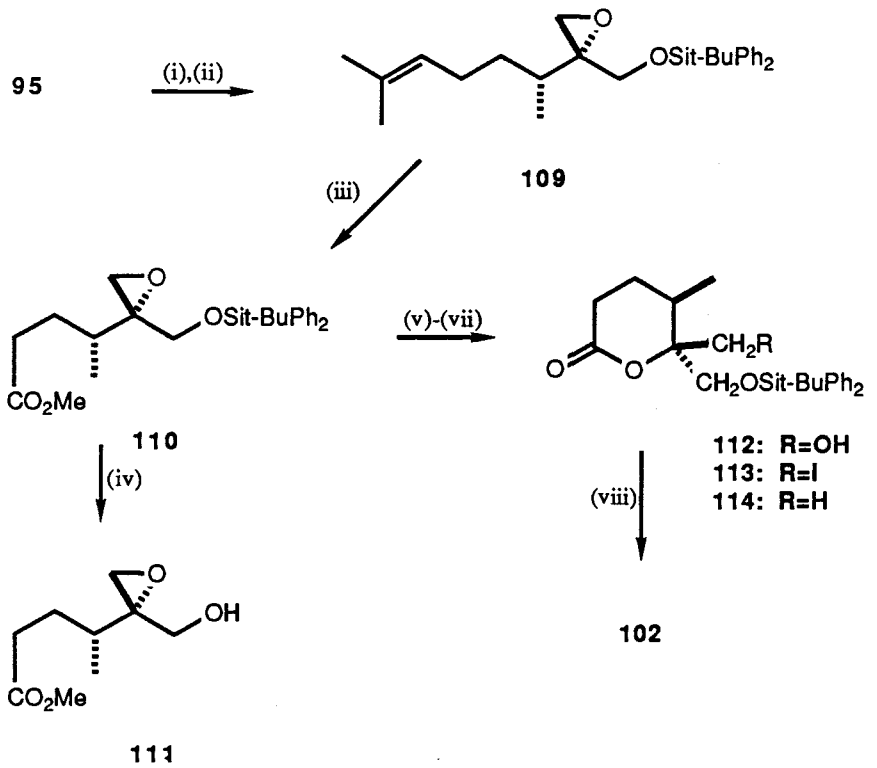


Figure 5. Proposed mechanism for the acid catalyzed epoxide opening.



(i) Cumene hydroperoxide, (+)-DIPT (cat), Ti(^{i}OPr)$_4$ (cat) (81%); (ii) t-BuPh$_2$SiCl, DMF, imidazole (90%); (iii) O_3, CH_2Cl_2, -78°C; CrO_3, H_2SO_4, acetone, 0°C; CH_2N_2 (45%); (iv) Bu_4NF, THF (75%); (v) CF_3CO_2H, $CHCl_3$, -10°C (50%); (vi) Ph_3P, I_2, imidazole, benzene (90%); (vii) n-Bu_3SnH, AIBN; (viii) Bu_4NF, THF (60% from **113**).

SCHEME 2O

It became clear from this sequence that a protecting group different from a 3,5-DNB was needed for the transformation of **98** to **102**. Consequently, **98** was protected as its t-butyldiphenylsilyl (TBDPS) ether **109** (scheme20). With the objective of improving the yield of the oxidative cleavage of the isopropylidene group, a two step oxidation process was investigated at this stage. It was found

that, olefin **109** was rapidly ozonized in methylene chloride at -78°C and , after oxidative work-up and treatment of the derived carboxylic acid with diazomethane, **110** was obtained in 45% yield. Removal of the TBDPS group from **110** afforded **111**, which was found to be the diastereomer of **108** (scheme 19), by comparison of optical rotation, ^{1}H NMR, and ^{13}C NMR data. This correlation circuitously confirms stereochemistry at the quaternary center of the lactone **106** and hence that of **104** .

Epoxide **110** was treated with trifluoroacetic acid to provide hydroxy lactone **112**[47] through an anchimerically assisted epoxide opening by the ester function. The mechanism again for this conversion is assumed to be similar to pathway a in figure 5. Thus, attack at the protonated epoxide by the oxygen atom of the ester carbonyl would result in inversion of configuration at the quaternary center to form **112** and (presumably) methyl triflouroacetate. The primary alcohol of **112** was reduced to a methyl group via iodide **113**,[46] and removal of the silyl blocking group from **114** then yielded **102**. The latter was found to be identical in all respects to the substance prepared from the route shown in scheme 18.

Collectively, these results represent a reasonably efficient synthesis of (+)-**31** in 9 steps and in high stereochemical purity from R-(+)-citronellal (**93**). The flexibility of this approach in providing access to other necic acids is illustrated in the section that follows.

APPROACHES TO THE SYNTHESIS OF THE MACROLACTONE PYRROLIZIDINE ALKALOID (+)-USARAMINE.

The macrolactone pyrrolizidine alkaloid (+)-usaramine (**5**) was first isolated by Culvenor and Smith[12] from the seeds of Crotalaria Usaramoensis E. G. Baker. The structure of (+)-usaramine (**5**), which was elucidated by Culvenor et al,[12] is very similar to (-)-integerrimine (**2**), differing only in the substituent at C-12. In **2** a methyl group with R configuration is present at this center whereas in **5** this is a 12S-hydroxymethyl substituent. In our route to (-)-integerrimine (**2**) the quaternary center at C-12 was generated by opening of the epoxide **97** with lithium aluminun hydride. In designing an approach to usaramine our objective was to adapt our earlier studies to the synthesis of a necic acid derivative, eg. **116** (figure 6), that could be coupled to naturally derived retronecine (**1**). This plan therefore necessitated the development of new chemistry for introducing the hydroxymethyl functionality at C-12 with the desired S configuration.

A crucial step in our approach to (+)-usaramine (**5**)[12] would involve a nucleophilic macrolactonization[22,23] analogous to that employed in the synthesis of intergerrimine (**2**).[25] In this scenario, **115**, which would be obtained by coupling 9-tert-butyldimethylsiloxyretronecine (**26**) to the retronecic acid derivative **116**, would be converted to its mesylate and the latter would undergo displacement by the carboxylate liberated in situ upon cleavage of the 2-(trimethylsilyl)ethyl ester with fluoride. The pyrrolizidine **26** can be obtained from retronecine (**1**), itself available from basic hydrolysis of monocrotaline (**24**).[30] We projected that **116** could be synthesized from the epoxide **98**, which was prepared from R-(+)-citronellal (**93**) in the course of our studies leading to integerrinecic acid (vide supra). Opening of

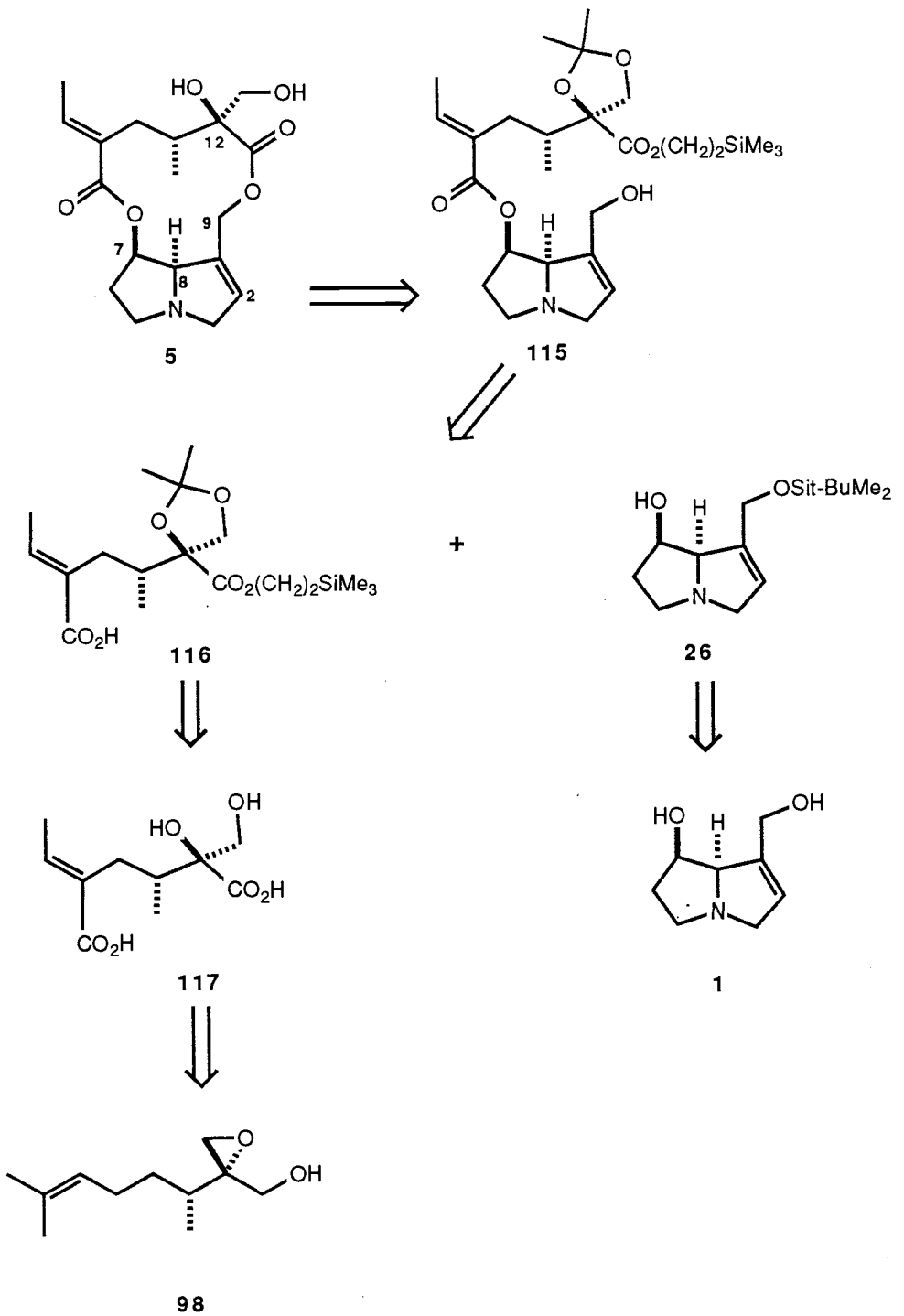
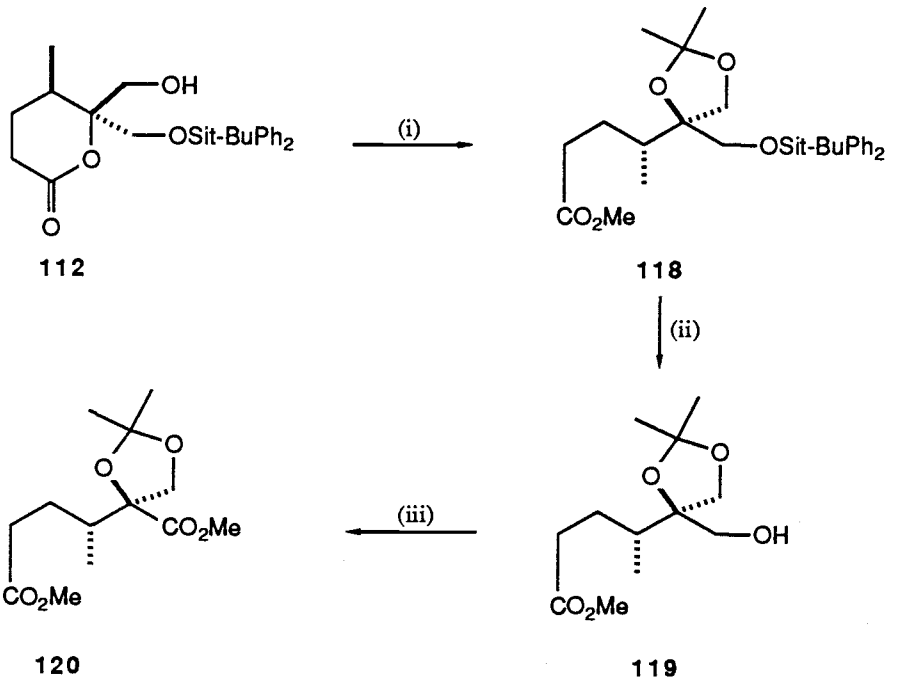


Figure 6. Retrosynthetic analysis of (+)-usaramine

the epoxide **98** under appropriate conditions and adjustment of functionality, including oxidative cleavage of the isopropylidene terminus, would lead to (+)-retronecic acid (**117**) and hence to **116**.

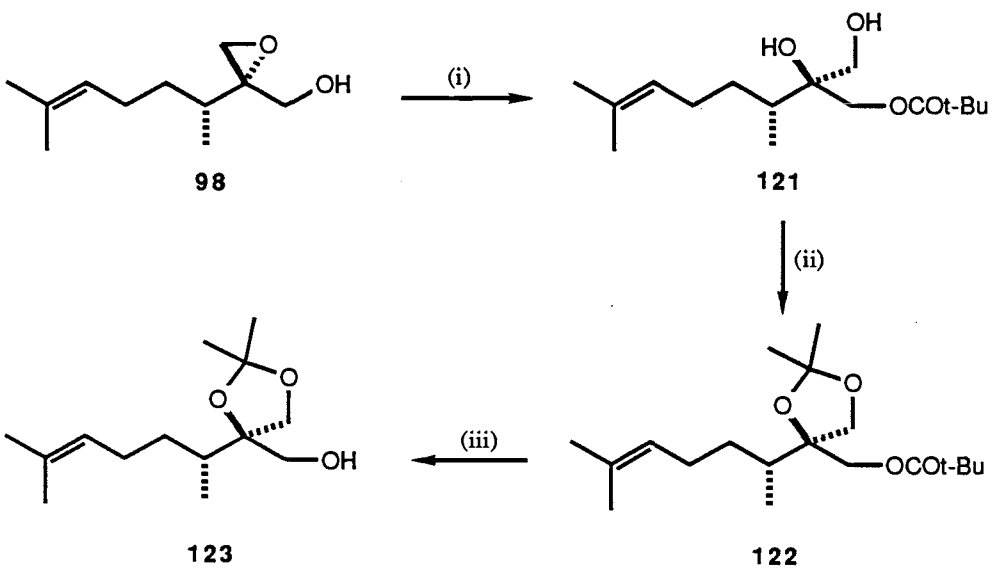


(i) 2,2-Dimethoxypropane, MeOH, camphorsulfonic acid (cat), C_6H_6(87%); (ii) Bu_4NF, THF, (85%); (iii) $RuCl_3.3H_2O$ (cat), $NaIO_4$; CH_2N_2 (61%).

SCHEME 21

Our initial approach toward the synthesis of (+)-retronecic acid (**117**)[48] started from lactone **112** (scheme 21), which had been synthesized in our previous work (scheme 20). Treatment of the hydroxy lactone **112** with methanol and 2,2-dimethoxypropane in the presence of a catalytic quantity of camphorsulfonic acid afforded the methyl ester **118** in 87% yield. Removal of the silyl protecting group from **118** provided **119**, which was converted to **120** by ruthenium(III) catalyzed

oxidation of the primary alcohol and subsequent treatment of the resulting carboxylic acid with diazomethane. The diester **120** contains the carbon skeleton and stereochemistry of retronecic acid but lacks the ethylidene side chain. Although insertion of the latter functionality appeared to present no problem, it was recognised that a potential difficulty awaited us in the need to distinguish the carboxyl groups in retronecic acid (**117**). This is clearly a requirement for regioselective coupling of any derivative of **117** to retronecine (**1**). For this reason, a more flexible and efficient sequence was developed that does, in fact, permit a convenient distinction to be made between the carboxyl termini of the necic acid.



(i) Pivalic acid, $Ti(^{i}OPr)_4$,C_6H_6, rt (51%); (ii) 2,2-Dimethoxypropane, camphorsufonic acid(cat), CH_2Cl_2 (98%); (iii) $LiAlH_4$, Et_2O, reflux, 1h (90%).

SCHEME 22

Epoxide **98**, containing a latent carboxyl terminus in the form of an isopropylidene group and a primary hydroxyl function at the opposite end of the carbon chain was an excellent starting material for this new route. The

titanium(IV)-mediated nucleophilic opening of an epoxy alcohol, as developed by Sharpless,[49] was utilized for introducing the C-12 hydroxymethyl group and it was found that treatment of **98** with pivalic acid in the presence of titanium(IV) isopropoxide provided **121** in fair yield (scheme 22). The resulting diol was then protected as its acetonide to yield **122**. A proposed mechanism for the nucleophilic opening of the epoxide of **98** is shown in figure 7. The alcohol of **98** would presumably first displace isopropoxide from the metal, permitting complexation between the epoxide oxygen and titanium. The complexed epoxide would thereby become activated toward nucleophilic attack at C-3, leading to **121**.

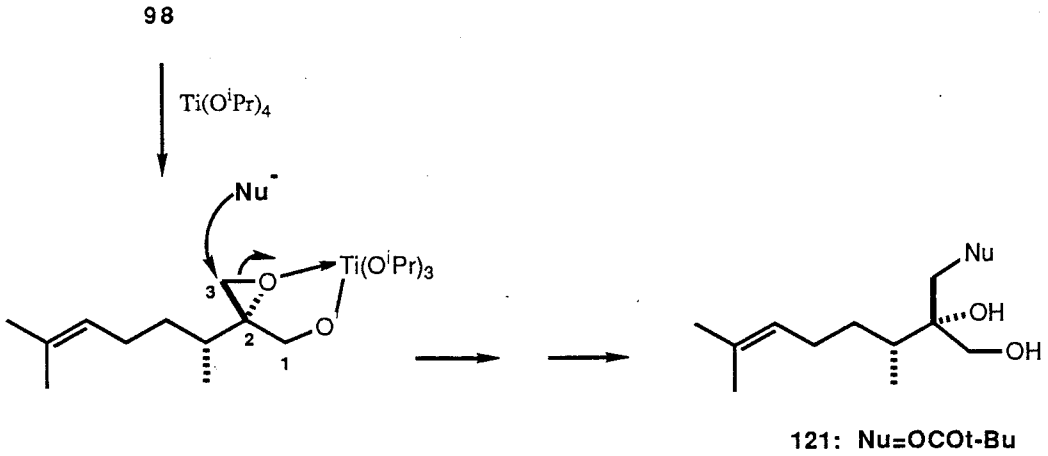
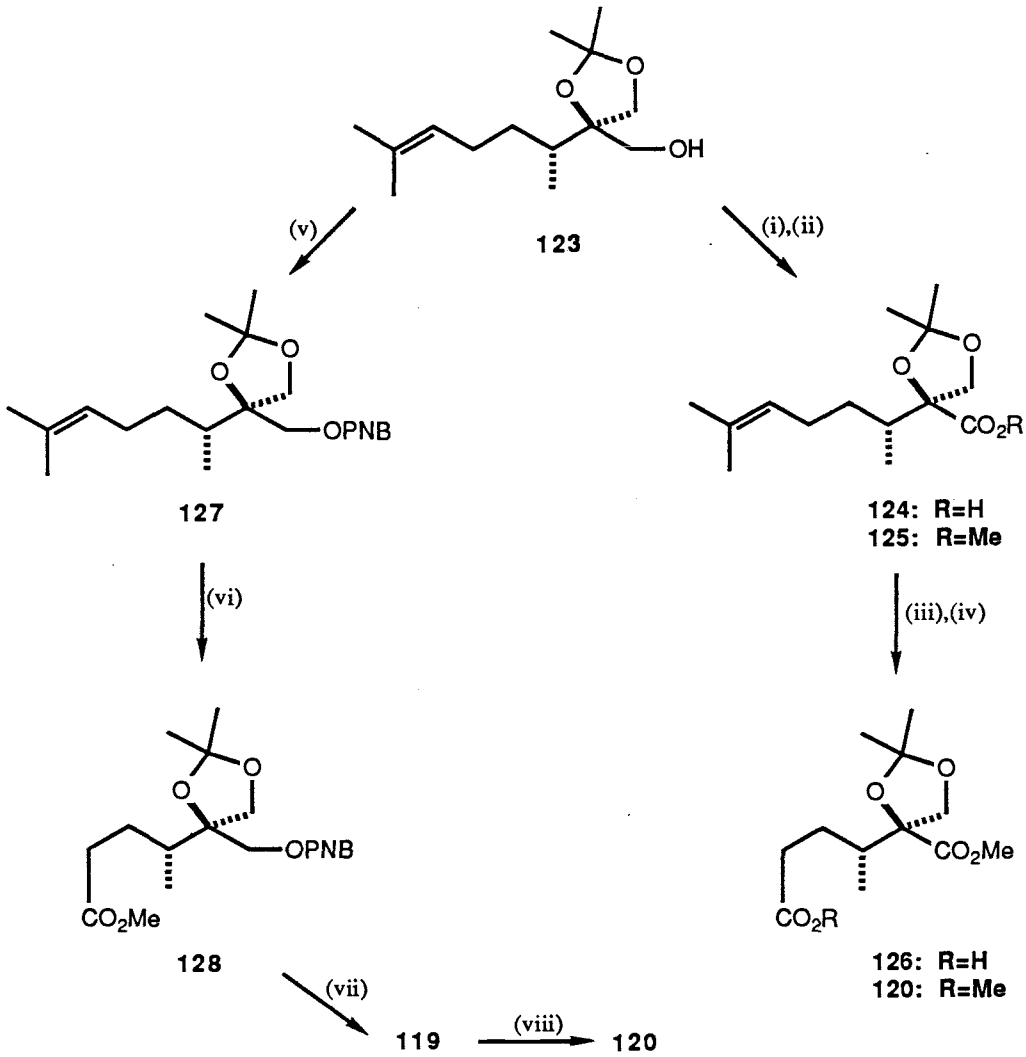


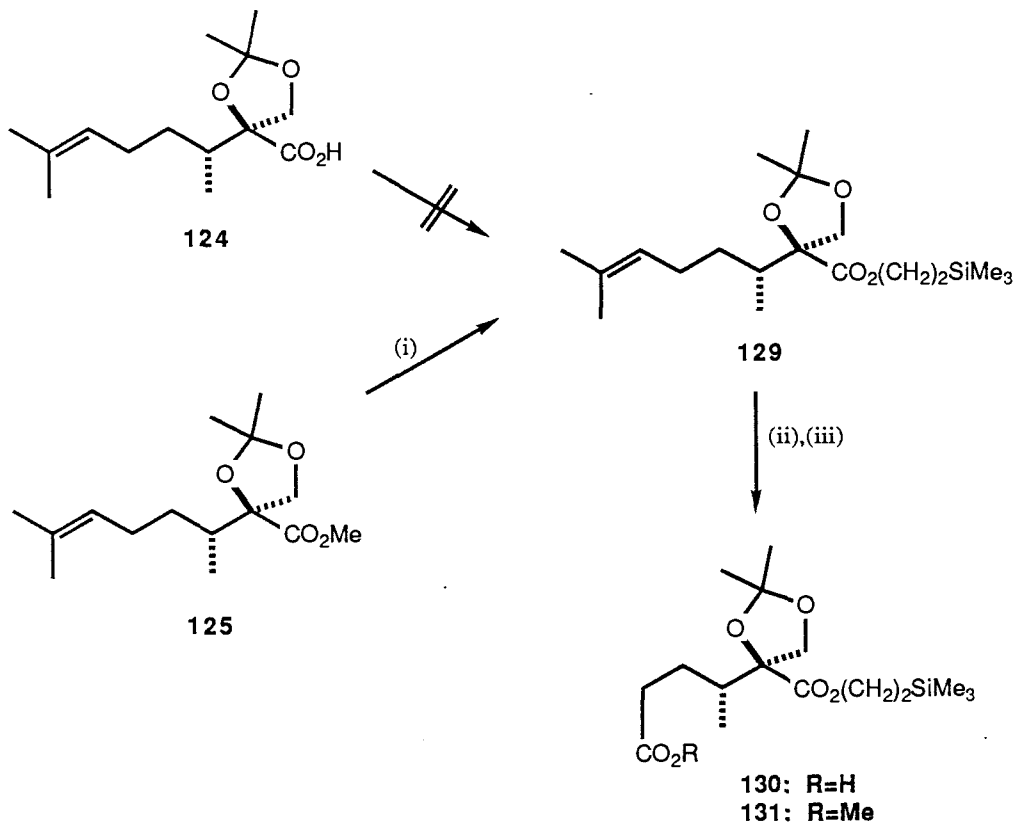
Figure 7. Proposed mechanism for the titanate-mediated nucleophilic opening of epoxide **98**.

Reduction of the pivalate ester of **122** with lithium aluminum hydride gave **123** in an overall 45% yield from **98**. The alcohol **123** was converted to dimethyl ester **120** by two different pathways, demonstrating that either terminus of the necic acid can be selectively functionalized (scheme 23). First, the primary alcohol of **123** was oxidized with pyridinium dichromate to carboxylic acid **124**, which yielded



(i) Pyridinium dichromate, DMF (67%); (ii) CH_2N_2, Et_2O (99%); (iii) $RuCl_3.3H_2O$ (cat), $NaIO_4$, 3h (69%); (iv) CH_2N_2, Et_2O (98%); (v) p-Nitrobenzoyl chloride, pyridine, DMAP (85%); (vi) O_3, CH_2Cl_2, -78°C; dimethyl sulfide; $RuCl_3.3H_2O$ (cat), $NaIO_4$, 15min; CH_2N_2 (58%) (vii) K_2CO_3 (cat), MeOH (65%); (viii) $RuCl_3.3H_2O$ (cat), $NaIO_4$; CH_2N_2 (61%);

SCHEME 23



(i) $Me_3Si(CH_2)_2OH$, $Ti(OEt)_4$, 100°C (93%); (ii) O_3, CH_2Cl_2, -78°C; dimethyl sulfide; $NaIO_4$, $RuCl_3.3H_2O$ (cat), 15 min (66%); (iii) CH_2N_2, Et_2O (99%).

SCHEME 24

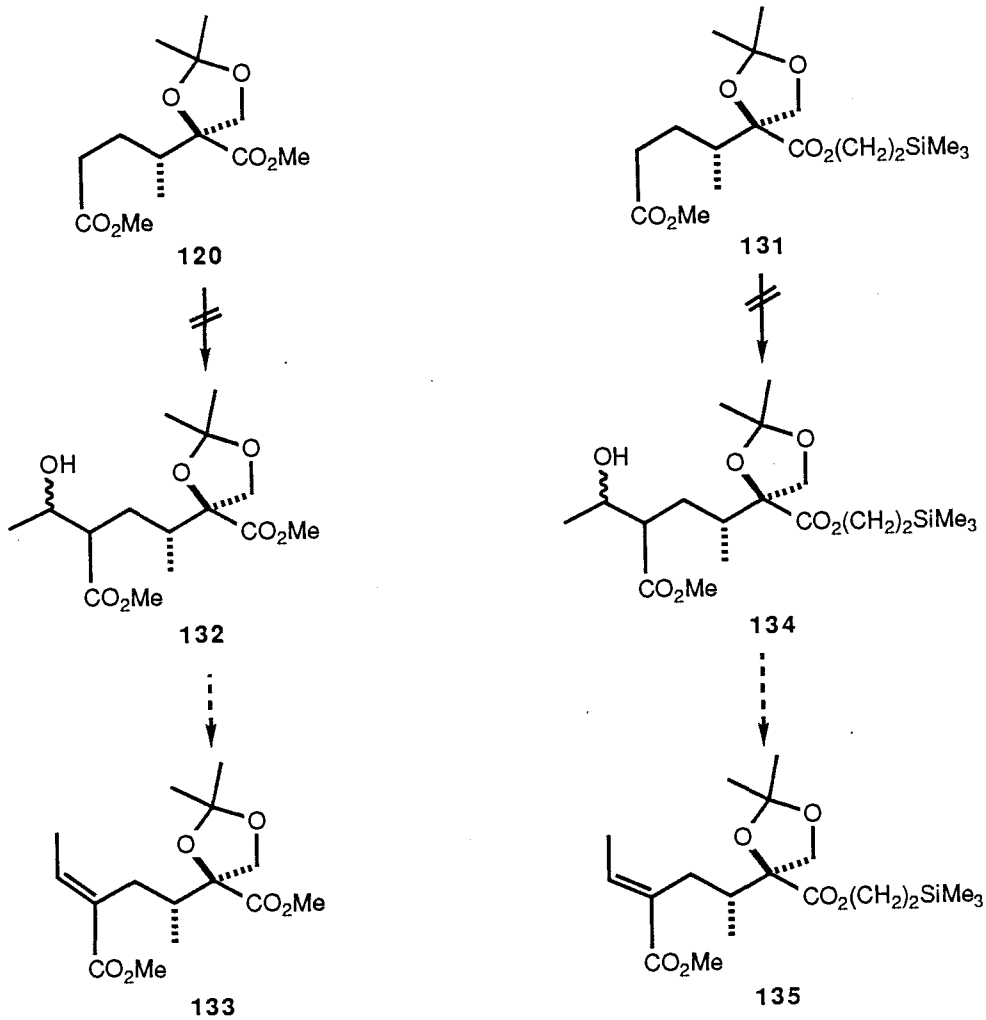
125 upon treatment with diazomethane. Truncation of the isopropylidene group with sodium periodate and subsequent treatment of the intermediate acid **126** with diazomethane provided **120**. In an alternative route, the alcohol **123** was protected as its p-nitrobenzoate (PNB) **127** before the olefin was cleaved. The oxidative cleavage of **127** with sodium periodate and catalytic ruthenium(III)[43] proved to be less efficient than with **125**, perhaps due to the instability of the p-nitrobenzoate group of **127** under the reaction conditions. Consequently, **127** was ozonized and

the crude aldehyde was oxidized rapidly with catalytic ruthenium(III) to a carboxylic acid, which was converted to the methyl ester **128**. Methanolysis of the p-nitrobenzoate **128** yielded **119**, which has previously been converted to **120** (scheme 21). These alternative pathways make available valuable retronecic acid derivatives that permit selective attachment of (+)-retronecine (**1**) at either terminus.

With synthetic routes to **120** firmly established we turned to synthesis of the key retronecic acid derivative **116** (figure 5). It was recognized that for protection of the C-1 carboxyl group of **116** as its 2-(trimethylsilyl)ethyl ester a convenient strategy would entail esterification of the relatively hindered carboxyl group of **124**. Unfortunately, under normal esterification conditions with 2-(trimethylsilyl)ethanol, **124** proved to be totally inert. Presumably the severe steric congestion around the carboxyl group of **124** provides the impediment toward this reaction. To circumvent this problem we explored a novel titanate-mediated transesterification method developed by Seebach.[50] Initially, it was found that treatment of methyl ester **125** with excess 2-(trimethylsilyl)ethanol in the presence of titanium(IV) isopropoxide provided the desired ester **129** in 55% yield, with 30% of recovered **125**. This transesterification reaction was later improved by using titanium(IV) ethoxide which afforded **129** in 93% yield. The double bond of **129** was oxidatively cleaved using ruthenium(IV) as previously described to furnish **130**, which was converted to its methyl ester **131** in an overall 66% yield from **129**.

It was anticipated that the ethylidene side chain of usaramine could be introduced by an aldol condensation of either **120** or **131** (scheme 25) with acetaldehyde and elimination of β-hydroxy ester **132** (or **134**). This sequence would be expected to provide the thermodynamically more stable E-ethylidene esters **133** and **135** as the major products. Unfortunately, treatment of **120** and **131** with

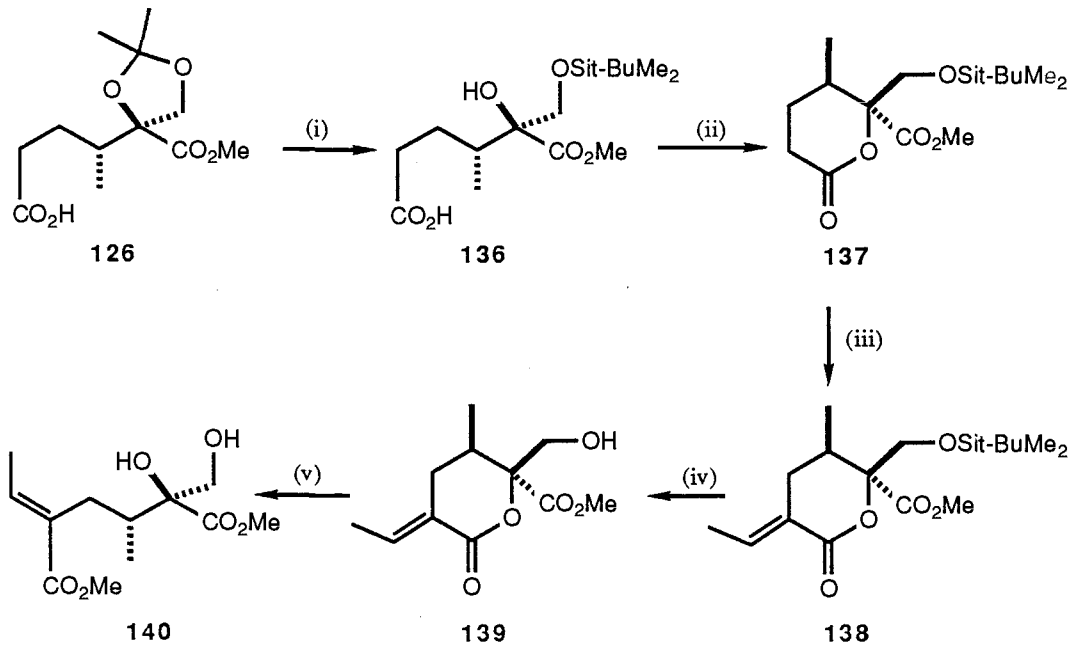
lithium diisopropylamide and acetaldehyde produced neither **132** nor **134**. Instead, it is believed that Dieckmann condensation takes place, converting these diesters to cyclopentanoid products.



SCHEME 25

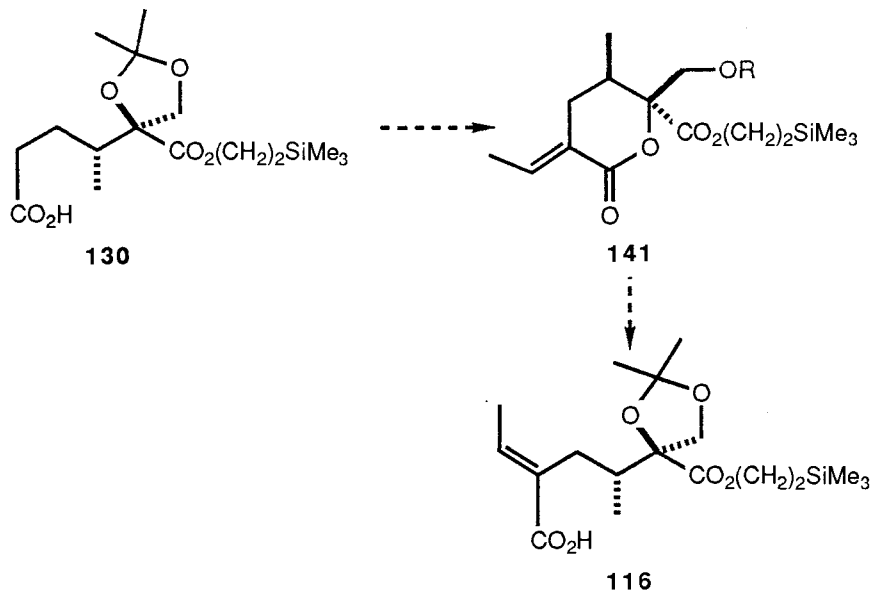
It seemed likely that Dieckmann condensation of **120** and **131** could be avoided if the aldol reaction was performed on an appropriate cyclic intermediate and in this context lactone **137** attracted our attention as a prospective substrate for the condensation with acetaldehyde. The synthesis of **137** and its conversion to

dimethyl (-)-retronecate (**140**) is shown in scheme 26. Hydrolysis of the acetonide of **126** gave a diol, the primary hydroxyl group of which was protected as its tert-butyldimethylsilyl ether **136**. This hydroxy acid underwent facile lactonization utilizing Mukaiyama's reagent[28] to afford **137** in 87% yield. The lithium enolate of **137** was treated with acetaldehyde and the resulting β-hydroxy lactone underwent elimination via its acetate to furnish exclusively the E isomer **138**. Removal of the silyl blocking group from **138** and methanolysis of the hydroxy lactone **139** afforded dimethyl (-)-retronecate (**140**). Our synthetic (-)-**140**, which is the dimethyl ester of naturally occurring (+)-retronecic acid (**117**),[12,48] displayed ^1H



(i) 80% Acetic acid, 65°C, 2h; t-$BuMe_2SiCl$, DMF, imidazole; acetic acid/THF/H_2O (3:3:1), rt (50%); (ii) 2-Chloro-1-methylpyridinum iodide, DMAP, CH_3CN, rt (87%); (iii) LDA, CH_3CHO, -78°C to -45°C; Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2; DBU; (iv) Bu_4NF, THF (15% from **137**); (v) NaOMe, MeOH (70%).

SCHEME 26



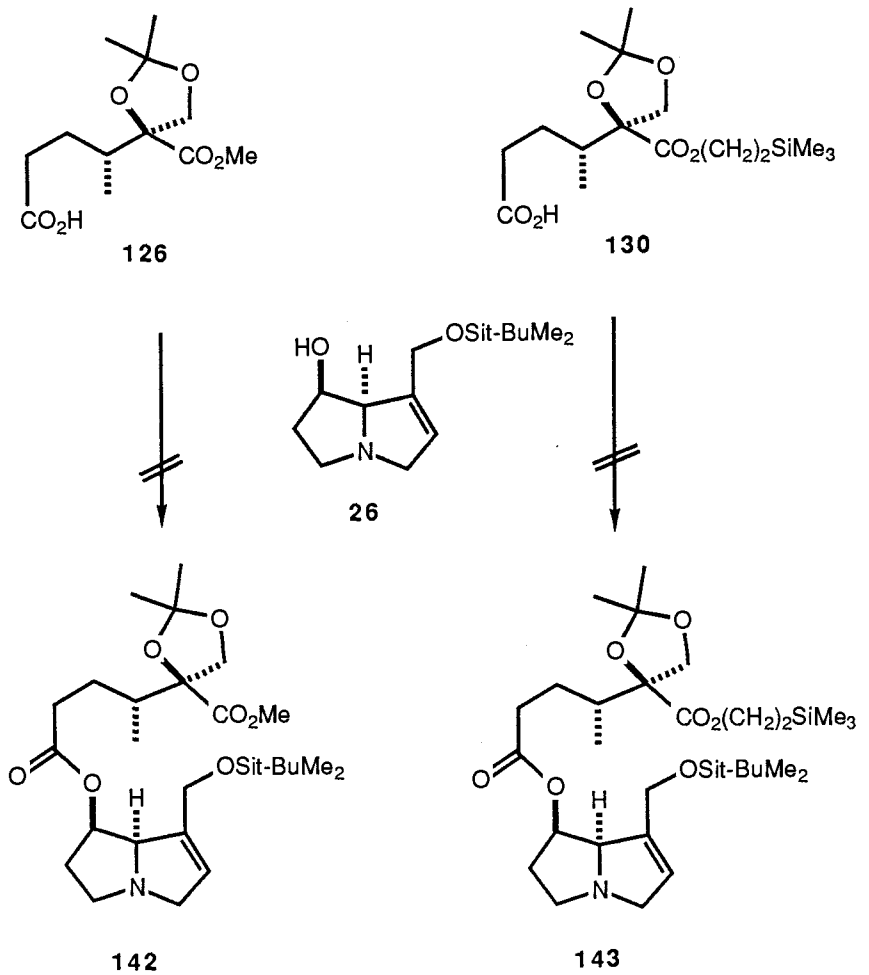
SCHEME 27

nuclear magnetic resonance (NMR), and ^{13}C NMR data that were identical to those reported by Drewes et al[48] for (±)-**140**.

This synthesis of (-)-**140**, which represents the first chiral route to the retronecic acid system, can now be adapted to a synthesis of (+)-usaramine (**5**) in a straightforward manner. The ester **130**, which has carboxyl termini conveniently differentiated, will be escorted through a route, shown in scheme 27, analogous to that employed with **136** (scheme 26). This sequence, which remains for a subsequent investigator, is expected to yield **116**, the necic acid derivative required for coupling to (+)-retronecine (**1**).

The foregoing chemistry makes evident the need to convert acyclic structures, such as **120** and **131**, to cyclic species for the purpose of introducing the ethylidene substituent. An alternative strategy that, in certain respects, was more appealing was to insert the ethylidene group after macrolactonization. This route

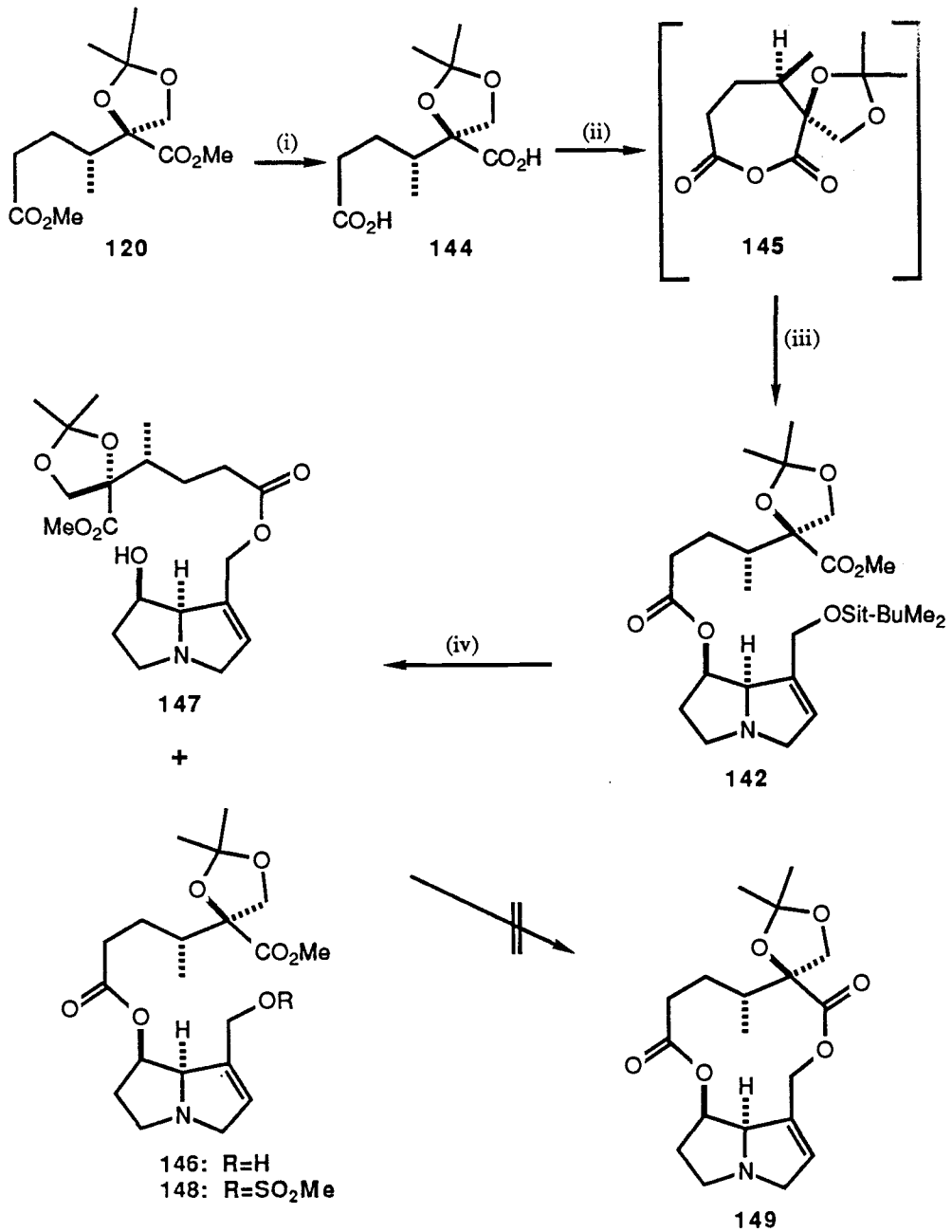
would be more direct in that it would avoid the synthesis and reopening of δ-lactone intermediates such as **138** and **141**. Since the carboxylic acids **126** and **130** were readily available (vide supra), these materials were utilized to explore tactics for coupling with (+)-**1** and for the macrolactonization reaction. Our intention was to then employ an ethylidenation sequence analogous to that used on **137** to reach the final target (+)-**5**.



SCHEME 28

(+)-Retronecine (**1**) was obtained by hydrolysis of monocrotaline (**24**) with barium hydroxide[30] and the primary hydroxyl group of (+)-**1** was selectively protected as its tert-butyldimethylsilyl ether to provide **26**. With a suitably protected form of retronecine in hand, various attempts were made to esterify the sterically hindered C-7 alcohol with **126** and **130** (scheme 28). Neither 2-chloro-1-methylpyridinium iodide,[28] nor N,N'-dicyclohexylcarbodiimide (DCC), nor the mixed anhydride of **126** or **130** prepared from diethyl chlorophosphate,[25] yielded any of the desired esters **142** or **143**. However, the cyclic anhydride **145**[26] reacted with the lithium alkoxide **36**, derived from **26** and butyllithium, to give **142** after treatment of the initial product with diazomethane. As expected, attack by **36** had occurred with complete regioselectivity at the sterically less hindered carbonyl group of **145**. Anhydride **145** was prepared by hydrolysis of diester **120** to dicarboxylic acid **144**, and this was converted to **145** with DCC as shown in scheme 29. The anhydride was used in coupling reactions with **36** without purification.

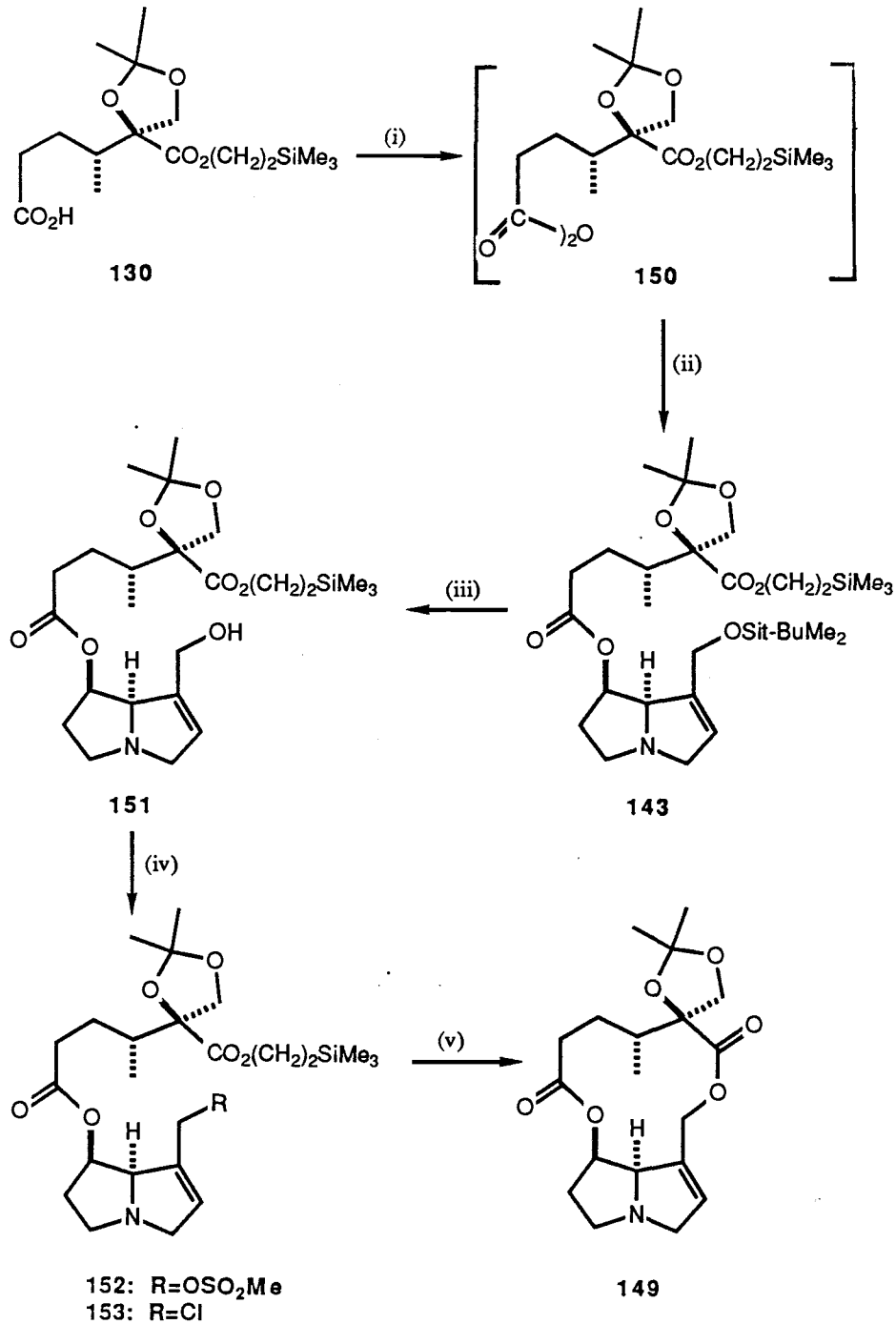
Desilylation of **142** with ammonium fluoride furnished the expected alcohol **146** along with the transesterified product **147** as an inseparable mixture. Clear evidence for the presence of **147** in this mixture was provided by its ^{1}H NMR spectrum which showed characteristic peaks for the C-2-hydrogen and C-9-hydrogens at δ 5.68(s, 1H) and δ 4.70(q, 2H, AB, J=11.1) respectively. It had been anticipated that the conversion of **146** to its methanesulfonate **148**, followed by cleavage of the methyl ester with lithium iodide, would afford **149** in analogy with the macrolactonization previously demonstrated with **61**.[25] However, when this macrolactonization was attempted on the **146/147** mixture, only decomposition products resulted.



(i) KOH, THF/H_2O (1:1); (ii) DCC, CH_2Cl_2; (iii) **36**, DMAP (cat), THF; CH_2N_2, Et_2O (55% from **120**) (iv) NH_4F, MeOH/H_2O (3:1), 60°C, (50%).

SCHEME 29

The difficulty experienced in our attempted macrolactonization of **146** can be attributed to the harsh conditions required for cleavage of the methyl ester, and the 2-(trimethylsilyl)ethyl ester **151**(scheme 30), therefore appeared to offer better prospect for success. Ester **151** was obtained by coupling **36** with the anhydride **150,** which was synthesized by treating **130** with DCC.[24] Acylation of **36** with **150** occurred smoothly to provide **143**, and selective removal of the silyl ether from **143** was accomplished with hydrogen fluoride in tetrahydrofuran to yield **151**. This alcohol appeared to be an ideal substrate for the nucleophilic macrolactonization reaction successfully employed by both Vedejs[22,23] and White[25] in their syntheses of pyrrolizidine alkaloids. Consequently, **151** was treated with methanesulfonyl chloride and triethylamine, and the presumed methanesulfonate intermediate **152** was added to excess tetrabutylammonium fluoride at room temperature. To our surprise, only the chloride **153** was isolated. However, when **153** was exposed to excess fluoride in acetonitrile and the reaction mixture heated to 50°C for two hours, a further reaction was observed by thin layer chromatography which proved to be the desired transformation to **149**. Comparison of the 400 MHz ^{1}H NMR spectrum of **149** with those of authentic retrorsine (**6**) and integerrimine (**2**)[25] provided firm evidence for the macrolactone structure. In particular, characteristic peaks at δ 6.25 (s, 1H) and δ 5.52 (d, 1H, J=12.4 Hz) for the C-2 and C-9 protons were clearly evidence. It is apparent from the behavior of **152** that cleavage of the trimethylsilylethyl ester is slower at room temperature than displacement of the allylic sulfonate with chloride, produced in its generation. This suggests that the Vedejs macrolactonization[22,23,25] route to pyrrolizidine alkaloids proceeds, not by direct displacement of mesylate with carboxylate ion as originally postulated, but via an intermediate allylic chloride.



(i) DCC, CH_2Cl_2; (ii) **36**, DMAP (cat), THF (64% from **130**); (iii) 5%HF/THF (56%); (iv) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; Bu_4NF, CH_3CN, rt; (v) Bu_4NF, CH_3CN, 50°C.

SCHEME 30

In conclusion, a formal total synthesis of (-)-integerrimine (**2**) and the first enantioselective synthesis of dimethyl (-)-retronecate (**140**) were accomplished from (+)-citronellal (**93**). This strategem affords an efficient and quite general approach to those necic acids bearing a 3R methyl substituent. Conditions were developed for introducing the ethylidene moiety of the necic acid portion, and a modified version of the nucleophilic macrolactonization reaction was demonstrated. This chemistry provides solutions to several major problems in pyrrolizidine alkaloid synthesis. Finally, although a total synthesis of (+)-usaramine (**5**) remains to be completed, the groundwork has been laid for an early conclusion of this project.

EXPERIMENTAL

General

Solvents were dried by distillation shortly before use from an appropriate drying agent. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium benzophenone ketyl under argon. Methylene chloride, dimethylformamide, pyridine, diisopropylamine, and triethylamine were distilled from calcium hydride under argon. Methanol was distilled from magnesium turnings. All solvents for routine chromatography and reaction workup were reagent grade and distilled through glass prior to use. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Reactions were routinely carried out under an inert atmosphere of argon or nitrogen. When the reaction temperature is not specified, it was carried out at room temperature. Brine refers to a saturated aqueous solution of sodium chloride.

For isolation of reaction products, solvents were removed at water aspirator pressure by rotary evaporation and the residual solvent was removed by vacuum pump at less than 0.5 Torr. Flasks and syringes were oven dried at 165 °C overnight and cooled in a desiccator over anhydrous calcium sulfate prior to use. Alternatively, flasks were flame-dried under a stream of argon.

Analytical thin layer chromatography (TLC) was done on 2.5 x 7.0 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Flash chromatography was carried out with E. Merck silica gel 60 (230-400 mesh ASTM). Spots were visualized by ultraviolet lamp, by spraying with 3% $CeSO_4$ in 3N H_2SO_4, or by dipping in a 3% solution of phosphomolybdic acid in ethanol followed by heating.

Melting points were measured on a Buchi melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on either a Perkin-Elmer 727B or a

Nicolet 5DXB FT-IR spectrometer. Optical rotations were measured in 1 decimeter cells (1 mL capacity) on a Perkin-Elmer model 243 polarimeter at ambient temperature. Nuclear magnetic resonance spectra (NMR) were recorded on either an IBM NR-80F or a Bruker AM-400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported down-field from internal tetramethylsilane on the δ scale. ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), number of protons, and coupling constant in Hertz. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High resolution mass spectra were determined on a Kratos MS-50. Elemental analyses were performed by Desert Analytics (formerly MicAnal), Tucson, Arizona.

(E)-4-Bromo-2-methyl-2-propenoic Acid (γ-Bromotiglic Acid) (**75**)

A refluxing solution of tiglic acid (**74**) (20 g, 0.2 mol) and N-bromosuccinimide (35.7 g, 0.2 mol) in carbon tetrachloride was irradiated with a 275W incandescent lamp under a nitrogen atmosphere for 2 h. The reaction mixture was kept at 0 °C overnight. Solid succiminide was filtered off and the filtrate was concentrated in vacuo. The residue was kept at 0°C for 24 h and the solid was further purified by fractional crystallization from ether-hexane and then from hexane to give 3.5 g (10%) of **75** as colorless crystals: mp 92-93°C, lit.[35] 93-94°C; IR (KBr) 3200 (broad), 1694, 1641 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$)δ 1.90 (s, 3H), 4.0 (d, 2H, J=8), 7.03 (t, 1H, J=8), 11.65 (bs, 1H,); MS m/z; 178 (M^+), 180 (M+2), 99 (100%).

Methyl (E)-2-acetyl-6-hydroxy-5-methyl-4-hexenoate (**77**)

A solution of **75** (2.98 g, 167 mmol) in dry tetrahydrofuran (10 mL) was added via cannula to a stirring suspension of sodium hydride (803 mg, 60% in oil) in tetrahydrofuran (10 mL) at -20 °C during 2.5 h. This mixture was cooled to -20 °C and 633 mg (16.7 mmol) of sodium borohydride was added. After stirring for 1h at -20°C the reaction was warmed to 0°C and stirred for 1.5 h, then was quenched with 5% hydrochloric acid (pH ≅ 3-4). The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvents in vacuo yielded 2.53 g (91%) of crude **76**, that was used without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.73 (d, 3H, J=1.0), 1.77 (s, 1H, exchanges with D_2O), 4.08 (s, 2H), 4.0 (d, 2H, J=7.2), 5.78 (dt, 1H, J=7.2,1.0).

To a stirring suspension of sodium hydride (258 mg, 60% in oil, 6.5 mmol) in tetrahydrofuran (10 mL) at 0°C was added 0.67 mL (6.2 mmol) of methyl acetoacetate (**73**). After 15 min the mixture was cooled to -20 °C and 484 mg (2.9 mmol) of **76** in tetrahydrofuran (10 mL) was added via cannula. The reaction mixture was stirred for 2.5 h at -20 °C and 1 h at 0 °C and was poured into cold water (50 mL). The mixture was extracted with ethyl acetate (4 x 50 mL) and the organic layer was dried over anhydrous sodium sulfate. Removal of solvents in vacuo and purification of the residue by flash column chromatography (2:1 ethyl acetate-hexanes) on silica gave 422 mg (73%) of **77** as a colorless oil: IR (neat) 3400 (broad), 1745, 1720 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$)δ 1.66 (bs, 3H), 2.23 (s, 3H), 2.57 (bt, 2H, J=6.0), 3.47 (t, 1H, J=6.0), 3.72 (s, 3H), 3.95 (s, 2H), 5.3 (bt, 1H, J=6.0); MS m/z 182 (M-18), 139, 124, 42 (100%); HRMS calcd for $C_{10}H_{14}O_3$: 182.094. Found: 182.094.

(E)-5-Carbomethoxy-2-methyl-2-hepten-1,6-diol (**79**)

A solution of β-keto ester **77** (647 mg, 3.2 mmol) in methanol (10 mL) was transferred via cannula to a stirring suspension of sodium borohydride (490 mg, 12.9 mmol) in methanol (20 mL) at 0°C. The reaction was quenched with saturated aqueous ammonium chloride after 10 min and the precipitate was filtered and washed with ethyl acetate (2 x 25 mL). The aqueous layer of the filtrate was extracted with ethyl acetate (2 x 40 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Flash column chromatographic purification (6:1 ethyl acetate-hexanes) of the crude product on silica gave 525 mg (80%) of **79** as an oil: IR (neat) 3400 (broad), 2950, 1720 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$)δ 1.23 (two d, 3H, J=7), 1.66 (bs, 3H), 2.4 (m, 4H), 3.67 (two s, 3H), 3.95 (m, 3H), 5.35 (m, 1H); MS m/z 184 (M-18), 169, 153, 109 (100%); HRMS calcd for $C_{10}H_{16}O_3$: 184.110. Found: 184.110.

(E)-3-Carbomethoxy-7-(tert-butyldiphenylsiloxy)-6-methyl-2-heptenol (**80**)

Method A. To a stirring solution of **79** (176 mg, 0.9 mmol) in N,N-dimethylformamide (5 mL) were added tert-butyldiphenylsilyl chloride (0.25 mL, 0.97 mmol) and imidazole (130 mg, 1.9 mmol) sequentially. After 5 h the reaction mixture was diluted with ether (40 mL) and washed with water (15 mL), and the organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromatography (1:3 ethyl acetate-hexanes) on silica yielded 315 mg (82%) of **80**: IR (neat) 3500 (broad), 2950, 1720 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$)δ 1.12 (s, 9H), 1.24 (two d, 3H, J=7), 1.6 (bs, 3H), 2.4 (m, 4H), 3.65 (two s, 3H), 4.05 (bs, 3H), 5.45 (m, 1H), 7.25-7.75 (m, 10H); MS m/z 440

(M^+), 383, 365, 305, 199 (100%); HRMS calcd for $C_{22}H_{27}SiO_4$: 383.168. Found: 383.166.

Method B. A solution of β–keto ester **81** (800 mg, 1.82 mmol) in methanol (10 mL) was added via cannula to a stirring suspension of sodium borohydride (207 mg, 5.5 mmol) in methanol (10 mL) at 0°C. The reaction was quenched with saturated aqueous ammonium chloride after 10 min and the precipitate was filtered and washed with ethyl acetate (2 x 25 mL). The aqueous layer of the filtrate was extracted with ethyl acetate (2 x 40 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromatography (1:3 ethyl acetate-hexanes) on silica yielded 641 mg (80%) of **80** as an oil.

Methyl (E)-2-acetyl-6-(tert-butyldiphenylsiloxy)-5-methyl-4-hexenoate (**81**)

To a stirring solution of **77** (393 mg, 22.0 mmol) in dimethylformamide (7 mL) were added tert-butyldiphenylsilyl chloride (0.56 mL, 2.2 mmol) and imidazole (294 mg, 4.3 mmol) sequentially. After 4.5 h the reaction mixture was diluted with ether (100 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (2 x 40 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Flash column chromatographic purification (1:5 ethyl acetate-hexanes) of the crude product on silica gave 800 mg (93%) of **81** as a thick oil: IR (neat) 2900, 1720, 1740, 1100, 900 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$)δ 1.1 (s, 9H), 1.6 (s, 3H), 2.2 (s, 3H), 2.6 (bt, 2H, J=7.7), 3.5 (t, 1H, J=7.7), 3.7 (s, 3H), 4.0 (bs, 2H), 5.4 (bt, 1H, J=7.7), 7.3-7.8 (m, 10H); MS m/z 438 (M^+), 407, 395, 381, 338, 307, 297 (100%).

(2E,5E/Z)-7-(tert-Butyldiphenylsiloxy)-3-carbomethoxy-6-methyl-2,5-heptdiene (**82**)

Methanesulfonyl chloride (0.07 mL, 0.93 mmol) and triethylamine (0.2 mL, 1.43 mmol) were added sequentially to a stirring solution of **80** (315 mg, 0.72 mmol) in methylene chloride (10 mL) at 0°C. The reaction mixture was allowed to warm to room temperature over a period of 1.5 h and 0.27 mL (1.8 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added. After 20h the reaction mixture was diluted with ether (75 mL) and was washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ether(2 x 20 mL) and the combined organic layer was dried over anhydrous sodium sulfate. Flash column chromatographic purification (1:7 ethyl acetate-hexanes) of the crude product on silica yielded 224 mg (74%) of **82** as a mixture of E:Z isomers in the ratio of 3:1(from 400 MHz ^{1}H NMR) respectively: IR (neat) 2900, 1715, 1090, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s) and 1.05 (s) (9H), 1.69 (s) and 1.61 (s) (3H), 1.81 (d, J=7.2) and 1.98 (d, J=7.3) (3H), 3.07 (d, J=7.1) and 2.30 (d, J=7.07) (2H), 3.72 (s) and 3.73 (s) (3H), 4.03 (s) and 4.06 (s) (2H), 5.37 (t, J=7.1) and 5.45 (t, J=7.0) (1H), 6.87 (q, J=7.2) and 5.98 (q, J=7.3) (1H), 7.4-7.77 (m, 10H); MS m/z 422 (M^+), 379, 391, 365 (100%), 334.

(2E,5E/Z)-5-Carbomethoxy-2-methyl-2,5-heptdien-1-ol (**83**)

To a stirring solution of **82** (223 mg, 0.53 mmol) in tetrahydrofuran (4 mL) was added tetrabutylammonium fluoride (1.06 mL in tetrahydrofuran). After 1 h the reaction mixture was diluted with ether (20 mL) and washed with brine solution. The organic layer was dried over anhydrous sodium sulfate. Purification of the crude product by flash column chromatography (1:1 ethyl acetate-hexanes) on silica gave 83 mg (85%) of the mixture **83** as an oil: IR (neat), 3300, 2895, 1720 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$)δ 1.77 (s) and 1.69 (s) (3H), 1.83 (d, J=7.1) and 1.98 (d, J=6.8) (3H), 3.08 (d, J=7.0) and 3.00 (d, J=7.2) (2H), 3.73 (s) and 3.75 (s) (3H), 4.00 (bs) and 4.02 (bs) (2H), 5.32 (t, J=7.0) and 5.42 (t, J=7.2) (1H), 6.88 (q, J=7.1) and 6.03 (q, J=6.8) (1H); MS m/z 184 (M^+), 166, 151, 135, 124, 107 (100%); HRMS calcd for $C_{10}H_{16}O_3$: 184.110. Found: 184.110.

(2S,3R)-4-Bromo-2,3-epoxy-2-methyl-1-butanol (**85**)

To a stirring solution of titanium(IV) isopropoxide (0.21 mL, 0.69 mmol) in methylene chloride (3.5 mL) at -20°C was added diisopropyl (+)-tartrate (0.15 mL, 0.69 mmol). After 5 min, **75** (114 mg, 0.69 mmol) in methylene chloride (3.5 mL) and 0.38 mL of tert-butylhydroperoxide (1.39 mmol, 3.6 M solution in methylene chloride) were added sequentially. The reaction mixture was stirred for 1 h and kept at -20 °C. After 48 h, 0.21 mL (2.76 mmol) of dimethyl sulfide was added and the mixture was stirred for 10 h at -20 °C. Then the reaction mixture was diluted with an equal volume of ether and saturated aqueous sodium sulfate (1 mL per mL of titanium(IV) isopropoxide used) was added and stirred vigorously for 2 h. The white precipitate was filtered through a short Celite pad, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 ethyl acetate-hexanes) on silica to provide 101mg (80%) of **85** as a colorless oil: $[\alpha]^{22}_D$ = (+) 7.82° (C = 1.0, $CHCl_3$); IR (neat) 3400 (broad) 2900; ^1H NMR (80 MHz, $CDCl_3$)δ 1.34 (s, 3H), 3.25 (t, 1H, J=6.0), 3.4 (m, 2H), 3.65 (bs, 2H); MS m/z 180 (M^+), 167, 165, 164, 162, 151, 149, 101, 43 (100%); HRMS calcd for $C_5H_9O_2$: 101.060. Found: 101.060.

(2R,3S)-4-(tert-Butyldimethylsiloxy)-2,3 epoxy-3-methyl-1-butyl Bromide (**86**)

To a stirring solution of **85** (101 mg, 0.56 mmol) in dimethylformamide (3 mL) were added tert-butyldimethylsilyl chloride (101 mg, 0.67 mmol) and imidazole (95 mg, 1.4 mmol) sequentially. After 17h the reaction mixture was diluted with ether (35 mL) and washed with water (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and flash column chromatographic purification (1:5 ether-hexanes) of the crude product on silica gave 113 mg (68%) of **86**; $[\alpha]^{22}_D$ = (+) 50.51° (C = 1.98, $CHCl_3$); IR (neat) 2950, 1250, 830; ^1H NMR (80 MHz, $CDCl_3$)δ 0.06 (s, 6H), 0.9 (s, 9H), 1.3 (s, 3H), 3.3 (m, 3H), 3.6 (s, 2H); HRMS calcd for $C_7H_{14}BrSiO_2$: 238.993. Found: 238.995.

Methyl (2R/S,4R,5S)-2-acetyl-6-(tert-butyldimethylsiloxy)-4,5-epoxy-5-methylhexanoate (**87**)

Methylacetoacetate (**73**) (37 mL, 0.34 mmol) was added to a stirring suspension of sodium hydride (16.4 mg, 60% in oil) in dimethylformamide (1 mL) at room temperature. After 15 min **86** (67.4 mg, 0.23 mmol) in dimethylformamide was added via cannula and the mixture was stirred overnight at 45 °C. The reaction mixture was diluted with ether (20 mL) and washed with water (10 mL). The aqueous layer was further extracted with ether (2 x 10 mL) and the combined organic layer was washed with brine, then was dried over anhydrous sodium sulfate. Purification of the crude product by flash column chromatography (1:3 ethyl acetate-hexanes) on silica gave 27.3 mg (36%) of **87**: IR (neat) 2950, 1740, 1725, 1280, 860 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$)δ 0.07 (s, 6H), 0.90 (s, 9H), 1.10 (s, 3H), 2.20 (m, 5H), 2.85 (m, 1H), 3.50 (d, 1H, J=10), 3.60 (d, 1H, J=10), 3.7 (s, 3H), 4.6 (t, 1H, J=8); MS m/z 330 (M^+), 299, 273, 257, 157; HRMS calcd for

$C_{16}H_{30}SiO_5$: 330.186. Found: 330.185.

(3R)-3,7-dimethyl-6-octen-1-ol (R-(+)-Citronellol) (**92**)

Hydrogen chloride gas was bubbled through R-(+)-pulegone (**90**) (27 g, 176 mmol) at -10°C for 1 h, with stirring, and the mixture was kept overnight at room temperature. To a 500 mL three-necked flask equipped with two dropping funnels, a mechanical stirrer, and a thermometer, 70 mL of water and 3.5 mL of 9.3 M sodium hydroxide were added. To this mixture pulegone (saturated with hydrogen chloride) and 9.3 M sodium hydroxide (50 mL) were added dropwise, using the two dropping funnels, over a period of 45 min, with rapid stirring. (The temperature was controlled at 10-15°C using water-ice bath). After the addition was over the mixture was stirred overnight at room temperature and residual pulegone was extracted with ether (3 x 50 mL). The aqueous layer was cooled to 0°C and 10 mL of sulfuric acid was added very slowly, with stirring. This mixture was extracted with ether (3 x 100 mL) and the organic layer was dried over anhydrous magnesium sulfate. Evaporation of solvents in vacuo yielded 16 g (53%) of citronellic acid (**91**) as a pale yellow oil. Also 11 g (40%) of pulegone (**90**) was recovered from this reaction. Citronellic acid (**91**) was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.98 (d, 3H, J=6.6), 1.22 (m, 1H), 1.26 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 2.0 (m, 3H), 2.26 (dd, 1H, J=14.8,8.2), 2.37 (dd, 1H, J=14.8,5.8), 5.1 (m, H), 10.8 (bs, 1H).

To a stirring suspension of lithium aluminum hydride (4.6 g, 120.8 mmol) in ether (150 mL) at 0°C was added **91** (13.7 g, 80.5 mmol) in ether (30 mL) over a period of 1h. To this mixture were added4.5 mL of 15% sodium hydroxide and 15 mL of water sequentially and stirred at room temperature for 10 min. The white solid was filtered off and washed with ethyl acetate (250 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate, brine, and

dried over anhydrous magnesium sulfate. Evaporation of solvents in vacuo, and purification of the crude product by flash column chromatography (1:5 ethyl acetate-hexanes) on silica yielded 12.1 g (97%) of 92: $[\alpha]^{21}_D$ = (+) 5.49° (neat), Lit.[39] $[\alpha]^{21}_D$ = (+) 5.47° (neat); ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.91 (d, 3H, J=6.6), 1.19 (m, 1H), 1.41 (m, 3H), 1.56 (m, 2H), 1.61(s, 3H), 1.68(s, 3H), 2.01(m, 2H), 3.69(m, 2H), 5.11(m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.61, 19.49, 25.42, 25.68, 29.13, 37.18, 39.68, 61.17, 124.68, 131.24.

(3R)-3,7-Dimethyl-6-octenal (R-(+)-Citronellal) (**93**)

Method A. To a stirring suspension of pyridinium chlorochromate (4.3 g, 19.8 mmol) and sodium acetate (325 mg, 3.95 mmol) in methylene chloride (30 mL) was added **92** (2.1 g, 13.2 mmol) in methylene chloride. The reaction mixture was stirred for 2h and diluted with ether (50 mL). The liquid was decanted from the black gum and this insoluble residue was washed thoroughly with ether (3 x 40 mL). The combined organic layer was passed through a short pad of Florisil and concentrated in vacuo. The crude product was purified by flash column chromatography (1:5 ether-hexanes) on silica to yield 1.43 g (70%) of **93** as a colorless oil: $[\alpha]^{20}_D$ = (+) 13.21° (neat), Lit. $[\alpha]^{18}_D$ = (+) 13.09° (neat); ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.97 (d, 3H, J=6.7), 1.34 (m, 2H), 1.60 (s, 3H), 1.69 (s, 3H), 2.02 (m, 3H), 2.25 (m, 1H), 2.39 (m, 1H), 5.09 (m, 1H), 9.76 (t, 1H, J=2.2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.67, 19.87, 25.40, 25.71, 27.76, 36.95, 51.01, 124.04, 131.75, 203.02.

Method B. 9-Borabicyclo[3.3.1]nonane (374 mL, 187 mmol) was added to a stirring solution of R-(-)-citronellen (**89**) (19 g, 139 mmol) in 150 mL

tetrahydrofuran at 0°C. The reaction mixture was stirred for 21h at room temperature and was treated with 6M sodium hydroxide (69 mL) followed by very slow addition of 30% hydrogen peroxide (55.5 mL) at 0°C. This was stirred for 3 h at 55°C and cooled to room temperature. The layers were separated and the aqueous layer was saturated with potassium carbonate and extracted with ether (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude citronellol (**92**) was oxidized with pyridinium chlorocromate as described in method A. Purification of the crude product by column chromatography (1:5 ethyl acetate-hexanes) on silica provided 9.0 g (42%) of **93**: $[\alpha]^{22}_D$ = (+) 9.52° (C = 1.11, $CHCl_3$), Lit. $[\alpha]^{18}_D$ = (+) 13.09 (neat).

(R)-3,7-Dimethyl-2-methylene-6-octenal (**94**)

To a stirring solution of diisopropylamine (0.36 mL, 2.56 mmol) in tetrahydrofuran (1.5 mL) at -78°C was added n-butyllithium (1.61 mL, 2.45 mmol). This mixture was warmed to 0 °C, stirred for 15 min and cooled back to -78 °C. To this lithium diisopropylamide solution was added **93**(344 mg, 2.2 mmol) in tetrahydrofuran (1.5 mL) and stirred for 45 min at -78°C. This reaction mixture was added via cannula to a stirring suspension of N,N-dimethylmethyleneammonium iodide(1.16 g, 6.3 mmol) in tetrahydrofuran (3 mL) at -78°C. This was stirred for 45 min at -78°C, 5h at room temperature and solvent was evaporated in vacuo.

The residue was dissolved in methanol (1.5 mL) and 0.43 mL of methyliodide (6.7 mmol) was added at 0 °C. This mixture was stirred overnight at 4 °C and at room temperature for additional 5 h. Then the solvent was evaporated in vacuo and remaining red solid was stirred with 5% aqueous sodium bicarbonate : methylene chloride (2 mL:2.5 mL) for 16h at room temperature. This mixture was diluted with methylene chloride (3 mL), layers were separated and the aqueous layer

was extracted with methylene chloride (5 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromatography (1:5 ether-hexanes) on silica yielded 289 mg (78%) of **94** as a pale yellow oil: $[\alpha]^{22}_D$ = (-) 9.38° (C = 20.15, $CHCl_3$); IR (neat) 2950, 1690, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)δ 1.07 (d, 3H, J=7.4), 1.40 (m, 1H), 1.54 (m, 1H); 1.57 (s, 3H), 1.67 (s, 3H), 1.93 (m, 2H), 2.71 (m, 1H), 5.08 (m, 1H), 5.99 (s, 1H), 6.23 (s, 1H), 9.53 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.64, 19.56, 25.68, 25.76, 30.99, 35.59, 124.15, 131.63, 133.02, 155.50, 194.62; MS m/z 166 (M^+), 151, 137, 136, 109 (100%); HRMS calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1358.

(3R)-3,7-Dimethyl-2-methylene-6-octen-1-ol (**95**)

Cerium(III) chloride hexahydrate (27.5 g, 77 mmol) was added to a stirring solution of **94** (12.8 g, 77 mmol) in methanol at 0°C. To this mixture was added sodium borohydride (3.8 g, 100 mmol) slowly and the reaction was quenched with saturated aqueous ammonium chloride after 5-10 min. Methanol was evaporated in vacuo and the residue was treated with 500 mL of water, then extracted with ethyl acetate (4 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromatography (1:1 ether-hexanes) on silica yielded 12.3 g (95%) of **95** as a colorless oil: $[\alpha]^{22}_D$ = (-) 10.00° (C = 74.08, $CHCl_3$); IR (neat) 3300 (broad), 2900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)δ 1.06 (d, 3H, J=6.5), 1.37 (m, 1H), 1.48 (m, 2H), 1.59 (s, 3H), 1.68 (d, 3H, J=1.0), 1.96 (m, 2H), 2.16 (m, 1H), 4.10 (bs, 2H), 4.89 (s, 1H), 5.05 (d, 1H, J=1.4), 5.09 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.68, 20.12,

25.72, 25.90, 35.84, 36.56, 64.51, 107.75, 124.52, 131.45, 153.89; MS m/z 168 (M^+), 150, 137, 135; HRMS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1511. **95** was converted to 4-phenylbenzoate derivative to carry out elemental analysis. Anal. calcd for $C_{24}H_{28}O_2$: C, 82.71; H, 8.11. Found: C, 82.49; H, 8.25.

(2R)-2[(1R)-1,5-Dimethyl-4-hexenyl]-2-hydroxymethyl Oxirane (**96**) and (2S)-2[(1R)-1,5-Dimethyl-4-hexenyl]-2-hydroxymethyl Oxirane (**98**)

To a stirring suspension of 3A° molecular sieves (powder, 500 mg) in methylene chloride (35 mL) were added diisopropyl (-)-tartrate (0.34 mL, 1.62 mmol) and **95** (3.9 g, 23.2 mmol) in methylene chloride sequentially at room temperature. This was cooled to -5°C and titanium(IV) isopropoxide (0.39 mL, 1.29 mmol) was added and stirred for 20 min. Then, cumene hydroperoxide (12 mL, 64.9 mmol) was added dropwise using a dropping funnel and the mixture was stirred for 8h at -5°C. After stirring overnight at 4°C, reaction was quenched very slowly with trimethyl phosphite (4.4 mL, 37.1 mmol) at -20°C and stirred for 1.5h . This mixture was filtered through a short Celite pad and the organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (1:1 ether-hexane) on silica to give 2.95 g (69%) of **96/98** as a 3:1 mixture: IR (neat) 3450 (broad), 2900, 1440, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J=7.0) and 1.04 (d, J=7.1) (3H), 1.25 (m, 2H), 1.56 (m, 2H), 1.58 (s, 3H), 1.60 (s, 3H), 2.04 (m, 2H), 2.62 (two d, 1H, J=4.7), 2.91 (d, J=4.7) and 2.93 (d, J=4.7) (1H), 3.70 (m) and 3.85 (m) (2H), 5.07 (m, 1H); MS m/z 184(M^+), 168, 166, 153, 81 (100%); Exact mass calcd for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1458.

(2S) -2[(1R)-1,5-Dimethyl-4-hexenyl]-2-hydroxymethyl Oxirane (**98**)

By using the same procedure described about with diisopropyl (+)-tartrate provided **98/96** in 96:4 ratio in 81% yield: $[\alpha]^{22}_D$ = (-) 2.15° (C = 41.74, $CHCl_3$); IR (neat) 3431 (broad), 2925, 1455, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=6.8), 1.26 (m, 1H), 1.58 (m, 2H), 1.60 (s, 3H), 1.69 (s, 3H), 2.07 (m, 2H), 2.61 (d, 1H, J=4.8), 2.91 (d, 1H, J=4.8), 3.72 (dd, 1H, J=12.4, 9.5), 3.83 (dd, 1H, J=12.4, 3.6), 5.09 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.05, 17.68, 25.71, 25.82, 33.01, 35.84, 48.65, 60.15, 62.46, 124.07, 131.84.

(2R)-2[(1R)-1,5-Dimethyl-4-hexenyl]-2(methyl 3,5-dinitrobenzoyloxy) Oxirane (**97**) and (2S)-2[(1R)-1,5-Dimethyl-4-hexenyl]-2(methyl 3,5-dinitrobenzoyloxy) Oxirane (**99**)

To a stirring suspension of 3,5-dinitrobenzoyl chloride (3.7 g, 16.1 mmol) in pyridine (40 mL) was added **96/98** (1.98 g, 10.7 mmol) in pyridine (10 mL). This mixture was stirred for 4h and pyridine was evaporated in vacuo. The remaining residue was dissolved in methylene chloride (100 mL) and washed with saturated aqueous sodium bicarbonate, brine, and then dried over anhydrous sodium sulfate. Flash column chromatographic purification (1:3 ethyl acetate-hexanes) of the crude product on silica gave 3.52 g (98%) of **97/99** mixture, which was separated by fractional crystallization.

Compound **97**: Mp (methylene chloride-hexanes) 56.5-57°C; $[\alpha]^{22}_D$ = (-) 2.44° (C = 16.59, $CHCl_3$); IR (KBr) 2968, 1738, 1630, 1165, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3H, J=6.7), 1.29 (m, 1H), 1.56 (m, 2H), 1.60 (s, 3H), 1.67 (s, 3H), 2.03 (m, 2H), 2.76 (d, 1H, J=4.5), 2.87 (d, 1H,m J=4.5),

4.46 (d, 1H, J=12.1), 4.73 (d, 1H, J=12.1), 5.06 (m, 1H), 9.14 (d, 2H, J=2.2), 9.24 (t, 1H, J=2.2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.26, 17.75, 25.69, 25.84, 32.58, 36.28, 50.53, 59.78, 65.79, 122.60, 123.67, 129.46, 132.33, 133.44, 148.73, 162.20; MS m/z 378 (M^+), 363, 195, 184, 69 (100%); HRMS calcd for $C_{11}H_{20}O_2$: 185.1497. Found: 185.1490; Anal. calcd for $C_{18}H_{22}N_2O_7$: C, 57.12; H, 5.86; N, 7.41. Found: C, 57.15; H, 5.68; N, 7.52.

Compound **99**: $[\alpha]^{22}_D$ = (-) 1.44° (C = 7.28, $CHCl_3$); IR (neat) 2923, 1730, 1630, 1095, 921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, 3H, J=6.8), 1.34 (m, 1H), 1.60 (s, 3H), 1.67 (s, 3H), 1.73 (m, 2H), 2.01 (m, 2H), 2.75 (d, 1H, J=4.5), 2.84 (d, 1H, J=4.5), 4.44 (d, 1H, J=12.3), 4.76 (d, 1H, J=12.3), 5.10 (m, 1H), 9.15 (d, 2H, J=2.1), 9.25 (t, 1H, J=2.1); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.29, 17.72, 25.69, 25.79, 33.21, 36.05, 49.51, 59.97, 66.00, 122.61, 123.73, 129.47, 132.24, 133.49, 148.76, 162.22; MS m/z 378 (M^+), 363, 195, 184, 69 (100%).

(2R,3R)-2,3,7-Trimethyl-6-octen-1,2-diol (**100**)

Lithium aluminum hydride (81 mg, 2.1 mmol) was added to a stirring solution of **97** (202 mg, 0.5 mmol) in tetrahydrofuran (8 mL) at room temperature. After 15 h, the reaction was quenched with 5% hydrochloric acid at 0 °C and diluted with methanol (50 mL). This mixture was refluxed for 5-10 min and the gray solid was filtered and washed with methanol. The filtrate was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Purification of the crude product by flash column chromatography (1:1 ethyl acetate-hexanes) on silica gave 81 mg (82%) of **100**: $[\alpha]^{21}_D$ = (+) 38.46° (C = 3.82, $CHCl_3$); IR (neat) 3400 (broad),

2900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3H, J=6.8), 1.05 (m, 1H), 1.06 (s, 3H), 1.61 (s, 3H), 1.64 (m, 2H), 1.69 (s, 3H), 1.83 (s, 1H), 1.94 (m, 2H), 2.17 (m, 1H), 3.43 (dd, 1H, J=10.7,6.2), 3.55 (dd, 1H, J=10.7,5.2), 5.13 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.48, 17.71, 19.10, 25.74, 26.48, 30.73, 39.34, 68.72, 75.34, 124.54, 131.66; MS m/z 186(M^+), 168 (M-18), 153, 137, 82 (100%); HRMS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1515.

(2R,3R)-2,3,7-Trimethyl-2-(3,5-dinitrobenzoyloxy)-6-octenyl-3,5-dinitrobenzoate (**101**)

To a stirring suspension of 3,5-dinitrobenzoyl chloride (1.7 g, 7.3 mmol) in pyridine (15 mL) was added **100** (270 mg, 1.5 mmol) in pyridine (5mL). The reaction mixture was stirred for 72 h and pyridine was evaporated in vacuo. The residue was dissolved in methylene chloride (50 mL), and washed with saturated aqueous sodium bicarbonate, brine, and then the organic layer was dried over anhydrous sodium sulfate. Purification of the crude product by flash column chromatography (1:3 ethyl acetate-hexanes) on silica gave 749 mg (87%) of **101**: $[\alpha]^{22}_D$ = (+) 7.90° (C = 6.49, $CHCl_3$); IR (neat) 2900, 1740, 1545, 1340, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3H, J=7.0), 1.30 (m, 1H), 1.61 (s, 3H), 1.67 (s, 3H), 1.69 (s, 3H), 2.06 (m, 1H), 2.17 (m, 2H), 2.55 (m, 1H), 4.92 (d, 1H, J=12.0), 5.00 (d, 1H, J=12.0), 9.06 (d, 2H, J=2.2), 9.12 (t, 1H, J=2.2), 9.21 (d, 2H, J=2.1), 9.25 (t, 1H, J=2.1); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.27, 17.73, 17.97, 25.66, 26.02, 31.10, 37.50, 67.52, 88.86, 122.53, 122.72, 123.38, 129.22, 129.34, 132.87, 133.81, 134.63, 148.77, 148.82, 161.28, 162.08; MS m/z 574 (M^+), 379, 363, 362, 195 (100%); HRMS calcd for $C_{18}H_{22}N_2O_6$: 362.1478. Found: 362.1479.

(4R,5R)-4,5-Dimethyl-5-hydroxymethyl-5-pentanolide (**102**)

Method A. To a stirring suspension of **101** (946 mg, 1.6 mmol) in carbon tetrachloride/ acetonitrile/ water (3 mL: 3 mL: 4.5 mL) were added sodium periodate (1.4 g, 6.8 mmol) and ruthenium(III) chloride trihydrate (9.5 mg) sequentially. After 24 h the reaction mixture was diluted with methylene chloride (50 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 15 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Solvent was evaporated and the residue was dissolved in ether (50 mL) and filtered through a short Celite pad. Crude acid obtained by evaporation of solvents in vacuo, was dissolved in methanol (10 mL) and stirred with anhydrous potassium carbonate (300 mg, 2 mmol) for 45 min. Methanol was evaporated and the residue was dissolved in chloroform (30 mL) and stirred with 5% hydrochloric acid (12 mL) for 24 h. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 30 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Flash column chromatographic purification (4:1 ethyl acetate-hexanes) of the crude product on silica providecd 143 mg (55%) of **102** as a colorless solid: mp 87-88°C (methylene chloride-hexanes), Lit.[26] 85-86 °C; $[\alpha]^{22}_D$ = (+) 42.87° (C = 1.17, $CHCl_3$); IR (KBr); 3400 (broad), 2950, 1730, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3H, J=6.72), 1.22 (s, 3H), 1.77 (m, 3H), 2.23 (m, 1H), 2.47-2.67 (m, 2H), 3.58 (d, 1H, J=12.4), 3.64 (d, 1H, J=12.4); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.10, 17.38, 24.35, 29.72, 30.54, 67.47, 88.11, 171.49; MS m/z 127 (M-31), 99, 82 (100%); HRMS calcd for $C_7H_{11}O_2$: 127.0759. Found: 127.0754. Anal. calcd for $C_8H_{14}O_3$: C, 60.72; H, 8.93. Found: C, 60.72; H, 9.16.

Lactone **102** crystallized with orthorhombic symmetry in space group $P2_12_12_1$ with lattice constants a = 6.909 (2) A°, b = 7.455 (1) A°, c = 33.604 (5) A°, z = 8, and d_{calcd} = 1.214 g cm^{-3}. The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination). Of the 1398 independent reflections for θ < 57°, 1081 were considered to be observed [I > 2.5 σ (I)].

The structure was solved by a multiple-solution procedure and was refined by full-matrix least squares. Five reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The final discrepancy indices are R = 0.043 and wR = 0.040 for the remaining 1076 observed reflections. The final difference map has no peaks greater than ± 0.1 eA^{-3}.

Method B. from **113**

To a stirring solution of **113** (17 mg, 0.03 mmol) in benzene (1.5 mL) were added tributyltin hydride (0.03 mL, 0.09 mmol) and azabisisobutyronitrile (3 mg) and this mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted with ether (30 mL) and washed with 1% hydrochloric acid, brine, and then the organic layer was dried over anhydrous magnesium sulfate. Solvent was evaporated and the crude product was passed through a silica column (1:2 ethyl acetate-hexanes) to obtain 20 mg of **114** with some impurities. This was used in the next reaction without further purifications.

To a stirring solution of **114** (20 mg) in tetrahydrofuran (1.5 mL) was added tetrabutylammonium fluoride (0.05 mL, 0.05 mmol). After 18h the reaction mixture was diluted with ether (30 mL) and washed with 1% hydrochloric acid. The

organic layer was dried over magnesium sulfate, and concentrated in vacuo. Purification of the crude product by flash column chromatography (4:1 ethyl acetate-hexanes) on silica provided 2.8 mg (60%) of **102** as a colorless solid. Compound **102** prepared from this method was found to be identical in all respects to the substance prepared from method A.

(4R,5R)-5-Carbomethoxy-4,5-dimethyl-5-pentanolide (**30**)

To a stirring suspension of **102** (48 mg, 0.3 mmol) in carbon tetrachloride / acetonitrile / water (2 mL : 2 mL : 3 mL) were added periodic acid (176 mg, 0.76 mmol) and ruthenium(III) chloride trihydrate (1.5 mg 2%) sequentially. After 1h, the reaction mixture was diluted with methylene chloride (50 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 25 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Solvents were evaporated in vacuo and the crude product was dissolved in ether, and then treated with diazomethane. Afer 7h solvent was evaporated and the crude compound was purified by flash column chromatography (3:7 ethyl acetate-hexanes) on silica to yield 30 mg (53%) of **30** as an oil: $[\alpha]^{22}_{D}$ = (+) 5.41° (C = 1.70, $CHCl_3$); IR (neat) 2950, 1746, 1732, 1173, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, 3H, J=6.9), 1.54 (s, 3H), 1.68 (m, 1H), 1.83 (m, 1H), 2.28 (m, 1H), 2.55 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.04, 21.54, 24.58, 25.57, 32.02, 52.99, 85.85, 169.93, 173.30; MS m/z 186 (M^+), 171, 155, 127, (100%); HRMS calcd for $C_7H_{11}O_2$: 127.0759. Found: 127.0759.

(4R,5R)-5-Carbomethoxy-4,5-dimethyl-2-(E)-ethylidene-5-pentanolide(**31**)

To a stirring solution of diisopropyl amine (0.033 mL, 0.24 mmol) in

tetrahydrofuran (1 mL) at -78°C was added n-butyllithium (0.15 mL, 0.22 mmol). This mixture was warmed to 0 °C, stirred for 15 min and cooled back to -78 °C. Then 0.1 mL (0.56 mmol) of hexamethylphosphoramide was added, and after 10 min freshly distilled acetaldehyde (0.04 mL, 0.7 mmol) was added and stirred further at -78 °C. After 10 min the reaction mixture was warmed to -45 °C, and stirred for 3 h at that temperature. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ether. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 5 mL), and then the combined organic layer was dried over anhydrous magnesium sulfate. Solvents were evaporated in vacuo and the crude product was dissolved in methylene chloride (2 mL). This crude β-hydroxy lactone solution was stirred overnight with acetic anhydride (0.06 mL, 0.6 mmol), triethylamine (0.08 mL, 0.57 mmol) and catalytic quantity of dimethylaminopyridine under argon. To this mixture 1,8-diaza bicyclo[5.4.0]undec-7-ene (0.05 mL, 0.33 mmol) was added and stirred for another 24 h at room temperature. The reaction mixture was diluted with ether and washed with 1% hydrochloric acid, brine and then the organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromatography (1:2 ethyl acetate-hexanes) on silica gave 14.8 mg (50%) of **31** as a colorless solid: mp 91-92°C (pentane-ether), Lit.[26] 92.5-94°C; $[\alpha]^{22}_D$ = (+) 46.43° (C = 0.14, $CHCl_3$), Lit.[26] $[\alpha]^{21}_D$ = (+) 47.3°; IR (KBr) 2958, 1745, 1725, 1638, 1255, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, 3H, J=6.8), 1.54 (s, 3H), 1.78 (d, 3H, J=7.2), 2.36 (m, 3H), 3.77 (s, 3H), 7.24 (m, 1H); MS m/z 212 (M^+), 197, 181, 153 (100%); HRMS calcd for $C_{11}H_{16}O_4$: 212.1049. Found: 212.1049.

(4R,5S)-5-Hydroxymethyl-5-(methyl 3,5-dinitrobenzoyloxy)-4-methyl-5-pentanolide (**104**)

To a stirring suspension of **99** (125.7 mg, 0.33 mmol) in carbon tetrachloride / acetonitrile / water (1.5 mL : 1.5 mL : 2.3 mL) were added sodium periodate (292 mg, 1.4 mmol) and ruthenium(III) chloride trihydrate (1.9 mg) sequentially. After 4h the reaction mixture was diluted with methylene chloride (25 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 10 mL) and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was dissolved in ether (30 mL) and pased through a short celite pad. Solvent was evaporated in vacuo and the crude epoxy acid (**103**) was dissolved in tetrahydrofuran (3 mL) and refluxed with camphorsulfonic acid (92 mg, 0.13 mmol) for 6h. The reaction mixture was diluted with methylene chloride (30 mL) and washed with saturated aqueous sodium bicarbonate, brine and then the organic layer was dried over anhydrous magnesium sulfate. Flash column purification (1:1 ethyl acetate-hexanes to 3:2 ethyl acetate-hexanes) of the crude product on silica provided 25.2 mg of **104** and 28.3 mg of **104/103** (4:1) mixture as thick oils:

Compound **104**: $[\alpha]^{22}_{D}$ = (+) 34.13° (C = 1.26, $CHCl_3$); IR (neat) 3422 (broad), 2970, 1738, 1730, 1281, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 3H, J=6.8), 1.88-2.09 (m, 2H), 2.24 (m, 1H), 2.51-2.75 (m, 2H), 3.20 (bs, 1H), 3.84 (d, 1H, J=12.5), 3.99 (d, 1H, J=12.5), 4.57 (d, 1H, J=12.1), 4.69 (d,1H, J=12.1), 9.10-9.25 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.58, 25.02, 29.39, 30.96, 62.37, 66.99, 86.37, 122.77, 129.53, 133.21, 148.76, 162.29, 171.10; MS m/z 337 (M-31), 212, 195, 55 (100%); HRMS calcd for $C_{14}H_{13}N_2O_8$: 337.0672. Found: 337.0672.

(4R,5R)-5-Iodomethyl-4-methyl-5-(methyl 3,5-dinitrobenzoyloxy)-5-pentanolide (**106**)

To a stirring solution of **104** (49 mg, 0.13 mmol) in benzene (4.5 mL) were added triphenylphosphine (30 mg, 0.31 mmol), imidazole (41 mg, 0.6 mmol) and iodine (74 mg, 2.2 mmol) sequentially and the mixture was refluxed for 1.5h. The reaction mixture was diluted with ether (50 mL) and washed with water (3 x 20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Flash column chromatographic purification (1:1 ethyl acetate-hexanes) of the crude product on silica yielded 51 mg (82%) of **106** as an oil: $[\alpha]^{22}_D$ = (+) 14.51° (C = 2.19, $CHCl_3$); IR (neat) 2968, 1735, 1732, 1164, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, 3H, J=7.2), 1.94 (m, 1H), 2.12 (m, 1H), 2.44 (m, 1H), 2.66 (m, 2H), 3.39 (d, 1H, J=11.1), 3.58 (d, 1H, J=11.1), 4.74 (d, 1H, J=12.1), 4.79 (d, 1H, J=12.1), 9.13-9.27 (m, 3H). Compound **106** was used without further analysis, due to its instability.

(2R)-2-[Methyl (4R)-4-methylbutanoate]-2-hydroxymethyl Oxirane(**108**)

To a stirring solution of **106** (43 mg, 0.09 mmol) in methanol (1 mL) was added anhydrous potassium carbonate (5 mg). After 30 min the reaction mixture was diluted with ethyl acetate and washed with brine solution and then the organic layer was dried over anhydrous magensiusm sulfate. Purification of the crude product by flash column chromatography (1:1 ethyl acetate-hexanes) on silica gave 13 mg (79%) of **108**: $[\alpha]^{22}_D$ = (+) 16.78° (C = 0.28, $CHCl_3$); IR (neat) 3417 (broad), 2930, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 3H, J=7.2), 1.49-1.86 (m, 4H), 2.37 (m, 2H), 2.66 (d, 1H, J=4.8), 2.92 (d, 1H, J=4.8), 3.68 (s, 3H),

3.68-3.84 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.10, 27.30, 32.16, 35.62, 49.41, 51.66, 60.31, 61.87, 173.85; MS m/z 170 (M-18), 157, 155, 142, 129, 98 (100%); HRMS calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0942.

(2S)-2-[(1R)-1,5-Dimethyl-4-hexenyl]-2-[(tert-butyldiphenylsiloxy)methyl] Oxirane (**109**)

To a stirring solution of **98** (1.5 g, 8.2 mmol) in dimethylformamide (15 mL) were added imidazole (1.4 g, 20.4 mmol), tert-butyldiphenylsilyl chloride (2.8 mL, 10.6 mmol) and catalytic quantity of dimethylaminopyridine sequentially. The reaction mixture was stirred for 5h, diluted with ether (200 mL), and washed with water (75 mL). The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The crude product was purified by flash column chromatography (1:6 ether-hexanes) on silica to provide 3.1 g (90%) of **109** as a colorless oil: $[\alpha]^{22}_D$ = (-) 0.40° (C = 4.02, $CHCl_3$); IR (neat) 2961, 1471, 1111, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, 3H, J=6.9), 1.04 (s, 9H), 1.10 (m, 1H), 1.54 (m, 1H), 1.57 (s, 3H), 1.66 (s, 3H), 1.69 (m, 1H), 1.94 (m, 2H), 2.57 (d, 1H, J=5.1), 2.78 (d, 1H, J=5.1), 3.74 (d, 1H, J=11.7), 3.78 (d, 1H, J=11.7), 5.05 (m, 1H), 7.37-7.76 (m, 10H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.26, 17.66, 19.27, 25.71, 25.92, 26.76, 33.04, 35.34, 48.80, 62.46, 63.63, 124.33, 127.70, 129.70, 129.81, 131.76, 133.05, 133.20, 135.59, 135.70; MS m/z 422 (M^+), 407, 365, 345, 288, 268, 69 (100%).

(2S)-2-[(tert-Butyldiphenylsiloxy)methyl]-2-[methyl (4R)-4-methylbutanoate] Oxirane (**110**)

Ozone was bubbled through a stirring solution of **109** (3.03 g, 7.2 mmol) in dichloromethane (10 mL), at -78°C, until a blue color persisted, and this mixture was stirred for additional 45 min at that temperature. The excess ozone was removed with a stream of nitrogen and the reaction mixture was warmed to room temperature. The solvent was evaporated and the resultant oil was dissolved in acetone and treated with Jones reagent, at -10°C, until the reaction mixture was orange in color, and stirred for additoinal 45 min. This mixture was treated with excess isopropanol and filtered through a celite pad. The filtrate was concentrated in vacuo and the residue was dissolved in ether (50 mL) and treated with diazomethane. After 5h, solvents were evaporated and the crude product was purified by flash column chromatography (1:7 ethyl acetate-hexanes) on silica to yield 1.38 g (45%) of **110** as a thick oil: $[\alpha]^{22}_D$ = (+) 1.14° (C = 3.59, $CHCl_3$); IR (neat) 2957, 1739, 1110, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=6.9), 1.04 (s, 9H), 1.60 (m, 2H), 1.85 (m, 1H), 2.35 (m, 2H), 2.54 (d, 1H, J=5.0), 2.75 (d, 1H, J=5.0), 3.64 (s, 3H), 3.73 (d, 1H, J=11.7), 3.78 (d, 1H, J=11.7), 7.37-7.68 (m, 10H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.54, 19.23, 26.75, 28.22, 32.14, 35.80, 48.88, 51.50, 61.93, 63.58, 127.73, 129.73, 129.76, 133.05, 133.19, 135.59, 135.69, 173.97; MS m/z 411 (M-15), 395, 369, 199 (100%); HRMS calcd for $C_{21}H_{25}SiO_4$: 369.1522. Found: 369.1525. Anal. calcd for $C_{25}H_{34}SiO_4$: C, 70.39; H, 8.04. Found: C, 70.07; H, 7.99.

(2S) -2-[Methyl (4R)-4-methylbutanoate]-2-hydroxymethyl Oxirane (**111**)

To a stirring solution of **110** (60 mg, 0.14 mmol) in tetrahydrofuran (2.5

mL) was added tetrabutylammonium fluoride (0.21 mL, 0.21 mmol). After 6h the reaction mixture was diluted with ether and washed with brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude produt by flash column chromatography (2:1 ethyl acetate-hexanes) on silica yielded 19.9 mg (75%) of **111** as an oil: $[\alpha]^{22}_D$ = (-) 6.41° (C = 1.53, $CHCl_3$); IR (neat) 3442 (broad), 2956, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, 3H, J=6.7), 1.63 (m, 2H), 1.93 (m, 2H), 2.41 (m, 2H), 2.60 (d, 1H, J=4.6), 2.88 (d, 1H, J=4.6), 3.68 (s, 3H), 3.69 (m, 1H), 3.88 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.17, 28.09, 32.00, 35.92, 48.56, 60.37, 61.99, 173.97; MS m/z 170 (M-18), 157, 129, 55 (100%); HRMS calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0942.

(4R,5S)-5-[(tert-Butyldiphenylsiloxy)methyl]-5-hydroxymethyl-4-methyl-5-pentanolide (**112**)

To a stirring solution of **110** (35 mg, 0.08 mmol) in chloroform (1 mL) at -10°C was added trifluoroacetic acid (0.03 mL, 0.39 mmol) and this mixture was allowed to warm to 0°C over a period of 1h. The reaction mixture was diluted with benzene (1 mL) and solvents were removed in vacuo. Purification of the crude product by flash column chromatography (1:1 ethyl acetate-hexanes) on silica yielded 16.8 mg (50%) of **112**: $[\alpha]^{22}_D$ = (+) 13.44° (C = 2.4, $CHCl_3$); IR (neat) 3402 (broad), 2958, 1711, 1110, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 3H, J=6.9), 1.05 (s, 9H), 1.85 (m, 2H), 2.31 (bs, 1H), 2.45 (m, 2H), 2.65 (m, 1H), 3.70 (m, 2H), 3.64 (d, 1H, J=11.0), 3.71 (d, 1H, J=11.0), 7.36-7.66 (m, 10H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.27, 19.29, 25.16, 26.84, 29.52, 29.63, 63.40,

65.31, 88.16, 127.88, 129.97, 132.54, 132.82, 135.63, 135.70, 171.49; MS m/z 381 (M-31), 355, 353, 278, 199 (100%); HRMS calcd for $C_{20}H_{23}SiO_4$: 355.1366. Found: 355.1366. Anal. calcd for $C_{24}H_{32}SiO_4$: C, 69.87; H, 7.84. Found: C, 69.49; H, 7.67.

(4R,5R)-5-[(tert-Butyldiphenylsiloxy)methyl]-5-iodomethyl-4-methyl-5-pentanolide (**113**)

To a stirring solution of **112** (17 mg, 0.04 mmol) in benzene (1.5 mL) were added triphenylphosphine (24 mg, .09 mmol), imidazole (13 mg, 0.18 mmol) and iodine (22 mg, 0.09 mmol) sequentially, then the mixture was refluxed for 1.5 h. The reaction mixture was diluted with ether (50 mL) and washed with water (3 x 20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by flash column chromatograpy (1:3 ethyl acetate-hexanes) on silica yielded 18.8 mg (90%) of **113**: $[\alpha]^{22}_D$ = (-) 2.24° (C = 0.94, $CHCl_3$); IR (neat) 2951, 1740, 1112, 811 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.05 (d, 3H, J=7), 1.4-1.8 (m, 3H), 2.4 (m, 2H), 3.25 (d, 1H, J=11), 3.55 (d, 1H, J=11), 3.8 (bs, 2H), 7.3-7.8 (m, 10H); MS m/z 465 (M-57), 395, 388, 338, 199 (100%); HRMS calcd for $C_{20}H_{22}SiIO_3$: 465.0383. Found: 465.0386.

(4S)-4-[(tert-Butyldiphenylsiloxy)methyl]-2,2-dimethyl-4[methyl (4R)-4-methyl-butanoate]-1,3-dioxalane (**118**)

To a stirring solution of **112** (107 mg, 0.25 mmol) in benzene(6 mL) were added 2,2-dimethoxypropane (0.3 mL), methanol (0.3 mL) and camphorsulfonic acid (5 mg) sequentially. After 4h the reaction was quenched with

solid sodium bicarbonate, stirred for 30 min and the solvents were evaporated in vacuo. Purification of the crude product by flash column chromatography (1:7 ethyl acetate-hexanes) on silica gave 105 mg (87%) of **118** as a thick oil: $[\alpha]^{23}_D$ = (+) 1.69° (C = 1.18, $CHCl_3$); 2924, 1740, 1088, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=6.8), 1.06 (s, 9H), 1.26 (s, 3H), 1.37 (s, 3H), 1.50 (m, 1H), 1.90 (m, 2H), 2.25 (m, 1H), 2.45 (m, 1H), 3.58 (d, 1H, J=10.4), 3.67 (d, 1H, J=10.4), 3.66 (s, 3H), 3.85 (d, 1H, J=8.8), 3.97 (d, 1H, J=8.8), 7.36-7.69 (m, 10H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.95, 19.25, 26.62, 26.88, 27.09, 27.12, 32.77, 37.49, 51.49, 65.50, 69.06, 85.67, 109.44, 127.71, 127.73, 129.75, 133.16, 135.69, 135.73, 174.14; MS m/z 469 (M-15), 453, 427, 407, 369 (100%); HRMS calcd for $C_{24}H_{31}SiO_5$: 427.1941. Found: 427.1940.

(4R)-2,2-Dimethyl-4-hydroxymethyl-4-[methyl (4R)-4-methylbutanoate]-1,3-dioxalane (**119**)

Method A. To a stirring solution of **118** (82 mg, 0.16 mmol) in tetrahydrofuran (4 mL) was added tetrabutylammonium fluoride (0.25 mL, 0.25 mmol). After 27h the reaction mixture was diluted with ether (15 mL) and washed with brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude product by flash column chromatogrpahy (1:1 ethyl acetate-hexanes) on silica yielded 33.4 mg (85%) of **119** as an oil: $[\alpha]^{22}_D$ = (+) 23.18° (C = 0.44, $CHCl_3$); IR (neat) 3495 (broad), 2983, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, 3H, J=7.0), 1.41 (s, 3H), 1.43 (s, 3H), 1.85 (m, 2H), 2.10 (t, 1H, J=6.5), 2.15(m, 1H), 2.30 (m, 1H), 2.45 (m, 1H), 3.56(dd, 1H, J=11.5,6.2), 3.65(dd, 1H, J=11.5,6.8), 3.68 (s, 3H), 3.88 (q,

2H, J=8.9,1.2, AB); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.96, 26.66, 26.72, 27.33, 32.40, 36.81, 51.66, 63.17, 68.67, 85.97, 109.68, 174.15; MS m/z 231 (M-15), 215, 200, 197, 157 (100%); HRMS calcd for $C_{11}H_{19}O_4$: 215.1283. Found: 215.1285.

Method B: from **128**. To a stirring solution of **128** (42 mg, 0.10 mmol) in methanol (2 mL) was added anhydrous potassium carbonate (5 mg). After 30min the solvent was removed in vacuo and the crude product was purified by flash column chromatography (1:2 ethyl acetate-hexanes) on silica to yield 16 mg (65%) of **119** as an oil.

(4S)-4-Carbomethoxy-2,2-dimethyl-4-[methyl (4R)-4-methylbutanoate]-1,3-dioxalane (**120**)

Method A: from **119**. To a stirring suspension of **119** (37.6 mg, 0.15 mmol) in carbon tetrachloride / acetonitrile / pH=7 phosphate buffer (2 mL:2 mL:3 mL) were added sodium periodate (98 mg, 0.44 mmol) and ruthenium(III) chloride trihydrate (2%) sequentially. After 2h the reaction mixture was diluted with methylene chloride (15 mL), layers were separated and the aqueous layer was extracted with methylene chloride (3 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was dissolved in ether and treated with excess diazomethane. Solvent was evaporated and the crude product was purified by flash column chromatography (1:2 ethyl acetate-hexanes) on silica to yield 25.6 mg (61%) of **120** as a colorless oil: $[\alpha]^{22}_D$ = (+) 11.63° (C = 1.63, $CHCl_3$); IR (neat) 2980, 1736, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=6.7), 1.39 (s, 3H), 1.44 (s, 3H), 1.45 (m, 1H), 1.80 (m, 1H), 1.94 (m, 1H), 2.27 (m, 1H), 2.41 (m, 1H), 3.67 (s, 3H), 3.79 (s,

3H), 3.94 (d, 1H, J=8.9), 4.32 (d, 1H, J=8.9); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.42, 25.46, 26.03, 27.02, 31.95, 38.33, 51.54, 52.27, 69.89, 87.17, 111.07, 173.66, 173.82; MS m/z 259 (M-15), 243, 215, 167, 157 (100%); HRMS calcd for $C_{12}H_{19}O_6$: 259.1182. Found: 259.1180; Anal. calcd for $C_{13}H_{22}O_6$: C, 56.90; H, 8.09. Found: C, 57.09; H, 8.07.

Method B: from **126**. Excess diazomethane was added to a solution of **126** (26 mg, 0.1 mmol) in ether at room temperature. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (1:2 ethyl acetate-hexanes) on silica to yield 27 mg (98%) of **120** as a colorless oil.

(2S,3R)-3,7-Dimethyl-2-hydroxy-2-hydroxymethyl-6-octenylpivalate (**121**)

To a stirring solution of **98** (119.2 mg, 0.64 mmol) and pivalic acid (100 mg, 0.96 mmol) in benzene (6 mL) was added titanium(IV) isopropoxide (0.28 mL, 0.96 mmol). After 20 min benzene was evaporated and the residue was dissolved in ether (100 mL) and stirred vigorously for 4h with 0.5 mL of saturated aqueous sodium sulfate solution. The thick white precipitate was filtered through a short Celite pad and the filtrate was dried over anhydrous magnesium sulfate. Solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (1:1 ethyl acetate-hexanes) on silica to provide 93.2 mg (51%) of **121** as an oil: $[\alpha]^{23}_D$ = (+) 26.56° (C = 1.77, $CHCl_3$); IR (neat) 3448 (broad), 2970, 1732, 1286 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, 3H, J=6.9), 1.12-1.26 (m, 3H), 1.22 (s, 9H), 1.61 (s, 3H), 1.65 (m, 2H), 1.68 (s, 3H), 1.92 (m, 1H), 2.12 (m, 1H), 3.54 (q, 2H, J=11.7,3.6, AB), 4.09 (d, 1H, J=11.7), 4.26 (d, 1H, J=11.7), 5.08 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.33, 17.72, 25.73, 26.22, 27.18, 30.62,36.82, 38.96, 64.09, 65.64, 75.47, 124.20, 131.90,

179.33; MS m/z 286 (M^+), 268, 201, 182, 82 (100%); HRMS calcd for $C_{16}H_{30}O_4$: 286.2144. Found: 286.2144.

(4S)-2,2-Dimethyl-4-[(1R)-1,5-dimethyl-4-hexenyl]-4-(methyl pivalyloxy)-1,3-dioxalane (**122**)

To a stirring solution of **121** (94.5 mg, 0.33 mmol) in methylene chloride (6 mL) were added 2,2-dimethoxypropane (0.4 mL, 3 mmol) and camphorsulfonic acid (10 mg) sequentially. After 5h the reaction was quenched with solid sodium bicarbonate, stirred for 15 min and solvent was evaporated in vacuo. Purification of the crude product by flash column chromatography (1:10 ethyl acetate-hexanes) on silica yielded 105 mg (98%) of **122**: $[\alpha]^{22}_D$ = (+) 5.98° (C = 3.59, $CHCl_3$); IR (neat) 2978, 1734, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3H, J=6.8), 1.16 (m, 1H), 1.21 (s, 9H), 1.39 (s, 3H), 1.41 (m, 1H), 1.43 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.76 (m, 1H), 1.90 (m, 1H), 2.15 (m, 1H), 3.83 (d, 1H, J=8.8), 3.90 (d, 1H, J=8.8), 3.97 (d, 1H, J=11.6), 4.16 (d, 1H, J=11.6); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.08, 17.70, 25.69, 26.35, 26.62, 27.21, 27.24, 32.06, 38.55, 28.85, 64.98, 69.41, 84.48, 109.71, 124.11, 131.93, 178.37; MS m/z 326 (M^+), 311, 269, 211, 157 (100%); HRMS calcd for $C_{18}H_{31}O_4$: 311.2222. Found: 311.2224.

(4R)-2,2-Dimethyl-4-[(1R)-1,5-dimethyl-4-hexenyl]-4-hydroxymethyl-1,3-dioxalane (**123**)

To a stirring suspension of lithium aluminum hydride (20 mg, 0.45 mmol) in ether (5 mL) was added **122** (105 mg, 0.30 mmol) in ether. The reaction mixture was refluxed for 1h and carefully quenched with 0.02 mL of water at 0°C.

Then, 0.02 mL of 15% sodium hydroxide and .06 mL of water were added and the mixture was stirred for 10 min at room temperature. White solid was filtered, and the precipitate was washed with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by flash column chromatography (1:3 ethyl acetate-hexanes) on silica gave 65.3 mg (90%) of **123**: $[\alpha]^{22}_D$ = (+) 13.41° (C = 0.81, $CHCl_3$); IR (neat) 3468 (broad), 2983, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, 3H, J=7.0), 1.07 (m, 1H), 1.38 (m, 1H), 1.42 (s, 3H), 1.44 (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.88 (m, 3H), 2.15 (m, 1H), 3.47 (dd, 1H, J=11.4,6.7), 3.66 (dd, 1H, J=11.4,5.8), 3.85 (q, 2H, J=8.7,4.2, AB), 5.08 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.15, 17.68, 25.68, 26.44, 26.83, 27.28, 31.84, 37.76, 62.73, 68.78, 86.38, 109.51, 124.13, 131.89; MS m/z 242 (M^+), 227, 224, 211, 69 (100%); HRMS calcd for $C_{13}H_{23}O_3$: 227.1647. Found: 227.1649. Anal. calcd for $C_{14}H_{26}O_3$: C, 69.37; H, 10.82. Found: C, 69.34; H, 11.08.

(4S)-4-Carbomethoxy-2,2-dimethyl-4-[(1R)-1,5-dimethyl-4-hexenyl]-1,3-dioxalane (**125**)

Pyridinium dichromate (3.5 g, 9.2 mmol) was added to a stirring solution of **123** (559 mg, 2.3 mmol) in dimethylformamide (6 mL) at room temperature. After 30h the reaction mixture was poured into 60 mL of water and extracted with ether (4 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to give 395 mg (67%) of acid **124** as an oil. This acid **124** was used without purification. IR (neat) 3200 (broad), 2932, 1721, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3H, J=6.7), 1.26 (m, 2H), 1.42 (m, 1H), 1.44 (s, 3H), 1.48 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.88

(m, 1H), 2.07 (m, 1H), 3.98 (d, 1H, J=9.3), 4.36 (d, 1H, J=9.3), 5.05 (m, 1H).

Acid **124** (395 mg, 1.54 mmol) was dissolved in ether and treated with excess diazomethane. Solvent was evaporated in vacuo and the crude product was purified by column chromatography (1:7 ethyl acetate-hexanes) on silica to provide 412 mg (99%) of **125** as a colorless oil: $[\alpha]^{22}_D$ = (+) 14.58° (C = 1.67, $CHCl_3$); IR (neat), 2986, 1731, 1380, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=6.8), 1.20 (m, 1H), 1.38 (m, 1H), 1.39 (s, 3H), 1.43 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.89-2.10 (m, 3H), 3.77 (s, 3H), 3.89 (d, 1H, J=8.9), 4.33 (d, 1H, J=8.9), 5.05 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.69, 17.69, 25.62, 25.69, 25.89, 26.10, 31.72, 38.49, 52.16, 69.85, 87.63, 110.87, 123.99, 131.93, 174.12; MS m/z 255 (M-15), 211, 194, 135 (100%); HRMS calcd for $C_{14}H_{23}O_4$: 255.1596. Found: 255.1596.

(4R)-4-[(4S)-4-carbomethoxy-2,2-dimethyl-1,3-dioxalane]-pentanoic Acid (**126**)

Sodium periodate (384 mg, 1.8 mmol) and ruthenium(III) chloride trihydrate (2%) were added sequentially to a stirring suspension of **125**(117.9 mg, 0.42 mmol) in carbon tetrachloride / acetonitrile / pH = 7 phosphate buffer (2 mL : 2mL:3 mL), and the mixture was stirred for 2.5 h. The reaction mixture was diluted with methylene chloride (10 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (4 x 10 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Solvents were evaporated and the crude product was purified by flash column chromatography (1:1 to 2:1 ethyl acetate-hexanes), on silica, to give 75.3 mg (69%) of **126** as an oil: $[\alpha]^{24}_D$ = (+) 14.18° (C = 1.22, $CHCl_3$); IR (neat) 3200 (broad), 1733, 1717, 1158 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 0.97 (d, 3H, J=6.7), 1.39 (s, 3H), 1.44 (s, 3H), 1.47 (m, 1H), 1.81 (m, 1H), 1.98 (m, 1H), 2.34 (m, 1H), 2.47 (m, 1H), 3.78 (s, 3H), 3.95 (d, 1H, J=9.1), 4.32 (d, 1H, J=9.1); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.27, 25.30, 25.89, 26.59, 31.64, 38.01, 52.18, 69.67, 86.98, 111.00, 173.70, 178.91; MS m/z 245 (M-15), 201, 167, 143 (100%); HRMS calcd for $C_{11}H_{17}O_6$: 245.1025. Found: 245.1026. Anal. calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 54.88; H, 7.75.

(4S)-2,2-Dimethyl-4-[(1R)-1,5-dimethyl-4-hexenyl]-4-(methyl p-nitrobenzoyloxy) (**127**)

To a stirring solution fo **123** (70.5 mg, 0.29 mmol) in pyridine (4 mL) were added p-nitrobenzoyl chloride (81 mg, 43 mmol) and dimethylaminopyridine (10 mg) sequentially. The reaction mixturre was stirred overnight, diluted with methylene chloride (50 mL) and the mixture was sequentially washed with saturated aqueous copper(II) sulfate (2 x 25 mL), water (25 mL), saturated aqueous sodium bicarbonate (25 mL) and brine solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by column chromatography (1:5 ethyl acetate-hexanes) on silica gave 95 mg (85%) of **127** as a pale yellow oil: $[\alpha]^{22}_D$ = (+) 3.19° (C = 1.06, $CHCl_3$); IR (neat) 2983, 1729, 1530, 1379, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, J=6.8), 1.18 (m, 1H), 1.40 (s, 3H), 1.42 (s, 3H), 1.47 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 1.96 (m, 2H), 2.13 (m, 1H), 3.91 (d, 1H, J=9.0), 4.04 (d, 1H, J=9.0), 4.40 (d, 1H, J=11.8), 4.42 (d, 1H, J=11.8), 5.08 (bt, 1H, J=7), 8.24 (d, 2H, J=7.4), 8.30 (d, 2H, J=7.4); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.35, 17.71, 25.68, 26.31,

26.47, 27.23, 32.15, 38.99, 66.42, 69.69, 84.52, 110.07, 123.61, 123.87, 130.82, 132.21, 135.47, 150.67, 164.61; MS m/z 391 (M^+), 376, 222, 150, 148 (100%); HRMS calcd for $C_{20}H_{26}NO_6$: 376.1760. Found: 376.1760.

(4S)-2,2-Dimethyl-4-[methyl (4R)-4-methylbutanoate]-4-[methyl p-nitrobenzoyloxyl -1,3-dioxalane (**128**)

p-Nitrobenzoate derivative **127** (65 mg, 0.16 mmol) was dissolved in methylene chloride and ozone was bubbled through this solution at -78°C until a blue color persisted. This mixture was stirred for 45 min at -78°C, and excess ozone was removed by a stream of nitrogen. The reaction mixture was treated with dimethyl sulfide (0.01 mL, 0.99 mmol) at -78°C, stirred for 7h at room temperature and then washed with brine solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude aldehyde (56 mg) obtained was dissolved in carbon tetrachloride / acetonitrile / pH = 7 phosphate buffer (1 mL : 1 mL:1.5 mL) and stirred with sodium periodate (63.7 mg, 0.29 mL) and ruthenium(III) chloride trihydrate (2%) for 15 min. The reaction mixture was diluted with methylene chloride (3 mL), and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 5 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. The solvents were evaporated and ether solution of the residue was treated with excess diazomethane. Evaporation of solvent and column chromatographic (1:2 ethyl acetate-hexanes) purification of the crude product on silica provided 27 mg (58%) of **128**: $[\alpha]^{22}_D$ = (+) 6.79° (C = 1.84, $CHCl_3$); IR (neat) 2984, 1729, 1529, 1348, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, J=7.0), 1.41 (s, 3H), 1.42 (s, 3H), 1.45 (m, 1H), 1.89 (m, 2H), 2.35 (m, 1H), 2.47 (m, 1H), 3.68 (s, 3H), 3.98 (d, 1H, J=8.9), 4.06 (d, 1H,

J=8.9), 4.42 (bs, 2H), 8.24 (d, 2H, J=8.7), 8.31 (d, 2H, J=8.7); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.12, 26.46, 27.18, 27.22, 32.34, 38.70, 51.64, 66.24, 69.53, 84.15, 110.26, 123.66, 130.87, 135.36, 150.70, 164.56, 173.70; MS m/z 380 (M-15), 364, 280, 157, 150 (100%); HRMS calcd for $C_{18}H_{22}NO_8$: 380.1345. Found: 380.1369.

(4S)-2,2-Dimethyl-4-[(1R)-1,5-dimethyl-4-hexenyl]-4-[2-(trimethylsilyl)ethoxycarbonyl]-1,3-dioxalane (**129**)

Titanium(IV) ethoxide (0.84 mL, 4.0 mmol) was added to a stirring solution of **125** (723 mg, 2.7 mmol) in trimethylsilylethanol (7.7 mL), under argon, and the mixture was stirred for 36h at 100°C. Methanol formed in the reaciton was removed in vacuo and the reaction mixture was stirred for another 24h at 100°C, after the addition of more trimethylsilylethanol (3 mL). This mixture was cooled to room temperature and solvent was evaporated in vacuo. The residue was dissolved in ether (150 mL) and stirred vigorously with saturated aqueous sodium sulfate (1 mL) for 2h, and then the thick white precipitate was filtered through a short Celite pad. Filtrate was concentrated and the product was purified by flash column chromatography (1:10 ethyl acetate-hexanes) on silica to yield 861 mg (93%) of **129** as a colorless oil: $[\alpha]^{22}_D$ = (+) 10.51° (C = 1.22, $CHCl_3$); IR(neat) 2984, 1724, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s,, 9H), 0.95 (d, 3H, J=6.7), 1.04 (t, 2H, J=8.6), 1.20 (m, 1H), 1.39 (s, 3H), 1.42 (s, 3H), 1.43 (m, 1H), 1.59 (s, 3H), 1.68 (s, 3H), 1.90 (m, 2H), 2.06 (m, 1H), 3.88 (d, 1H, J=9.0), 4.24 (m, 2H), 4.31 (d, 1H, J=9.0), 5.06 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.59, 13.59, 17.61, 17.65, 25.66, 25.76, 25.85, 26.07, 31.67, 38.32, 63.54, 69.78, 87.46, 110.74, 124.04, 131.78, 173.73; MS m/z 356 (M^+), 341, 311, 73 (100%);

HRMS calcd for $C_{18}H_{33}SiO_4$: 341.2148. Found: 341.2146. Anal. calcd for $C_{19}H_{36}SiO_4$: C, 64.00; H, 10.19. Found: C, 64.21; H, 10.48.

(4R)-4-{(4S)-2,2-dimethyl-4-[2-(trimethylsilyl)ethoxycarbonyl]-1,3-dioxalane}-pentanoic Acid (**130**)

Ozone was bubbled through a stirring solution of **129** (251 mg, 0.70 mmol) in methylene chloride (4 mL) at -78°C until a blue color persisted. This mixture was stirred for 45 min at -78°C and excess ozone was removed by a stream of nitrogen. The reaction was quenched by treating with dimethyl sulfide (0.31 mL, 4.2 mmol) at -78°C and the mixture was stirred for 7h at room temperature and then washed with brine solution. The organic layer was dried over anhydrous magensium sulfate and concentrated in vacuo to yield 226 mg (98%) of crude aldehyde. The aldehyde was dissolved in carbon tetrachloride / acetonitrile / pH = 7 phosphate buffer (1.6 mL:1.6 mL:2.4 mL) and stirred with sodium periodate (220 mg, 1.02 mmol) and ruthenium(III) chloride trihydrate (2%) for 20 min at room temperature. The reaction mixture was diluted with methylene chloride (10 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (4 x 10 mL) and the combined organic layer was dried over anhydrous magnesium sulfate. Solvent was evaporated and the crude product was purified by column chromatography (1:1 to 2:1 ethyl acetate-hexanes) on silica to provide 160 mg (67%) of **130** as a colorless oil: $[\alpha]^{22}_D$ = (+) 11.94° (C = 1.29, $CHCl_3$); IR (neat) 3200 (broad), 2956, 1747, 1721, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.97 (d, 3H, J=6.7), 1.05 (bt, 2H, J=8.8), 1.40 (s, 3H), 1.44 (s, 3H), 1.47 (m, 1H), 1.81 (m, 1H), 1.98 (m, 1H), 2.32 (m, 1H), 2.47 (m, 1H), 3.94 (d, 1H, J=9.15), 4.27 (m, 2H), 4.31 (d, 1H, J=9.15); ^{13}C NMR (400 MHz, $CDCl_3$) δ

-1.57, 13.47, 17.58, 25.52, 26.06, 26.73, 31.88, 38.13, 63.86, 69.83, 87.04, 111.08, 173.56, 179.43; MS m/z 331 (M-15), 301, 287, 201, 73 (100%); HRMS calcd for $C_{15}H_{27}SiO_6$: 331.1577. Found: 331.1577.

(4S)-2,2-Dimethyl-4-[methyl (4R)-4-methylbutanoate]- 4-[2-(trimethylsilyl)ethoxy-carbonyl]-1,3-dioxalane (**131**)

Excess diazomethane was added to a solution of **130** (160 mg, 0.46 mmol) in ether (4 mL) at room temperature. Solvent was evaporated in vacuo and the crude product was purified by column chromatography (1:7 ethyl acetate-hexanes) on silica to give 164 mg (99%) of **131** as a colorless oil: $[\alpha]^{22}_D$ = (+) 10.45° (C = 2.46, $CHCl_3$); IR (neat) 2955, 1743, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.97 (d, 3H, J=6.7), 1.05 (t, 2H, J=8.9), 1.40 (s, 3H), 1.43 (s, 3H), 1.46 (m, 1H), 1.82 (m, 1H), 1.93 (m, 1H), 2.27 (m, 1H), 2.42 (m, 1H), 3.66 (s, 3H), 3.93 (d, 1H, J=8.9), 4.31 (d, 1H, J=8.9), 4.28 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.55, 13.46, 17.61, 25.57, 26.09, 27.07, 32.05, 38.35, 51.57, 63.80, 69.92, 87.12, 111.03, 173.57, 173.80; MS m/z 345 (M-15), 259, 215, 200, 157 (100%); HRMS calcd for $C_{16}H_{29}SiO_6$: 345.1733. Found: 345.1735. Anal. calcd for $C_{17}H_{32}SiO_6$: C, 56.64; H, 8.95. Found: C, 56.66; H, 9.12.

(4R,5S)-5-Carbomethoxy-5-hydroxy-4-methyl-6-(tert-butyldimethylsiloxy)-hexanoic Acid (**136**)

Compound **126** (202 mg, 0.77 mmol) was stirred with 80% aqueous acetic acid (5 mL) at 65°C for 2h. The reaction mixture was cooled to room temperature and solvent was evaporated in vacuo. The residue was left overnight in high vacuum pump and then azeotropically dried with benzene. This crude product

was dissolved in dimethylformamide (3 mL) and stirred with tert-butyldimethylsilyl chloride (258 mg, 1.7 mmol) and imidazole (238 mg, 3.5 mmol) for 12h under argon. The reaction mixture was diluted with ether (30 mL) and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product obtained was stirred with tetrahydrofuran / acetic acid / water (3mL:3mL:1mL) for 9h at room temperature. The reaction mixture was diluted with chloroform, washed with brine solution, and dried over anhydrous magnesium sulfate. Solvent was evaporated and the crude compound was purified by column chromatography (1:2 to 2:1 aethyl acetate-hexanes) on silica to yield 128 mg (50%) of **136** as an oil: $[\alpha]^{22}_D$ = (+) 13.89° (C = 0.54, $CHCl_3$); IR (neat) 3535 (broad), 2955, 1740, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 0.95 (d, 3H, J=7.0), 1.58 (m, 2H), 1.91 (m, 1H), 2.30 (m, 1H), 2.42 (m, 1H), 3.35 (bs, 1H), 3.68 (d, 1H, J=9.6), 3.76 (s, 3H), 3.83 (d, 1H, J=9.6); ^{13}C NMR (400 MHz, $CDCl_3$) δ -5.67, -5.48, 12.70, 18.11, 25.66, 26.70, 31.48, 36.41, 52.41, 67.92, 81.61, 175.38, 178.89; MS m/z 303 (M-31), 277, 259, 219, 89 (100%); Exact mass calcd for $C_{11}H_{21}SiO_6$: 277.1107. Found: 277.1106.

(4R,5S)-5-Carbomethoxy-4-methyl-5-[(tert-butyldimethylsiloxy)methyl]-5-pentanolide (**137**)

To a stirring solution of **136** (128 mg, 0.38 mmol) in acetonitrile (3 mL) were added 2-chloro-1-methylpyridinium iodide (294 mg, 1.2 mmol) and dimethylamino- pyridine (234 mg, 1.9 mmol) sequentially. After 6.5h, the reaction mixture was diluted with acetonitrile and yellow solid was filtered. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography (1:2 ethyl acetate-hexanes) on silica to yield 104 mg (87%) of **137** as an oil: $[\alpha]^{22}_D$

= (+) 12.68° (C = 0.82, $CHCl_3$); IR (neat) 2954, 1756, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.07 (d, 3H, J=7.2), 1.78 (m, 2H), 2.39 (m, 1H), 2.56 (m, 2H), 3.78 (s, 3H), 3.93 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.40, 18.11, 24.99, 25.66, 26.12, 30.28, 52.64, 65.80, 88.86, 169.57, 171.38; MS m/z 285 (M-31), 259, 257, 231 (100%), 201; HRMS calcd for $C_{11}H_{19}SiO_5$: 259.1002. Found: 259.1001; Anal. calcd for $C_{15}H_{28}SiO_5$: C, 56.96; H, 8.92. Found: C, 57.09; H, 8.82.

(4R,5S)-5-Carbomethoxy-2-(E)-ethylidene-5-hydroxymethyl-4-methyl-5-pentanolide (**139**)

To a stirring solution of diisopropylamine (0.02 mL, 0.14 mmol) in tetrahydrofuran (0.5 mL) at -78°C was added n-butyllithium (1.99 M in hexane, 0.07 mL, 0.14 mmol). This mixture was warmed to 0°C, stirred for 10 min and was cooled back to -78°C. To this lithiumdiisopropylamide solution at -78°C was added **137** (27 mg, 0.085 mmol) in tetrahydrofuran (0.5 mL) via cannula and the mixture was stirred for 50 min. Then hexamethylphosphoramide (0.1mL) was added to the reaction mixture at -78°C , followed by acetaldehyde (0.03 mL, 0.5 mmol) after 10 min. The reaction mixture was stirred for 2h at -45°C, 2h at room temperature and quenched with saturated aqueous ammonium chloride. The emulsion obtained was diluted with ether and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude β-hydroxylactone was dried azeotropically with benzene and then stirred overnight with acetic anhydride (0.09 mL, 0.9 mmol), triethylamine (0.17 mL, 1.2 mmol) and dimethylamino pyridine (3 mg) in methylene chloride under argon. To this mixture 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 mL, 0.75 mmol) was added and stirred for

another 24 h. The reaction mixture was diluted with ether and washed sequentially with 1% hydrochloric acid, brine solution, and dried over anhydrous magnesium sulfate. Solvent was evaporated and crude product was purified by flash column chromatography (1:3 ethyl acetate-hexanes) on silica to obtain 15 mg of **138** with some impurities. This was used without further purifications. **138**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.01 (d, 3H, J=7.0), 1.78 (d, 3H, J=7.0), 1.88 (m, 2H), 2.55 (m, 1H), 3.76 (s, 3H), 3.93 (s, 2H), 7.23 (q, 1H, J=7.0).

To a tetrahydrofuran (1 mL) solution of **138** (15 mg) was added tetrabutyl ammonium fluoride (0.07 mL, 0.07 mmol) and this mixture was stirred for 7.5h under argon. The reaction mixture was diluted with ether and washed with brine solution. The organic layer was dried over anhydrous magnesium sulfate. Purification of the crude product by flash column chromtography (2:1 ethyl acetate-hexanes) on silica provided 2.9 mg (15%) of the **139**: $[\alpha]^{22}_D$ = (+) 25.20° (C = 0.079, $CHCl_3$); IR (neat) 3300 (broad), 1746, 1702, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, 3H, J=7.1), 1.25 (bs, 1H), 1.79 (d, 3H, J=7.3), 2.37 (m, 2H), 2.54 (m, 1H), 3.82 (s, 3H), 3.95 (m, 2H), 7.30 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.88, 14.18, 28.97, 29.70, 53.04, 65.82, 87.52, 122.94, 143.74, 171.81, 173.17; MS m/z 228 (M^+), 197, 169 (100%), 151; HRMS calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.1005.

Dimethyl Retronecate (**140**)

A methanol (0.5 mL) solution of **139** (2.0 mg, 0.009 mmol) was added via canula to excess sodium methoxide in methanol, and the mixture was stirred for

6h at room temperature under argon. The reaction was quenched with saturated aqueous ammonium chloride and the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography (2:1 ethyl acetate-hexanes) on silica to provide 1.6 mg (70%) of **140**: $[\alpha]^{23}_D$ = (-) 14.00° (C = 0.07, $CHCl_3$); IR (neat) 3468 (broad), 2951, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3H, J=6.9), 1.25 (m, 1H), 1.80 (d, 3H, J=7.2), 2.21-2.36 (m, 3H), 3.55 (s, 1H), 3.72 (s, 3H), 3.80 (m, 2H), 3.84 (s, 3H), 6.95 (q, 1H, J=7.2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.01, 14.69, 28.26, 36.95, 51.67, 52.92, 66.59, 80.92, 130.76, 139.59, 168.10, 175.84; MS m/z 229(M-31), 207, 169, 58(100%); HRMS calcd for $C_{11}H_{17}O_5$: 229.1076. Found: 229.1076.

9-tert-Butyldimethylsiloxyretronecine (**26**)

To a stirring solution of retronecine (**1**) (75.4 mg, 0.48 mmol) in dimethylformamide (1 mL) were added tert-butyldimethylsilyl chloride (86.9 mg, 0.55 mmol) and triethylamine sequentially. After 6h the reaction was quenched with 0.5% sodium hydroxide (7 mL) at 0°C and the mixture was extracted with chloroform (4 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (20:1 methylene chloride (saturated with ammonium hydroxide) - methanol) on silica to give 110 mg (85%) of **26** as a pale yellow oil:

Methylene chloride saturated with ammonium hydroxide was prepared by shaking methylene chloride with 29% ammonium hydroxide (5:1 ratio) and drying the organic layer quickly with anhydrous potassium carbonate. **26**: $[\alpha]^{21}_D$ = (+) 66.01° (C = 1.07, $CHCl_3$); IR (neat) 3300 (broad), 2954, 1101 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.93 (s, 9H), 1.94 (m, 1H), 2.03 (dd, 1H, J=12.9,5.6), 2.74 (m, 1H), 3.25 (t, 1H, J=7.9), 3.40-3.48 (m, 2H), 3.87 (dd, 1H, J=15.6,1.9), 4.15 (m, 2H), 4.25 (t, 1H, J=3.6), 4.37 (d, 1H, J=11.1), 5.74 (bs, 1H); MS m/z 269 (M^+), 212, 182 (100%), 154, 138; HRMS calcd for $C_{14}H_{27}SiNO_2$: 269.1811. Found: 269.1811.

Methyl Ester (**142**)

Dimethyl ester **120** (52.1 mg, 0.19 mmol) was stirred with potassium hydroxide (107 mg, 1.9 mmol) in tetrahydrofuran / water (1mL:1mL) for 24h at room temperature. The solvents were evaporated and the residue was carefully acidified (pH = 3) with 5% hydrochloric acid, and extracted with ethyl acetate (4 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to obtain 46.1 mg (99%) of **144** as an oil. This was used without further purification. **144**: IR (neat) 3200 (broad), 2988, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, 3H, J=6.7), 1.45 (s, 3H), 1.46 (s, 3H), 1.58 (m, 1H), 1.82 (m, 1H), 1.99 (m, 1H), 2.34(m, 1H), 2.49 (m, 1H), 4.02 (d, 1H, J=9.4), 4.34 (d, 1H, J=9.4).

The diacid **144** (44.8 mg, 0.18 mmol) was stirred with 1,3-dicyclohexylcarbodiimide (39.5 mg, 0.19 mmol) in methylene chloride for 5 h. Solvent was evaporated in vacuo, the residue was dissolved in tetrahydrofuran and passed through a cotton wool plug. This tetrahydrofuran solution of crude anhydride **145** was used without further purification. In a separate flask, n-butyl- lithium (0.19 mL, 0.26 mmol) was added to a stirring solution of **26** (70.2 mg, 0.26 mmol) and dimethylaminopyridine (10 mg) in tetrahydrofuran at 0°C. After 10 min, tetrahydrofuran solution of **145** was added via cannula, and stirring was continued

overnight at room temprature. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with methylene chloride (4 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was dissolved in ether (5 mL) and excess dizaomethane was added. Solvent was evaporated and the crude product was purified by column chromatography on neutral alumina (Brockman activity III, 1:2 to 2:1 ethyl acetate-hexanes) to give 50.6 mg (55%) of **142** as an oil: $[\alpha]^{23}_D$ = (+) 13.35° (C = 1.67, $CHCl_3$); IR (neat) 2954, 1733, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 0.93 (d, 3H, J=6.8), 1.39 (s, 3H), 1.41 (m, 1H), 1.43 (s, 1H), 1.75 (m, 1H), 1.90-2.04 (m, 3H), 2.21-2.32 (m, 2H), 2.60 (m, 1H), 3.31 (m, 2H), 3.78 (s, 3H), 3.90 (m, 1H), 3.92 (d, 1H, J=9.2), 4.15 (q, 2H, AB, J=9.7), 4.24 (bs, 1H), 4.33 (d, 1H, J=9.2), 5.48 (bt, 1H, J=3.32), 5.65 (bd, 1H, J=1.3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.52, 18.37, 25.51, 25.91, 26.14, 26.88, 32.40, 34.62, 38.35, 52.29, 53.62, 60.61, 62.87, 69.78, 73.96, 87.14, 111.06, 123.37, 138.68, 172.43, 173.75; MS m/z 496(M-15), 454, 452, 396, 380, 120 (100%); HRMS calcd for $C_{22}H_{36}SiNO_7$: 454.2261. Found: 454.2263.

Methyl Ester (**146**) and Methyl Ester (**147**)

To a stirring solution of **142** (17 mg, .034 mmol) in methanol/water (1.5mL:0.5 mL) was added ammonium fluoride (30 mg, 0.8 mmol) and the mixture was heated at 65°C for 4h. Solvents were evaporated in vacuo, the residue was treated with 15% sodium carbonate and extracted with chloroform (4 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography, on neutral alumina (Brockman, activity II, 30:1 methylene chloride-methanol) to give 6.6 mg (50%) of

146/147 mixture: IR (neat) 3355 (broad), 2935, 1733, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J=7.1) and 0.96 (d, J=7.0) (3H), 1.38 (s) and 1.39 (s) (3H), 1.44 (s, 3H), 3.34-3.49 (m, 2H), 3.79 (bs, 3H), 3.93 (m, 1H), 4.07 (m) and 4.70 (q, AB, J=11.1) (1H), 4.17 (bs, 1H), 4.31 (m, 1H), 4.33 (bs) and 5.31 (s) (1H), 5.68 (s) and 5.83 (s) 1H); MS m/z 397 (M^+), 382, 338, 153, 120; HRMS calcd for $C_{20}H_{31}NO_7$: 397.2100. Found: 397.2099.

2-(Trimethylsilylethyl) Ester (**143**)

The acid **130** (46.3 mg, 0.13 mmol) was stirred with 1,3-dicyclo hexylcarbodiimide (16.6 mg, 0.08 mmol) in methylene chloride for 6h. The solvent was evaporated in vacuo and the crude anhydride **150** was used in the next reaction without further purification. In a separate flask, n-butyllithium (0.16 mL, 0.23 mmol) was added to a stirring solution of **26** (63.6 mg, 0.23 mmol) and dimethylaminopyridine (5 mg) in tetrahydrofuran at 0°C. After 10 min, tetrahydrofuran solution of **150** was added to this mixture via cannula, through a cotton wool plug, and stirring was continued overnight at room temperature. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with methylene chloride (4 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on neutral alumina (Brockman activity III, 1:2 to 2:1 ethyl acetate-hexanes) to provide 24.8 mg (64%) of **143** as an oil: $[\alpha]^{23}_D$ = (+) 13.53° (C = 0.75, $CHCl_3$); IR (neat) 2955, 1732, 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 0.92 (d, 3H, J=6.8), 1.04 (bt, 2H, J=5.8), 1.39 (s, 3H), 1.42 (s, 3H), 1.70-2.10 (m, 5H), 2.20-2.45 (m, 2H), 2.65 (m, 1H), 3.32 (m, 2H), 3.90 (d, 1H, J=8.9), 3.93 (m, 1H), 4.20 (q, 2H, AB,

J=9.2), 4.25 (m, 3H), 4.32 (d, 1H, J=8.9), 5.27 (bt, 1H, J=2.9), 5.64 (bd, 1H, J=1.6); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.58, 13.53, 17.60, 18.34, 25.57, 25.89, 26.07, 26.81, 32.42, 34.58, 38.31, 53.60, 60.55, 62.78, 63.75, 69.75, 69.67, 73.83, 75.37, 87.00, 110.92, 123.22, 138.63, 172.43, 173.46; MS m/z 597 (M^+), 582, 540, 453, 120 (100%); HRMS calcd for $C_{26}H_{46}NSi_2O_7$: 540.2813. Found: 540.2814.

Desethylideneusaramine Acetonide (**149**)

To a stirring solution of **153** (1 mg) in acetonitrile was added tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 0.1mL). The reaction mixture was stirred for 2h at 50°C and quenched with saturated aqueous ammonium chloride at room temperature. The solvents were evaporated, the residue was dissolved in methylene chloride and poured into 15% sodium carbonate. The layers were separated and the aqueous layer was extracted with methylene chloride (4 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica (30:1 methylene chloride saturated with (ammonium chloride)- methanol) gave 0.5 mg (69%) of **149**: IR (neat) 2961, 1742, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, 3H, J=6.5), 1.45 (s, 3H), 1.46 (s, 3H), 2.45 (m, 2H), 4.04 (d, 1H, J=12.4), 4.11 (m, 3H), 4.59 (m, 1H), 5.02 (bs, 1H), 5.52 (d, 1H, J=12.4), 6.26 (bs, 1H); MS m/z 365 (M^+), 350, 321, 250, 120 (100%); HRMS calcd for $C_{19}H_{27}NO_6$: 365.1838. Found: 365.1838.

2-(Trimethylsilylethyl) Ester (**151**)

tert-Butyldimethylsilyl ether **143** (12 mg, 0.02 mmol) in tetrahydrofuran

(0.5 mL) was stirred with 5% hydrofluoric acid / tetrahydrofuran at room temperature for 9 h. The reaction mixture was diluted with methylene chloride and poured into 15% sodium carbonate (5 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (4 x 5 mL). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Purification of the crude product by flash column chromatography, on silica (20:1 methylene chloride (saturated with ammonium hydroxide) - methanol) yielded 5.4 mg (56%) of **151**: $[\alpha]^{24}_D$ = (+)33.93° (C = 0.28, $CHCl_3$); IR (neat) 3382 (broad), 2950, 1731, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J=7.0), 1.04 (bt, 2H, J=5.8), 1.39 (s, 3H), 1.43 (s, 3H), 1.78 (m, 1H), 1.94 (m, 1H), 2.09 (m, 2H), 2.24 (m, 1H), 2.36 (m, 1H), 2.71 (m, 2H), 3.38 (m, 2H), 3.90 (d, 1H, J=8.9), 3.99 (d, 1H, J=14.7), 4.17 (bs, 1H), 4.28 (bt, 2H, J=5.8), 4.32 (d, 1H, J=8.9), 4.36 (bs, 2H), 5.32 (bs, 1H), 5.68 (bd, 1H, J=1.3); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.57, 13.46, 17.60, 25.48, 26.05, 26.90, 32.49, 34.47, 37.94, 53.29, 59.94, 62.86, 63.95, 69.42, 74.26, 75.89, 86.94, 110.96, 123.37, 138.95, 172.82, 173.55; MS m/z 483 (M^+), 468, 465, 338, 138 (100%); HRMS calcd for $C_{24}H_{41}SiNO_7$: 483.2652. Found: 483.2658.

2-(Trimethylsilylethyl) Ester (**153**)

To a stirring solution of **151** (4.2 mg, 0.009 mmol) in methylene chloride (0.5 mL) at 0°C were added methanesulfonyl chloride (1.3 μL, 0.016 mmol) and triethylamine (3.0 μL, 0.02 mmol) sequentially and the mixture was stirred for 1h. This methylene chloride solution of presumed mesylate **152** was used in the next reaction.

To a separate flask was added tetrabutylammonium fluoride (0.13 mL, 1

M solution in tetrahydrofuran) and solvent was evaporated in vacuo. The residue was dried in high vacuum pump for 1.5 h and dissolved in acetonitrile. To this solution at 30°C was added methylene chloride solution of **152** very slowly with a micro syringe over a period of 2-3h . The stirring was continued for another 1.5h and the reaction was quenched with saturated aqueous ammonium chloride. The solvents were evaporated and the residue was dissolved in methylene chloride (5 mL) and poured into 15% sodium carbonate. The layers were separated and the aqueous layer was extracted with methylene chloride (4 x 5 mL). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica (35:1 methylene chloride (saturated with ammonium hydroxide) - methanol). The only product 1 mg (45%) isolated was characterized as the chloride **153**. IR (neat) 2955, 1738, 1172, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J=6.9), 1.02 (m, 2H), 1.39 (s, 3H), 1.42 (s, 3H), 2.85 (m, 1H), 3.56 (m, 2H), 3.90 (d, 1H, J=9.2), 4.10 (q, 2H, AB, J=13.4), 4.26 (m, 3H), 4.31 (d, 1H, J=9.2), 5.49 (bs, 1H), 5.88 (bs, 1H); MS m/z 501 (M^+), 466, 358, 356, 174, 172, 158, 156 (100%); HRMS calcd for $C_8H_{11}NOCl$: 172.0529. Found: 172.0531.

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