2-(*N,N*-Dimethylamino)phenyl potassium sulfate (11) was synthesized by persulfate oxidation of *N,N*-dimethylaniline according to Boyland et al.[14] Tan needles from 95% ethanol, mp 226–228 °C dec. IR (Nujol): 1605, 1500, 1275, 1255, 1050, 945, 870, 745 cm^{-1}. UV (water): λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 240, 5725; 278.5 (sh), 1390. ^1H NMR (D_2O): δ H-3 and -4 7.1 (m), H-5 7.03 (ddd, $J_{4,5}$ 5.9, $J_{5,6}$ 7.5, $J_{3,5}$ 3.2), H-6 7.44 (dd, $J_{5,6}$ 8.2, $J_{4,6}$ 1.1), $-NMe_2$ 2.66.

4-(*N,N*-Dimethylamino)phenyl Sodium Sulfate Monohydrate (12). (*N,N*-dimethylamino)-4-anisidine (Dixon Fine Chemicals) was converted to 4-(*N,N*-dimethylamino)phenol by the procedure of Slotta and Behnisch.[18] The phenol was converted to the sulfate by the general procedure of Feigenbaum and Neuberg,[17] but isolated as the sodium salt according to Eyer and Gaber.[19] Colorless plates from acetone-ether, mp 210–215 °C dec. IR (Nujol): 3640, 3410, 1645, 1525, 1475, 1390, 1270, 1250, 1075, 1065, 955, 875, 830, 775 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 246, 10, 160; 290 (sh), 1470. ^1H-NMR (D_2O): δ H-2 and -6 7.14 (dd, J_{ortho} 6.8, J_{meta} 2.3), H-3 and -5 6.92 (dd, J_{ortho} 6.8, J_{meta} 2.3), $-NMe_2$ 2.75. Anal. Calcd for $C_8H_{10}NO_4SNa \cdot H_2O$: C, 37.3; H, 4.70. Found: C, 37.4; H, 4.54.

***N,N*-Dimethylaniline *N*-oxide** was prepared by treatment of *N,N*-dimethylaniline with 30% H_2O_2 according to Oae et al.[13] After 5 days at rt, the clear solution was evaporated to about one-third of its initial volume on a rotary evaporator at 55 °C. The solution was then extracted three times with ether to remove excess dimethylaniline. Excess H_2O_2 was decomposed by treatment with 3A molecular sieves (caution: exothermic) according to Edward and Whiting.[7] The product was extracted with $CHCl_3$ (not benzene). Evaporation of the solvent gave an oil which crystallized. The crystals were slurried with CCl_4, filtered rapidly, and dried over P_2O_5 to give slightly yellow, very hygroscopic crystals of *N,N*-dimethylaniline *N*-oxide, mp 144–145 °C, raised to 152–3 °C by recrystallization from benzene (lit.[20] mp 154 °C). IR: (neat, slightly wet): 1580, 1475, 1440 (s), 1380, 1310, 1240, 1190, 1170, 1110, 1050, 1010, 950 (s), 930, 860, 740 (s), 690 (s). ^1H NMR (DMSO-d_6, TMS): δ H-2 and -6 8.095 (ddd, $J_{2,3}$ 8, $J_{2,4}$, $J_{2,6}$ 1.5), H-3 and -5 7.461 (ddd, $J_{2,3}$ 8, $J_{3,4}$ 5.5, $J_{3,5}$ 2), H-4 7.388 (tt, J_{ortho} 5.5, J_{meta} 1.5), $-NMe_2$ 3.397 (s).

A 1:1 H_2O_2 adduct of *N,N*-dimethylaniline *N*-oxide was isolated from a reaction mixture in which the excess H_2O_2 had not been destroyed. The proton NMR of this adduct in D_2O was identical to that of authentic *N,N*-dimethylaniline *N*-oxide. The IR spectra taken as a mull in Nujol or in KBr were similar to those of the parent compound but the N–O stretch was less intense and was shifted to 975 cm^{-1}. There was also a new broad multiplet centered at 850 cm^{-1} attributable to the O–O stretch. H_2O_2 was measured quantitatively by reaction with Ti(IV).[21] A useful characteristic of this compound is that, in contrast to its parent, it is not hygroscopic. Colorless plates and needles from $CHCl_3$, mp 112–113 °C. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.65; N, 8.18. Found: C, 55.8; H, 7.48; N, 8.16.

Reaction between *N,N*-Dimethylaniline *N*-Oxide and Sulfur Trioxide.[22] *N,N*-Dimethylaniline *N*-oxide (1.37 g, 0.01 mol) was partially dissolved in 20 mL of dry pyridine (CaH_2) at rt. Sulfur trioxide–pyridine complex (Aldrich, 1.9 g, 0.012 mol) was added. A homogeneous brown solution formed rapidly with some warming. After 15 min, 75 mL of hexane was added to precipitate the products and to extract the pyridine. The hexane-soluble fraction was decanted and the oily residue washed with 5 × 50 mL of hexane. Residual pyridine was removed with an oil pump. The IR spectrum of the crude products lacked the bands reported by Edward and Whiting[7] for *N,N*-dimethylanilino sulfate at 1340 and 615 cm^{-1}. Water (10 mL) was added to the products at rt whereupon a granular solid formed. The pH of the mixture was about 5. The solid was filtered and washed with cold water, 95% ethanol, and ether to yield 0.8 g of crude product. The mother liquors, after the addition of a little HCl and cooling gave a second crop (0.12 g) for a total yield of 0.92 g (42%) of 2-(*N,N*-dimethylamino)phenyl hydrogen sulfate. Recrystallization from water with a little Norite gave nearly colorless needles, mp 212–214 °C dec (lit.[14] mp 217–219 °C). IR (KBr): 1605, 1490, 1475, 1460, 1400, 1370, 1280 (s), 1240 (s), 1235 (s), 1185, 1040 (s), 845, 775, 685. ^1H NMR (DMSO-d_6, internal TMS): δ H_6 7.749 (dd, $J_{5,6}$ 8, $J_{4,6}$ 1.1), H_3 7.634 (dd, $J_{3,4}$ 8, $J_{3,5}$ 1.5), H_4 7.462 (ddd, $J_{3,4}$ 8, $J_{4,5}$ 8, $J_{4,6}$ 1.4), H_5 7.298 (ddd, $J_{4,5}$ 8, $J_{5,6}$ 8, $J_{3,5}$ 1.3), $-NMe_2$ 3.187 (s). UV (water, pH 7) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 240, 5860; 278 (sh), 1250. The sodium salt of this material gave IR and NMR spectra identical to those of the potassium salt 11 (see above).

Acknowledgment. I thank K. Ault, A. S. Batra, C. Cummings, R. Gupta, D. Myszka, and H. Truong for help with experimental work and Profs. G. Means and W. Becktel for helpful discussions. The FT-NMR spectra were taken at The Ohio State University Chemical Instrument Center by Dr. C. E. Cottrell using equipment funded in part by NIH Grant No. 1 S10 RR01458-01A1.

Supplementary Material Available: ^1H NMR spectra of reaction mixtures (3 pages). Ordering information is given on any current masthead page.

(18) Slotta, K. H.; Behnisch, R. *J. Prakt. Chem.* **1932**, *135*, 225.
(19) Eyer, P.; Gaber, H. *Biochem. Pharmacol.* **1978**, *27*, 2215.
(20) Linton, E. P. *J. Am. Chem. Soc.* **1940**, *62*, 1945.
(21) Eisenberg, G. M. *Ind. Eng. Chem. Anal. Ed.* **1943**, *15*, 327. The reagent may be more easily prepared from $TiCl_4$ and H_2SO_4.
(22) A preliminary account of some of this work has appeared: Behrman, E. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 305.

Stereoselective Synthesis of the Pyrrolizidine Alkaloids (-)-Integerrimine and (+)-Usaramine

James D. White,* John C. Amedio, Jr., Samuel Gut, Susumu Ohira, and Lalith R. Jayasinghe

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

Received December 11, 1991

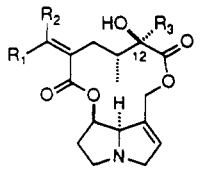
Two routes to the pyrrolizidine alkaloid (-)-integerrimine (1) are described. The first, starting from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate, proceeded in 19 steps to integerrinecic acid lactone (5) which was transformed to the necic acid derivative 30. The latter was coupled to protected retronecine 31, and the synthesis of 1 was completed by lactonization employing Vedejs' protocol. A second, shorter synthesis of (-)-1 was accomplished via 5, starting from (*R*)-(+)-β-citronellol (36). This pathway invoked Katsuki–Sharpless epoxidation of 42 for stereoselective construction of the tertiary alcohol of integerrinecic acid. A parallel sequence proceeding via the stereoisomeric epoxide 44 led to the necic acid segment 75 of the alkaloid (+)-usaramine (2). This acid was coupled to the retronecine borane 82 and then lactonized to 2.

Alkaloids of the pyrrolizine family are widespread in nature, occurring in over 150 plant species and nearly 70 genera.[1] Extensive pharmacological investigation of the pyrrolizidine alkaloids[2] has shown that many are acute

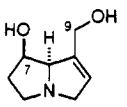
0022-3263/92/1957-2270$03.00/0

hepatotoxins[3] while others exhibit carcinogenic properties.[1] The high level of hepatotoxicity associated with alkaloids of this group presents a potentially serious human health problem since ingestion of the alkaloids from dietary sources has proved fatal.[4]

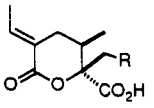
Pyrrolizidine alkaloids are frequently isolated as macrocyclic dilactones in which a pyrrolizine diol (necine base) is esterified with a dicarboxylic acid (necic acid) to produce 11-, 12-, 13-, or 14-membered rings.[5] Integerrimine (1), the diol usaramine (2), and its geometrical isomer retorsine (3) are 12-membered dilactones in which a necic acid spans the C-7 and C-9 hydroxyl fundtions of (+)-retronecine (4). The novel structural features of these necic acids and the physiological properties of the parent alkaloids have prompted several syntheses of 1,[6] 2[7] and related systems.[8] However, although previous investigations of the chemistry of macrolactone pyrrolizine alkaloids have laid valuable groundwork for assembling these structures from their constituent necic acids and necine bases, no unifying synthetic strategy has emerged.



1, R_1 = H, R_2 = R_3 = Me
2, R_1 = H, R_2 = Me, R_3 = CH_2OH
3, R_1 = Me, R_2 = H, R_3 = CH_2OH



4



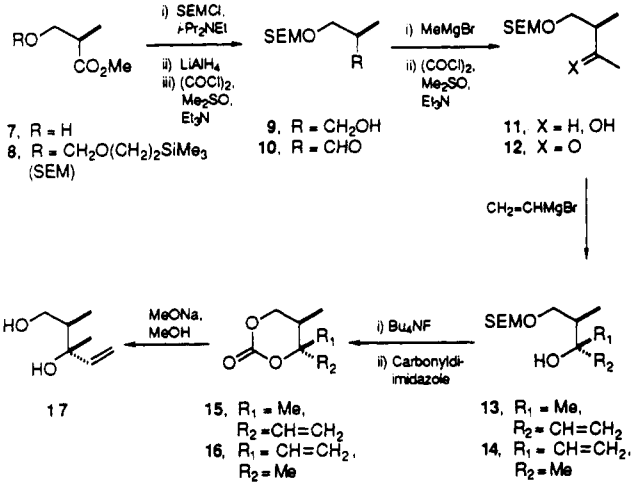
5, R = H
6, R = OH

Several years ago we initiated a program aimed at completing a total synthesis of 1 while developing a broad approach to other structurally related pyrrolizidine alkaloids. Herein, we describe a full account of two indepennet stereoselective syntheses of (-)-integerrimine and the application of our general strategy to the synthesis of (+)-usaramine.

Results

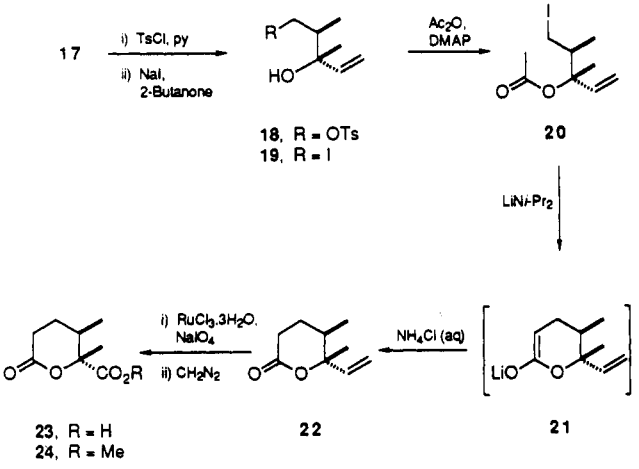
An examination of the necic acid segment of structures 1–3 reveals that the nature and arrangement of functional group show only minor variations, implying that it should be possible to synthesize these compounds from a common precursor. More explicitly, the carbon skeleton of the necic acid portions present in 1–3 suggested that lactones 5 and 6 could serve as synthetic precursors. We chose initially to develop an approach to the functionally less complex alkaloid (-)-integerrimine (1), and in our original plan, we

Scheme I



7, R = H
8, R = $CH_2O(CH_2)_2SiMe_3$ (SEM)
9, R = CH_2OH
10, R = CHO
11, X = H, OH
12, X = O
17
15, R_1 = Me, R_2 = $CH=CH_2$
16, R_1 = $CH=CH_2$, R_2 = Me
13, R_1 = Me, R_2 = $CH=CH_2$
14, R_1 = $CH=CH_2$, R_2 = Me

Scheme II



18, R = OTs
19, R = I
20
21
22
23, R = H
24, R = Me

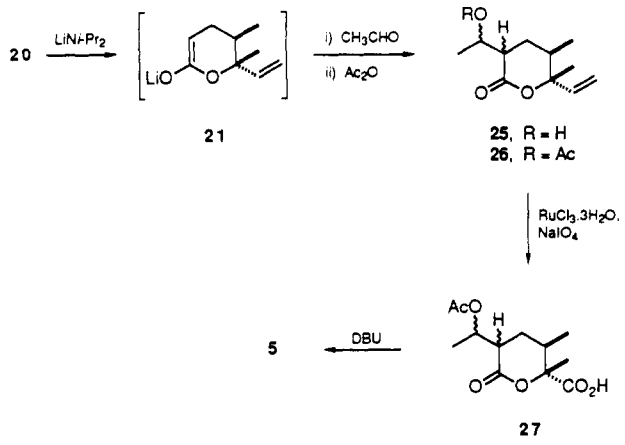
envisaged a route to 5 or a suitable ester derivative via a sequence in which the stereogenicity of the center bearing the secondary methyl group would confer stereocontrol on the formation of the adjacent quaternary center. Our synthetic strategy would thus be reduced to elaboration of a chiral synthon containing a secondary methyl group of the required configuration. Methyl 3-hydroxy-2-methylpropionate (7) appeared to be an ideal candidate for this purpose since it contains functionality easily amenable to further synthetic manipulation and each antipode is available in optically pure form.

Protection of methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (7) with [2-(trimethylsilyl)ethoxy]methyl (SEM) chloride[9] in the presence of diisopropylethylamine afforded the ether 8 (Scheme I). Reduction of 8 with lithium aluminum hydride gave alcohol 9 which, upon oxidation under Swern's conditions,[10] furnished the aldehyde 10. Transformation of the latter to the methyl ketone 12 was accomplished by treatment of 10 with methylmagnesium bromide, followed by Swern oxidation[10] of the resultant alcohol 11.

Our plan now required conversion of the carbonyl carbon of 12 into a quaternary center in a stereocontrolled manner, and an examination of molecular models indicated that a chelation-controlled Grignard reaction should result in attack at the *si* face of the ketone function.[11] In the event,

(1) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, U.K., 1986.
(2) McLean, E. K. *Pharm. Rev.* **1970**, *22*, 429.
(3) (a) Huxtable, R. J. *Gen. Pharmacol.* **1979**, *10*, 159. (b) Culvenor, C. C. J.; Edgar, J. A.; Jago, M. V.; Outteridge, A.; Peterson, J. E. *Chem.-Biol. Interactions* **1976**, *12*, 299.
(4) (a) Hirono, I. *Crit. Rev. Toxicol.* **1980**, *8*, 235. (b) Smith, L. W.; Culvenor, C. C. J. *J. Nat. Prod.* **1981**, *44*, 129. (c) Culvenor, C. C. J.; Edgar, J. A.; Frahn, J. L.; Smith, L. W. *Aust. J. Chem.* **1980**, *33*, 1105. (d) Culvenor, C. C. J.; Clarke, E.; Edgar, J. A.; Frahn, J. L.; Jago, M. V.; Peterson, J. E.; Smith, L. W. *Experientia* **1980**, *36*, 377.
(5) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *42*, 115.
(6) (a) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954. (b) White, J. D.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492. (c) White, J. D.; Jayasinghe, L. R. *Tetrahedron Lett.* **1988**, *29*, 2139. (d) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4601. (e) Niwa, H.; Miyachi, Y.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4609.
(7) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268.
(8) (a) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030. (b) Brown, K.; Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1819. (c) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861.
(9) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(10) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(11) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1035.

Scheme III



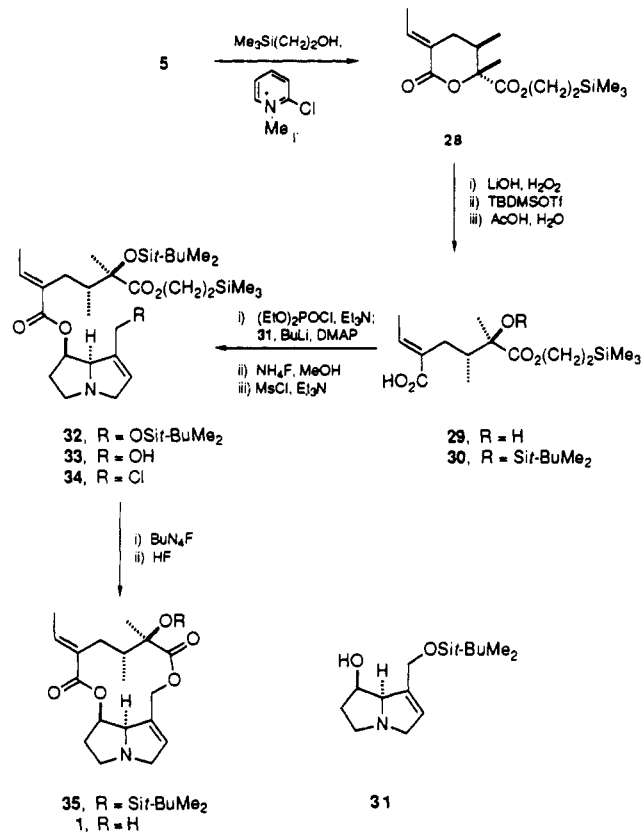
addition of vinylmagnesium bromide to **12** yielded a 4:1 mixture of the desired alcohol **13** and its diastereomer **14**, respectively. Since **13** and **14** proved difficult to separate they were taken to the cyclic carbonates **15** and **16** by exposure to tetra-*n*-butylammonium fluoride in hexamethylphosphoramide followed by treatment of the resultant diols with carbonyldiimidazole. The major carbonate **15** was separated from the minor component **16** (HPLC, μ-Porasil) and was hydrolyzed to afford the pure diol **17**.

Homologation of **17** by the two carbons required to transform it into lactone **22** was achieved via a novel intramolecular alkylation (Scheme II). Selective conversion of **17** to the primary tosylate **18** and then to iodide **19** was followed by acetylation to furnish iodo acetate **20**. This sequence conveniently established the functionality for cyclization to **22** and exposure of **20** to excess lithium diisopropylamide, followed by protonation of the resultant enolate **21**, afforded the δ-lactone **22** in 94% yield. The stereochemical assignment to this key intermediate was confirmed by oxidative cleavage[12] of the olefin and esterification of the resultant acid **23** with diazomethane to provide the known methyl ester **24**.[13] As expected, the IR and ^{1}H NMR spectra of the previously prepared racemic methyl ester **24** were identical with those of our optically active material.

With the structure of δ-lactone **24** firmly established, the introduction of an α-ethylidene function and manipulation of the vinyl group to a suitably derivatized ester moiety was next examined (Scheme III). It was anticipated that enolate **21**, acquired directly from **20**, would undergo aldol condensation with acetaldehyde to provide β-hydroxy lactone **25** and, in practice, this transformation was realized in an overall 87% yield. Acetylation of the mixture of diastereomeric β-hydroxy lactones **25**, followed by treatment of the resultant acetates **26** with sodium periodate in the presence of a catalytic amount of ruthenium(III) chloride trihydrate,[12] yielded a mixture of the corresponding acids **27**. The diastereomeric acetoxy acids **27** were smoothly converted into lactone **5** of *E* configuration upon exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry dichloromethane.[13] The synthesized material, (+)-integerrinecic acid lactone (**5**), exhibited spectral properties identical with those reported for (±)-**5** by Culvenor and Geissman.[14]

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(13) Narasaka, K.; Uchimaru, T. *Chem. Lett.* **1982**, *57*.
(14) Culvenor, C. C. J.; Geissman, T. A. *J. Am. Chem. Soc.* **1961**, *83*, 1647.

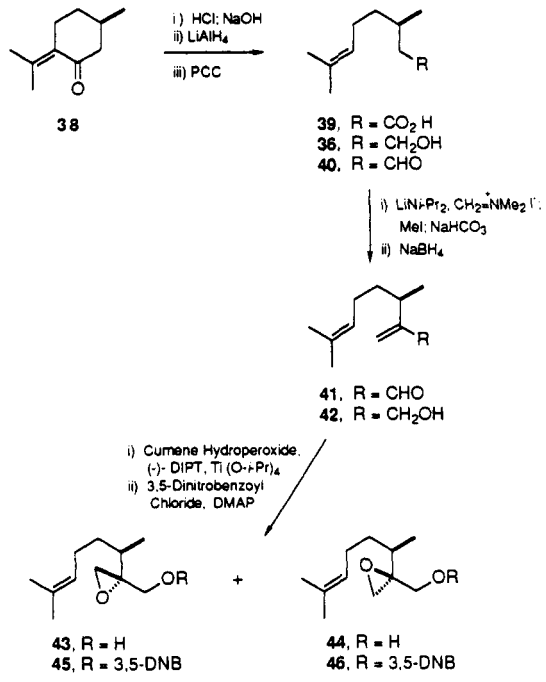
Scheme IV



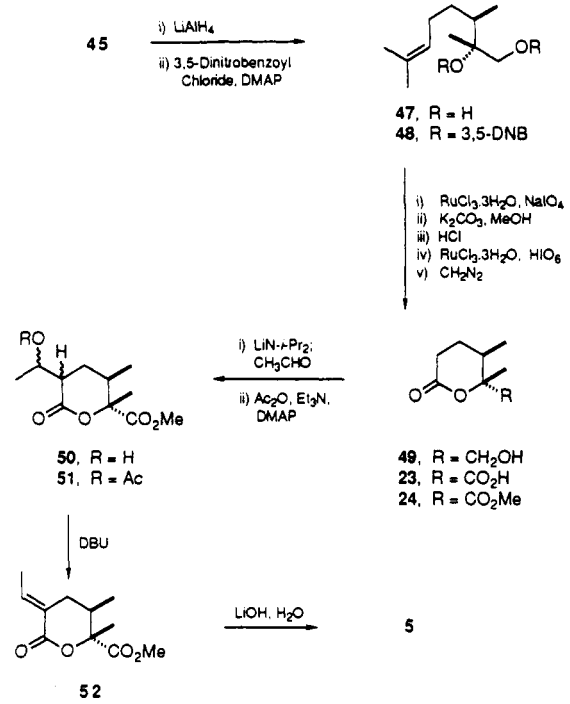
After several unproductive exploratory studies,[15] coupling of the necic acid and necine base segments of integerrimine was realized using the macrolactonization procedure of Vedejs.[16] Thus, **5** was converted to its (trimethylsilyl)ethyl ester **28** which was selectively hydrolyzed to the hydroxy acid **29** (Scheme IV). In order to prevent relactonization, **29** was treated with *tert*-butyldimethylsilyl triflate to yield, after hydrolysis of the intermediate *tert*-butyldimethylsilyl ester, the carboxylic acid **30**. Esterification of the 9-*tert*-butyldimethylsilyl ether (**31**) of retronecine, obtained from (+)-retronecine[17] as described previously,[13] with the acyl phosphate from **30** required forcing conditions due to the hindered environment of the C-7 alcohol function but provided **32** in moderate yield. Exposure of **32** to ammonium fluoride selectively removed the primary silyl ether function to give the alcohol **33**, which underwent reaction with methanesulfonyl chloride and then tetrabutylammonium fluoride to afford the marocyclic diester **35** in good overall yield (75%). Closer inspection of this sequence revealed that the intermediate which lactonized was not a mesylate as previously thought[16] but rather the allylic chloride **34**. The facility with which macrolactonization of **33** proceeds is notable in light of the difficulties usually associated with synthesis of 12-membered lactones.[18] Cleavage of the *tert*-butyldimethylsilyl ether function of **35**, followed by

(15) Direct coupling of **5** with the C-9 hydroxyl of retronecine (**4**) followed by translactonization did not lead to the formation of integerrimine (see ref 6b).
(16) (a) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030. (b) Vedejs, E.; Ahmad, S.; Larsen, S. D.; Westwood, S. *J. Org. Chem.* **1987**, *52*, 3938.
(17) (+)-Retronecine was obtained by basic hydrolysis of commercially available monocrotaline (see Crout, D. H. G.; Davies, N. M.; Smith, E. H.; Whitehouse, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 671).
(18) Boeckman, R. K.; Goldstein, M. *The Total Synthesis of Natural Products*; Wiley-Interscience; New York, 1988; pp 1-140.

Scheme V



Scheme VI



purification of the crude product, resulted in synthetic (-)-integerrimine (1) with spectral properties and optical rotation identical to those of an authentic sample.

Our interest in pyrrolizidine alkaloids containing more highly functionalized lactones than 1 prompted a search for a general route to the necic acids that could be modified to accommodate additional functional groups such as that present in usaramine (2). Our goal therefore became a stereoselective pathway that would lead to both lactones 5 and 6 from a common intermediate. Comparison of 5 and 6 suggested that the methyl and hydroxymethyl substituents of these δ-lactones could be installed by either hydride or alkoxide addition to a terminal epoxide, respectively. This strategy necessitated a change in our original synthetic plan departing from 7, whilst retaining the requirement for a progenitor from the chiral pool that would provide the 3(*R*)-methyl substituent of the necic acids. (*R*)-(+)-β-citronellol (36) seemed ideally suited for this purpose, and all of our subsequent approaches to necic acids have employed this monoterpene as the starting material.

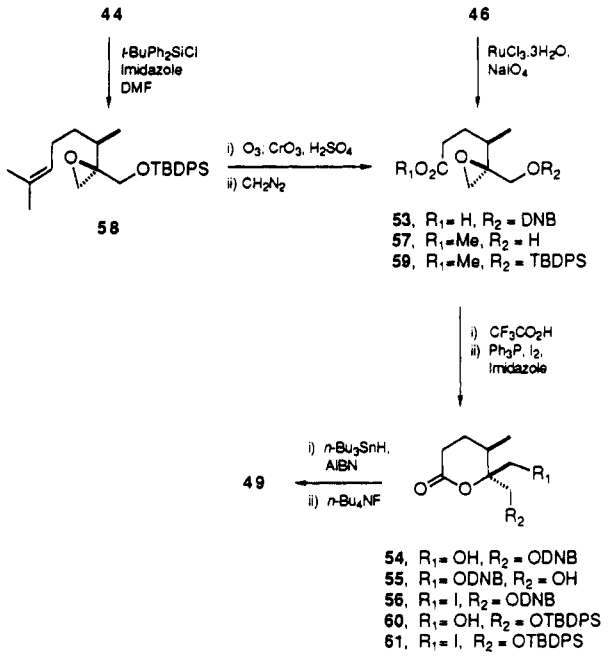
Initially 36 was prepared by hydroboration–oxidation of (*R*)-(-)-β-citronellene (37). However, variability in the optical purity of commercially available 37 led to subsequent stereochemical difficulties and we therefore chose to obtain 36 by a known route from (*R*)-(+)-pulegone (38).[19] Thus, exposure of 38 to anhydrous hydrogen chloride, followed by hydrolysis with base and reduction of the resultant acid 39, furnished optically pure (*R*)-(+)-β-citronellol (36, Scheme V). The latter was oxidized with pyridinium chlorochromate[20] to yield citronellal (40). Alkylation of the lithium enolate derived from 40 with Eschenmoser's salt, followed by methylation of the resulting amine and subsequent treatment with aqueous sodium bicarbonate, gave 41 in 78% overall yield.[21] Selective carbonyl reduction of the unsaturated aldehyde 41 occurred smoothly with sodium borohydride in the presence of cerium chloride[22] and provided the allylic alcohol 42.

It was expected[23] that Katsuki–Sharpless catalytic asymmetric epoxidation of 42 employing titanium(IV) isopropoxide and diisopropyl (-)-tartrate[24] would afford mainly the epoxy alcohol 43, but in fact, a 3:1 mixture of 43 and its diastereomeric epoxide 44 was obtained. The asymmetric center in 42 apparently exerts a steric bias on the epoxidation which results in a substrate–catalyst mismatch and consequent poor stereoselectivity. Support for this postulate was obtained by epoxidation of 42 with the enantiomeric (matched) (+)-tartrate, which yielded diastereoisomers 43 and 44 in a ratio of 4:96, respectively. Unequivocal evidence for the stereochemical assignment of 43 was obtained by conversion of the mixture of epoxy alcohols to their separable, crystalline 3,5-dinitrobenzoates 45 and 46 and subsequent correlation of 45 with 49 whose configuration was established independently (vide infra).

With optically pure dinitrobenzoate 45 in hand we turned our attention to conversion of this substance into lactone 5. Reduction of 45 with lithium aluminum hydride afforded the diol 47, which now possessed the two stereogenic centers present in 5 (Scheme VI). Protection of the diol function of 47 was required prior to oxidative cleavage of the olefin, and to this end, 47 was treated with excess 3,5-dinitrobenzoyl chloride to give the bis-3,5-dinitrobenzoate derivative 48. Oxidative scission of the isopropylidene group of 48 was accomplished with catalytic ruthenium trichloride and sodium metaperiodate.[12] Subsequent methanolysis of the 3,5-dinitrobenzoate esters, followed by acid-catalyzed lactonization, provided 49 in 55% overall yield. The crystalline nature of 49 enabled an X-ray analysis to be carried out which confirmed the structural assignments shown. Oxidation of 49 with a catalytic amount of ruthenium(III) chloride and periodic acid,[25] followed by esterification of the resulting crude

(19) Overberger, C. G.; Weise, J. K. *J. Am. Chem. Soc.* **1968**, *90*, 3525.
(20) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.
(21) Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, *19*, 1621.
(22) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(23) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1985; Vol. 5, Chapter 8.
(24) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(25) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

Scheme VII



carboxylic acid **23**, gave the methyl ester **24**, identical in all respects to the substance prepared previously (see Scheme II).

In a sequence parallel to that carried out in the racemic series by Narasaka,[6a] the lithium enolate derived from **24** was condensed with acetaldehyde, and the resultant aldol product **50** was acetylated to give **51**. The latter underwent elimination with DBU affording *E*-lactone **52** in 50% overall yield from **24**. Hydrolysis of **52** with lithium hydroxide furnished (+)-**5** and a small amount of the corresponding *Z*-isomer. Since synthesis of (−)-integerrimine from (+)-**5** has been previously accomplished (see Scheme IV), this route constitutes a second, enantioselective pathway to the alkaloid.

The synthetic route from (*R*)-(+)-β-citronellol to integerrinecic acid lactone (**5**) described above is unfortunately marred by poor diastereoselectivity in the Katsuki–Sharpless epoxidation as compared to that observed in related systems.[24] Recognizing that the stereochemical efficiency of our plan would be enhanced if epoxide **44**, resulting from a *matched* substrate–catalyst reaction, were employed, we devised a modification of the pathway whereby **49** could be accessed from this isomer (Scheme VII). Transformation of **44** to **49** effectively requires inversion of the quaternary center, a process which, in principle, could be accomplished by epoxide opening with attack by an internal carboxyl function. Experimentally, acidification of epoxy acid **53**, obtained by oxidative cleavage of **46**, led to the formation of two diastereomeric lactones **54** and **55** in a 4:1 ratio. The major lactone **54** was converted to iodide **56** which was treated with tributyltin hydride. This procedure led to the consumption of **55** without formation of a new methyl substituent, presumably due to interception of the intermediate alkyl radical by the dinitrobenzoyl function (vide infra). An attempt to remove the 3,5-dinitrobenzoate by treatment of **56** with sodium methoxide furnished the epoxy ester **57**, a result that can be rationalized via opening of the lactone, subsequent displacement of iodide by the derived alkoxide, and finally methanolysis of the dinitrobenzoate ester.

The unanticipated formation of **57** indicated that a protecting group different from the 3,5-dinitrobenzoate was required for conversion of **44** to **49**. The *tert*-butyldiphenylsilyl (TBDPS) ether **58** appeared to be suitably robust, and in a further improvement, oxidative cleavage of the olefin was carried out with ozone followed by workup using Jones' reagent.[26] The resultant acid was esterified to give **59** in 45% overall yield from **58**. Upon treatment of **59** with trifluoroacetic acid a single hydroxy lactone **60** was produced in which epoxide opening with assistance by the ester function and consequent inversion had taken place. The primary alcohol **60** was converted to its iodide **61** and, in contrast to **56**, underwent uneventful reduction upon treatment with tri-*n*-butyltin hydride. Removal of the *tert*-butyldiphenylsilyl ether then yielded **49**, identical in all respects to the substance prepared by the route shown in Scheme VI. Collectively, these results represent efficient and convergent approaches to integerrinecic acid lactone (**5**), and hence to (−)-integerrimine (**1**), in high stereochemical purity from (*R*)-(+)-citronellol (**36**). The flexibility of this approach also provides an entry to other necic acids, as demonstrated in the synthesis of (+)-usaramine (**2**) which follows.

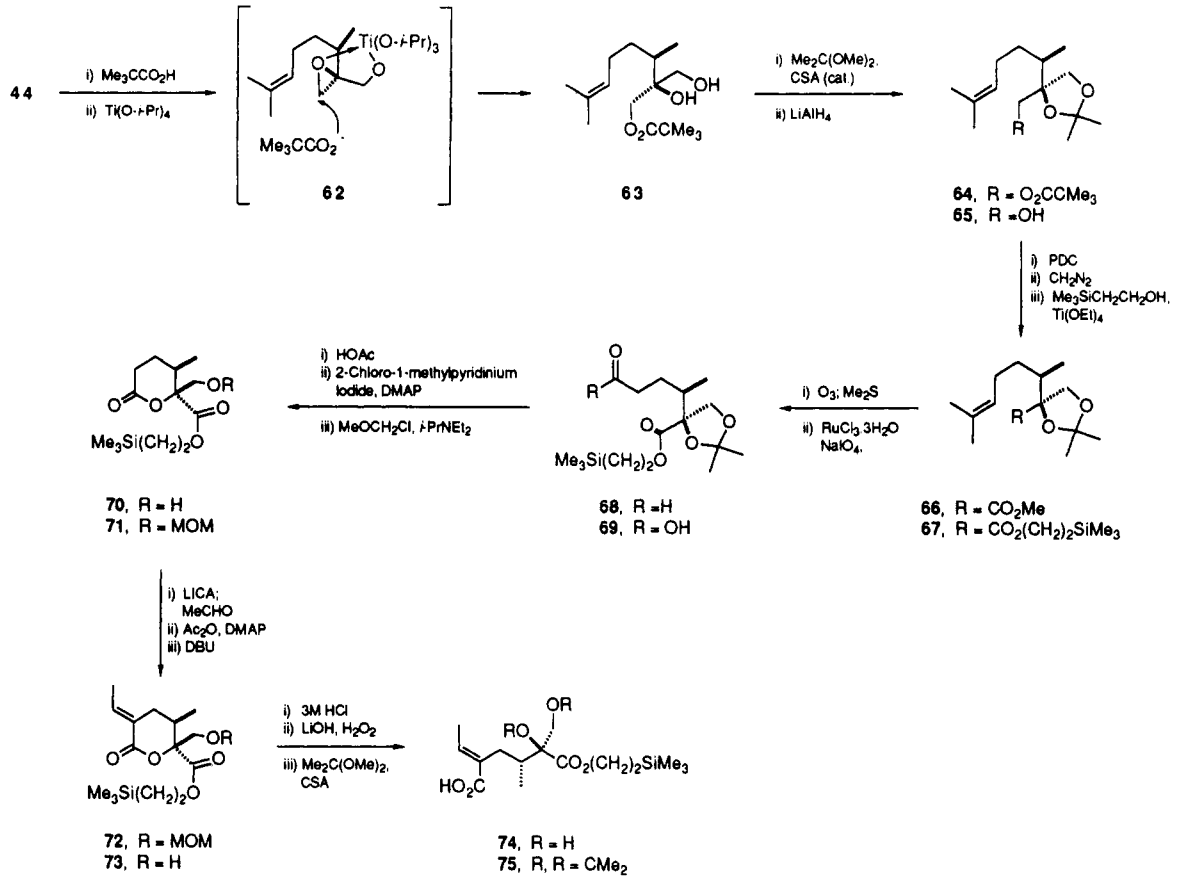
The structure of (+)-usaramine (**2**), elucidated by Culvenor et al.[4c] differs from that of (−)-integerrimine (**1**) only in the presence of a hydroxymethyl substituent in place of the methyl group at C-12. In planning an approach to the necic acid portion of **2** our objective was to employ the same epoxide(s) that had been used for the synthesis of **2**. In this case, however, hydrolytic rather than reductive opening of the epoxide function was required.

Epoxide **44**, prepared in high diastereoselective excess via the epoxidation procedure described previously (see Scheme V), was subjected to titanium isopropoxide-mediated ring opening[27] in the presence of pivalic acid (Scheme VIII). Nucleophile attack occurred via **62** at the more accessible methylene carbon to afford pivalate **63**. Careful manipulation of functionality was required at this stage since loss of the pivalate from **63** would erase a stereogenic center, and the diol function was therefore protected as the acetonide **64**. Reduction of the latter to **65**, followed by oxidation with PDC, led to an unstable carboxylic acid which was isolated as its methyl ester **66**. Transesterification of **66** to SEM ester **67**, required for eventual coupling to retronecine and macrolactonization, was achieved in 93% yield using titanium(IV) ethoxide in a modification of the method developed by Seebach.[28] By contrast, use of titanium(IV) isopropoxide as originally described[28] gave the desired ester **67** in only 55% yield, with 30% recovery of **66**.

Cleavage of the isopropylidene group of **67** occurred cleanly upon ozonolysis to yield **68** and oxidation of this material afforded the truncated carboxylic acid **69**. However, attempts at condensation of the methyl ester of **69** with acetaldehyde was thwarted by a facile Dieckmann condensation. This problem was circumvented by converting **69** to δ-lactone **70** prior to introduction of the ethylidene group, a transformation that was accomplished by hydrolysis of the acetonide and lactonization of the resulting dihydroxy acid with Mukaiyama's reagent.[29] After protection of **70** as its MOM ether, condensation of the enolate derived from **71** with acetaldehyde, followed by acetylation and elimination of the resulting β-acetoxy lactone, gave the *E*-olefin **72** with only a trace of the *Z*-isomer present. Hydrolysis of **72** to the open-chain di-

(26) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.
(27) Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1557.
(28) (a) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138. (b) Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.* **1987**, *65*, 230.
(29) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

Scheme VIII

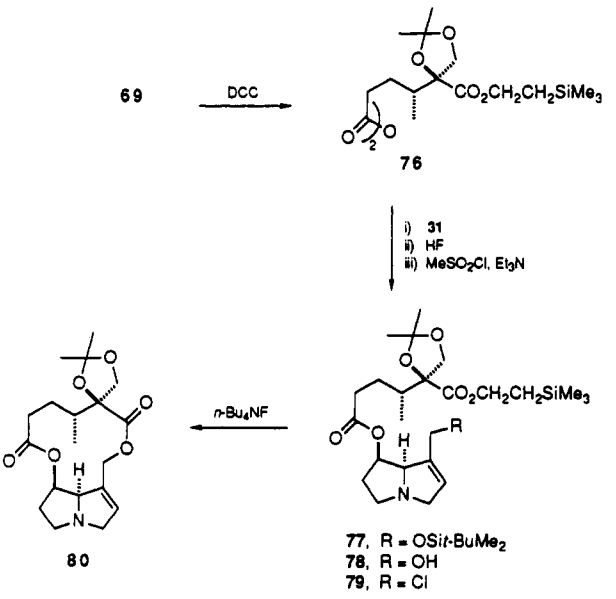


hydroxy carboxylic acid **74** was carried out, first with mineral acid and then with basic peroxide, and the diol moiety was protected as its acetonide **75** in prepartion for its coupling with **31**.

Before attempting the final steps en route to **2**, a coupling–lactonization sequence employing **69** was investigated to determine whether the (*E*)-ethylidene group and perhaps other substituents could be introduced after closure of the macrodiolide. Activation of **69** with dicyclohexylcarbodimide (DCC) and addition of **31** afforded ester **77** in good yield (Scheme IX). Inspection of this reaction revealed that the effective acylation species was the necic anhydride **76**, which could be isolated in crude form but could not be purified. The *tert*-butyldimethylsilyl ether was removed selectively from **77** with hydrofluoric acid, and the resulting alcohol **78** was reacted with methanesulfonyl chloride in triethylamine to yield chloride **79**. Upon treatment with tetra-*n*-butylammonium fluoride this substance underwent cleavage of the trimethylsilylether ester, and displacement of the allylic chloride by carboxylate then furnished latone **80**. However, all attempts to react **80** with acetaldehyde were fruitless, Dieckmann cyclization again prevailing over aldol condensation.

The disappointing outcome with **80** prompted our return to **75** but, to our surprise, esterification of this acid with **31** afforded, in addition to the desired Δ^3-pyrroline ester, a considerable amount of the pyrrole **81** (Scheme X). Details of the pathway to **81** remain obscure[30] but it was surmised that an *N*-acylpyrrolizidine was a plausible in-

Scheme IX

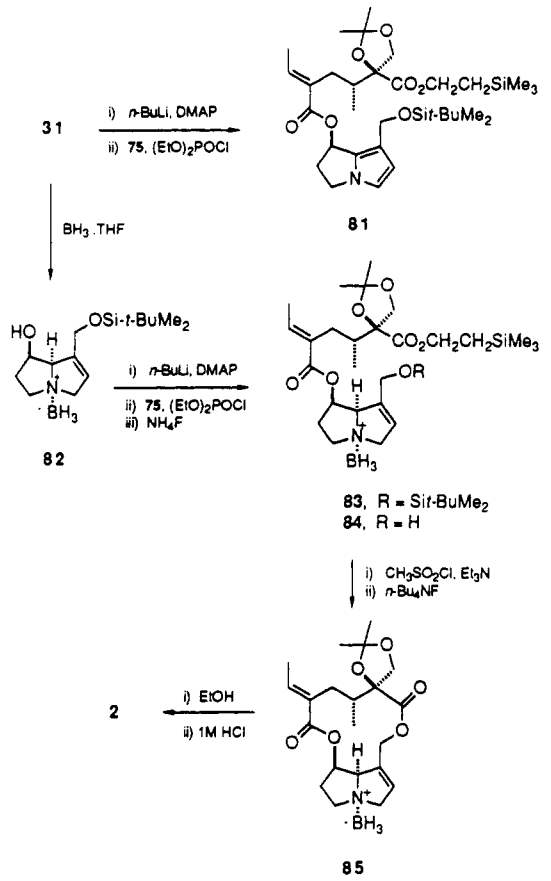


termediate in the aromatization. This conjecture led to the suggestion that the pyrrolizidine borane **82**, obtained by treatment of **31** with borane–THF, would suppress formation of **81**, a hypothesis that proved to be accurate.[31] Coupling of the lithium alkoxide, prepared from **82** with *n*-butyllithium, and the acylphosphate derived from treatment of **75** with diethyl chlorophosphate resulted in efficient synthesis of the ester **83**. Thus, protection of the

(30) Formation of **77** was observed even under stringently anaerobic conditions, suggesting disproportionation as the source of the pyrrolic structure. Acylation of **31** with **72** was markedly slower than with other necic acid derivatives, thus providing opportunity for this adventitious process.

(31) Cf. Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612.

Scheme X



pyrrolizidine nitrogen as a borane appears to be a useful device for preventing reaction at this center, particularly since N-boration proceeds without interference with the $\Delta^{2,3}$-bond and subsequent removal of borane can be effected under mild conditions (vide infra).

Macrolactonization of pyrrolizidine–borane **83** proceeded without incident. Thus, selective cleavage of the silyl ether function of **83**, followed by sequential treatment of the resultant alcohol **86** with methanesulfonyl chloride and tetra-*n*-butylammonium fluoride, afforded the dilactone **85** in 75% overall yield. Removal of borane from **85** occurred quantitatively in ethanol at reflux and final acidic hydrolysis of the acetonide moiety afforded (+)-usaramine (**2**), identical with the natural material by comparison of TLC behavior, optical rotation, and IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Since natural usaramine has been isomerized photochemically to retrorsine (**3**),[32] this route also represents a formal synthesis of the latter alkaloid.

In summary, the stereocontrolled synthesis of (−)-integerrimine (**1**) and (+)-usaramine (**2**) from (*R*)-β-citronellol demonstrates that the latter is a valuable entry point to the necic acids, and we foresee access to more highly functionalized pyrrolizidine alkaloids, e.g. swazine and doronenine, based on this strategem. Furthermore, the use of borane for blocking reactivity at the pyrrolizidine nitrogen is a tactic that should find other applications in this area of alkaloid chemistry.

Experimental Section

General. Melting points were measured on a Büchi 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-dm 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. Chemical shifts are reported downfield from internal tetramethylsilane on the δ scale. ^{1}H NMR coupling constants (*J*) are given in hertz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad). Mass spectra (MS) and exact mass determinations were obtained with either a Varian MAT CH-7, a Finnigan 4500, or a Kratos MS-50 spectrometer. Elemental analyses were performed by Desert Analytics (formerly MicAnal), Tucson, AZ.

Tetrhydrofuran (THF), diethyl ether (Et_2O), and benzene (C_6H_6) were distilled from sodium benzophenone ketyl under argon. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF), pyridine, diisopropylamine (i-Pr_2NH), and triethylamine (Et_3N) were distilled from calcium hydride under argon. Methanol (MeOH) was distilled from magnesium turnings.

Analytical thin-layer chromatography (TLC) was done on 2.5- × 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).

Methyl (2*R*)-3-[[2-(Trimethylsilyl)ethoxy]methoxy]-2-methylpropionate (8). To a cold (0 °C) CH_2Cl_2 solution (35 mL) of methyl 3-hydroxy-2-methylpropionate (**7**) (4.00 g, 33.9 mmol) were added diisopropylethylamine (7.20 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (4.50 mL, 35.2 mmol). After stirring for 15 h at room temperature, 1 M HCl and crushed ice were added to the mixture. The aqueous phase was extracted with CH_2Cl_2 and the organic phase was dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was purified by flash column chromatography on silica (1:5 Et_2O–hexane) to give 6.70 g (80%) of **8** as an oil: $[\alpha]^{20}_D$ −8.7° (*c* = 1.77, $CHCl_3$); IR (neat) 1745, 1055 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.07–1.08 (m, 2 H), 1.18 (d, 3 H, *J* = 7.0 Hz), 2.52–3.00 (m, 1 H), 3.42–3.88 (m, 4 H), 3.69 (s, 3 H), 4.63 (s, 2 H). Anal. Calcd for $C_{11}H_{24}O_4Si$: C, 53.19; H, 9.74. Found: C, 53.18; H, 10.04.

(3*S*)-4-[[2-(Trimethylsilyl)ethoxy]methoxy]-3-methyl-2-butanone (12). To a cold (0 °C) suspension of $LiAlH_4$ (905 mg, 23.82 mmol) in Et_2O (130 mL) was added **8** (5.916 g, 23.82 mmol). After 2 h the solution was cooled to 0 °C, and 10% aqueous NaOH was added until a white precipitate was formed. The aqueous phase was extracted with Et_2O, the organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was dried by azeotropic distillation with C_6H_6 and used without purification. A small sample of **9** was purified for characterization: $[\alpha]^{20}_D$ −8.7° (*c* = 1.25, $CHCl_3$); IR (neat) 3450, 1040 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.07–1.04 (m, 2 H), 0.90 (d, 3 H, *J* = 6.5 Hz), 1.72–2.28 (m, 1 H), 2.08 (s, 1 H), 3.37–3.75 (m, 4 H), 4.70 (s, 2 H).

To a cold (−78 °C) CH_2Cl_2 solution (60 mL) of $(COCl)_2$ (2.49 mL, 28.5 mmol) was added a CH_2Cl_2 solution (4 mL) of DMSO (4.06 mL, 57.2 mmol). A CH_2Cl_2 solution (30 mL) of **9** was added, and after 30 min, neat Et_3N (24.1 mL, 173 mmol) was added. The reaction was allowed to warm to room temperature over 30 min, the solution was cooled to 0 °C, and water and 1 M HCl (105 mL) were added. The aqueous phase was extracted with CH_2Cl_2, the organic phase was dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in Et_2O and filtered. The crude aldehyde **10** was dried by azeotropic distillation with C_6H_6 and used immediately in the next reaction.

An Et_2O solution of methylmagnesium bromide (12.6 mL, 35.9 mmol) was added to a cold (0 °C) THF solution (25 mL) of the crude aldehyde **10**. After 1 h aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), and the solvent was evaporated to give a crude mixture of stereoisomeric alcohols **11**.

Oxidation of **11** using the same scale and procedure as described for the conversion of **9** to **10** furnished crude **12**. Purification of the product by flash chromatography (1:7 EtOAc–hexane) gave 4.724 g (83%) of **12**: $[\alpha]^{19}_D$ −4.4° (*c* = 1.37, $CHCl_3$); IR (film) 1720, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.92–0.97 (m, 2 H), 1.11 (d, 3 H, *J* = 6.8 Hz), 1.63 (bs, 1 H), 2.20 (s, 3 H), 2.81–2.87 (m, 1 H), 3.56–3.61 (m, 2 H), 3.71 (dd, 2 H, *J* = 7.4, 9.6 Hz), 4.64 (s, 2 H); ^{13}C NMR (80 MHz, $CDCl_3$) δ −1.4, 13.4, 18.2, 28.7, 47.2, 65.2, 69.6, 95.0, 210.3. Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.77; H, 10.69.

(32) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1967**, *20*, 2499.

(3*R*,4*R*)- and (3*S*,4*R*)-5-[[2-(Trimethylsilyl)ethoxy]-methoxy]-3-hydroxy-2,4-dimethyl-1-pentene (13 and 14). To a cold (−78 °C) THF solution (90 mL) of **12** (4.724 g, 19.7 mmol) was added 1 M vinylmagnesium bromide in THF (29.6 mL, 29.6 mmol), and the mixture was stirred for 1 h at −78 °C and was then warmed to room temperature over 0.5 h. Aqueous NH_4Cl was added, the solvent was removed, and the residue was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude product by flash column chromatography (1:8 EtOAc–hexane) gave 4.784 g (93%) of a 4:1 mixture of the alcohols **13** and **14**. **13**: IR (neat) 3480, 1640, 1040 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.76–1.11 (m, 2 H), 1.02 (d, 3 H, J = 7.0 Hz), 1.23 (s, 3 H), 1.52–2.03 (m, 1 H), 3.08 (bs, 1 H), 3.44–3.79 (m, 4 H), 4.63 (s, 2 H), 5.07 (dd, 1 H, J = 10.0, 2.0 Hz), 5.27 (dd, 1 H, J = 17.0, 2.0 Hz), 5.95 (dd, 1 H, J = 17.0, 10.0 Hz).

Cyclic Carbonates 15 and 16. To a HMPA solution (5 mL) of the alcohols **13** and **14** (1.50 g, 5.76 mmol) at room temperature was added 1 M tetra-*n*-butylammonium fluoride in THF (12.0 mL, 12.0 mmol). The THF was removed by distillation (90–100 °C) at atmospheric pressure and the reaction mixture was maintained at 100 °C for 7 h. After the mixture was cooled, water was added and the mixture was extracted with Et_2O. The aqueous phase was acidified with dilute HCl and then was continuously extracted with Et_2O for 10 h. The organic phase was dried ($MgSO_4$), the solvent was removed, and the residue was chromatographed on silica (1:1 EtOAc–hexane) to give 613 mg (82%) of a mixture of diols.

A toluene solution (11 mL) of the diols (151 mg, 1.16 mmol) and 1,1′-carbonyldiimidazole (747 mg, 4.61 mmol) was stirred for 18 h at 90 °C. After the mixture was cooled, water was added, the aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by flash column chromatography on silica (1:1 EtOAc–hexane) to give 152 mg (84%) of a mixture of **15** and **16**.

The carbonates **15** and **16** were separated by high-performance liquid chromatography using a μ-Porasil column (1:3 EtOAc–hexane, 1.3 mL/min). From 2.07 g of the mixture of **15** and **16** was obtained 1.30 g (63%) of pure **15**, 0.14 g of pure **16**, and 0.69 g of a mixture of the two isomers. **15**: $[\alpha]^{19}_D$ +0.66° (c = 1.13, $CHCl_3$); IR (neat) 1740, 1645 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.07 (d, 3 H, J = 7.0 Hz), 1.44 (s, 3 H), 1.87–2.30 (m, 1 H), 4.07 (dd, 1 H, J = 11.0, 7.0 Hz), 4.40 (dd, 1 H, J = 11.0, 4.5 Hz), 5.27 (dd, 1 H, J = 10.0, 1.0 Hz), 5.36 (dd, 1 H, J = 17.0, 1.0 Hz), 5.91 (dd, 1 H, J = 17.0, 10.0 Hz). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.49; H, 7.66.

(3*S*,4*R*)-3,5-Dihydroxy-3,4-dimethyl-1-pentene (17). To a cold (0 °C) MeOH solution (27 mL) of **25** (1.259 g, 8.06 mmol) was added a MeOH solution of NaOMe (27 mL, 40.5 mmol). The mixture was allowed to warm to room temperature, and after 8 h, solid NH_4Cl (3 g) was added. The suspension was filtered, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and was filtered. The crude product was purified by flash column chromatography (1:1–2:1 EtOAc–hexane) on silica to give 995 mg (91%) of **17**: $[\alpha]^{20}_D$ +16.9° (c = 1.17, $CHCl_3$); IR (neat) 3330, 1645 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.96 (d, 3 H, J = 7.0 Hz), 1.97–1.55 (m, 1 H), 1.27 (s, 3 H), 2.52 (s, 2 H), 3.72 (d, 2 H, J = 4.5 Hz), 5.10 (dd, 1 H, J = 10.0, 2.0 Hz), 5.27 (dd, 1 H, J = 17.0, 2.0 Hz), 5.99 (dd, 1 H, J = 17.0, 10.0 Hz). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.43; H, 11.09.

(3*S*,4*S*)-3-Hydroxy-3,4-dimethyl-5-iodo-1-pentene (19). To a cold (0 °C) pyridine solution (4 mL) of *p*-toluenesulfonyl chloride (783 mg, 4.10 mmol) was added a pyridine solution (4 mL) of **17** (446 mg, 3.43 mmol). The mixture was stirred overnight at room temperature and then was poured into 3 M HCl containing crushed ice and was extracted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated to give the crude *p*-toluenesulfonate **18**, which was used without purification.

A 2-butanone solution (12 mL) of **18** and dry NaI (1.54 g, 10.3 mmol) was refluxed for 3 h. The mixture was filtered, and the solvent was evaporated. CH_2Cl_2 was added to the residue which was subsequently washed with water and dilute sodium thiosulfate. The solution was dried (Na_2SO_4), the solvent was removed, and the crude product was purified by flash column chromatography (1:8 EtOAc–hexane) on silica to give 713 mg (87%) of **19**: $[\alpha]^{20}_D$ +19.0° (c = 1.40, $CHCl_3$); IR (neat) 3400, 1640, 1190 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.17 (d, 3 H, J = 7.0 Hz), 1.25 (s, 3 H), 1.44 (s, 1 H), 1.43 (s, 3 H), 1.67–2.09 (m, 1 H), 2.90 (d, 1 H, J = 10.0, 9.5 Hz), 3.61 (dd, 1 H, J = 9.5, 2.5 Hz), 5.12 (dd, 1 H, J = 10.0, 9.5 Hz), 5.22 (dd, 1 H, J = 17.0, 1.5 Hz), 5.92 (dd, 1 H, J = 17.0, 10.0 Hz).

(3*S*,4*S*)-3-Acetoxy-3,4-dimethyl-5-iodo-1-pentene (20). To a cold (0 °C) CH_2Cl_2 (20 mL) solution of **19** (1.387 g, 5.78 mmol) was added Ac_2O (5.45 mL, 57.8 mmol) and 4-(dimethylamino)-pyridine (2.12 g, 17.4 mmol). After being stirred for 20 h at 0 °C, the mixture was poured into 2 M HCl containing crushed ice and was extracted with Et_2O. The organic phase was washed sequentially with water, saturated aqueous $NaHCO_3$, and dilute solution thiosulfate and was dried (Na_2SO_4). Removal of the solvent and purification of the crude product by flash column chromatography (1:10 EtOAc–hexane) on silica gave 1.088 g (72%) of **20**: $[\alpha]^{19}_D$ +20.2° (c = 1.28, $CHCl_3$); IR (neat) 1740, 1645, 1240 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.08 (dd, 3 H, J = 7.0, 1.0 Hz), 1.54 (s, 3 H), 2.00 (s, 3 H), 2.08–2.51 (m, 1 H), 2.87 (dd, 1 H, J = 11.0, 9.5 Hz), 3.58 (ddd, 1 H, J = 9.5, 2.5, 1.0 Hz), 5.11 (dd, 1 H, J = 17.0, 1.5 Hz), 5.20 (dd, 1 H, J = 10.0, 1.5 Hz), 5.94 (dd, 1 H, J = 17.0, 10.0 Hz).

(4*R*,5*S*)-4,5-Dimethyl-5-vinyl-5-pentanolide (22). To a cold (−78 °C) stirred THF solution (16 mL) of LDA, prepared from *i*-Pr_2NH (1.86 mL, 13.3 mmol) and 1.55 *n*-BuLi in hexane (7.8 mL, 12.1 mmol), was added a THF solution (5 mL) of **20** (938 mg, 3.32 mmol). The solution was allowed to warm to 0 °C over 1 h, and the saturated aqueous NH_4Cl was added. The aqueous phase was extracted with CH_2Cl_2, and the organic extract was dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by flash column chromatography (1:3 EtOAc–hexane) on silica to give 482 mg (94%) of **22**: $[\alpha]^{20}_D$ +17.7° (c = 1.16, $CHCl_3$): IR (neat) 1725, 1640, 1250 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.04 (d, 3 H, J = 7.0 Hz), 1.38 (s, 3 H), 1.52–2.25 (m, 1 H), 2.44–2.63 (m, 2 H), 5.16 (dd, 1 H, J = 10.0, 1.5 Hz), 5.26 (dd, 1 H, J = 17.0, 1.5 Hz), 5.91 (dd, 1 H, J = 17.0, 10.0 Hz). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.23.

(4*R*,5*R*)-5-Carboxy-4,5-dimethyl-5-pentanolide (23). To a suspension of **22** (38 mg, 0.246 mmol) in a mixture of MeCN (1 mL), CCl_4 (1 mL), and water (1.5 mL) were added solid $NaIO_4$ (221 mg, 1.03 mmol) and $RuCl_3 \cdot 3H_2O$ (3 mg, 0.01 mmol). After 3 h the mixture was extracted with CH_2Cl_2, the organic layer was dried (Na_2SO_4), and the solvent was evaporated. Flash column chromatography of the crude product (0.5:1:20 HOAc–MeOH–CH_2Cl_2) on silica gave 31 mg (73%) of **23** which was recrystallized from *i*-Pr_2O: mp 118–120 °C; $[\alpha]^{20}_D$ −2.4° (c = 1.47, $CHCl_3$); IR (neat) 3600–2500, 1750, 1680 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.11 (d, 3 H, J = 7.2 Hz), 1.56 (s, 3 H), 1.64–2.67 (m, 5 H), 7.93 (bs, 1 H). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.83; H, 7.23.

(4*R*,5*R*)-5-Carbomethoxy-4,5-dimethyl-5-pentanolide (24). From **23**. An Et_2O solution of **23** (31 mg, 0.180 mmol) and CH_2N_2 was stirred briefly, and then the solvent was removed. The crude product was purified by flash column chromatography (1:2 EtOAc–hexane) on silica to give 25.0 mg (75%) of **24**: $[\alpha]^{20}_D$ +5.30 (c = 1.37, $CHCl_3$); IR (neat) 1746, 1732, 1173, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3 H, J = 7.2 Hz), 1.54 (s, 3 H), 1.64–1.71 (m, 1 H), 1.77–1.87 (m, 1 H), 2.26–2.32 (m, 1 H), 2.54–2.58 (m, 2 H), 3.80 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.0, 21.5, 24.6, 25.6, 32.0, 53.0, 85.9, 169.9, 173.3. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.74; H, 7.54.

From **49**. To a suspension of **49** (48 mg, 0.3 mmol) in a mixture of CCl_4 (2 mL), MeCN (2 mL), and water (3 mL) were added HIO_5 (176 mg, 0.76 mmol) and $RuCl_3 \cdot 3H_2O$ (1.5 mg, 7.2 μmol). After 1 h the mixture was diluted with CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the organic phase was dried ($MgSO_4$). The solvent was removed, and the resultant acid **23** was dissolved in Et_2O and was treated with CH_2N_2. After 7 h the solvent was removed and the crude ester was purified by flash column chromatography (3:7 EtOAc–hexane) on silica to yield 30 mg (53%) of **24** as an oil.

(4*R*,5*R*)-5-Carboxy-4,5-dimethyl-2(*E*)-ethylidene-5-pentanolide (5). From **20**. To a cold (−78 °C) stirred THF solution (8 mL) of LDA, prepared from *i*-Pr_2NH (0.40 mL, 2.85 mmol) and 1.55 *n*-BuLi in hexane (1.60 mL, 2.48 mmol), was added a

THF solution (4 mL) of **20** (200 mg, 0.709 mmol). After 30 min freshly distilled, neat acetaldehyde (0.16 mL, 2.86 mmol) was added and stirring was continued for a further 30 min at −78 °C. Aqueous NH_4Cl was added, and the solution was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by flash column chromatography (1:2 EtOAc–hexane) on silica to give 122 mg (87%) of **25**: IR (neat) 3450, 1700, 1645 cm^{-1}.

To a cold (0 °C) CH_2Cl_2 (4.5 mL) solution of **25** (88 mg, 0.44 mmol) were added Ac_2O (0.43 mL, 4.6 mmol), Et_3N (0.63 mL, 4.5 mmol), and a CH_2Cl_2 (0.5 mL) solution of 4-(dimethylamino)-pyridine (3 mg, 0.02 mmol). The mixture was stirred for 3 h at room temperature, and 1 M HCl was added. The mixture was extracted with Et_2O, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by flash column chromatography (1:2 EtOAc–hexane) on silica to give 96 mg (90%) of **26**: IR (neat) 1740, 1730, 1640, 1245 cm^{-1}.

To a suspension of **26** (93 mg, 0.39 mmol) in a mixture of MeCN (2 mL), CCl_4 (2 mL), and water (3 mL) were added solid $NaIO_4$ (348 mg, 1.63 mmol) and $RuCl_3 \cdot 3H_2O$ (5 mg, 0.02 mmol). After 3 h EtOAc was added and the aqueous layer was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in Et_2O and passed through a short column of silica gel. Removal of the solvent gave crude **27**, which was used without further purification.

Crude **27** was dissolved in dry CH_2Cl_2 (1 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.16 mL, 1.07 mmol) was added. After 20 h, Et_2O was added and the mixture was washed with aqueous $NaHCO_3$. The aqueous phase was acidified with 6 M HCl and was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was evaporated. Flash column chromatography of the crude product (1:1:60–0.7:1:40 HOAc–MeOH–CH_2Cl_2) on silica gave a mixture of **5**, a small amount of the corresponding *Z*-isomer, and acetate **27** (80 mg). The entire mixture was treated with ethereal CH_2N_2, the solvent was removed, and the crude product was purified by flash column chromatography (2:3–1:1 Et_2O–hexane) on silica to give 56 mg (68% from **27**) of the methyl ester of **5**, which was recrystallized from pentane–Et_2O.

To a cold (0 °C) THF–H_2O solution (1:1, 2 mL) of the methyl ester (51 mg, 0.24 mmol) was added, $LiOH \cdot H_2O$ (12 mg, 0.28 mmol). After 3 h at 0 °C, the mixture was acidified with 0.3 M HCl and was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was evaporated to give 45 mg (65%) of **5** which was recrystallized from C_6H_6: mp (hexane/Et_2O) 153–153.5 °C; $[\alpha]^{22}_D$ +46.9° (*c* = 1.20, $CHCl_3$), +41° (*c* = 0.33, EtOH); IR (KBr) 3600–2800, 1740, 1680, 1625 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.07 (d, 3 H, *J* = 7.0 Hz), 1.59 (s, 3 H), 1.78 (d, 3 H, *J* = 7.5 Hz), 2.43 (bs, 3 H), 6.46 (bs, 1 H), 7.22 (tq, 1 H, *J* = 7.0, 2.0 Hz). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.40; H, 7.33.

From **52**. To a cold (0 °C) THF solution (1 mL) of **52** (51 mg, 0.24 mmol) were added solid $RuCl_3 \cdot 3H_2O$ (12 mg, 0.50 mmol) and water (1 mL). After 3 h, the solution was acidified with 0.3 M HCl and the aqueous phase was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), the solvent was removed, and the crude product was purified by flash column chromatography (60:2:1 $CHCl_3$–MeOH–HOAc) on silica to give 45 mg (95%) of **5**.

(4*R*,5*R*)-5-[[2-(Trimethylsilyl)ethoxy]carbonyl]-4,5-dimethyl-2(*E*)-ethylidene-5-pentanolide (28). To a cold (0 °C) CH_2Cl_2 solution (2 mL) of 2-chloro-1-methylpyridinium iodide (95 mg, 0.372 mmol), 2-(trimethylsilyl)ethanol (0.053 mL, 0.370 mmol), and **5** (37 mg, 0.187 mmol) was added neat Et_3N (0.105 mL, 0.753 mmol). The mixture was stirred overnight at room temperature, and then water and $CHCl_3$ were added. The phases were separated, and the aqueous phase was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the crude product was purified by flash column chromatography (1:5 EtOAc–hexane) on silica to give 50 mg (90%) of **28**: $[\alpha]^{19}_D$ +17.6° (*c* = 0.58, $CHCl_3$); IR (neat) 1745, 1725, 1640 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.88–1.10 (m, 2 H), 1.03 (d, 3 H, *J* = 7.0 Hz), 1.51 (s, 3 H), 1.75 (bd, 3 H, *J* = 7.0 Hz), 2.36 (bs, 3 H), 4.12–4.34 (m, 2 H), 7.18 (tq, 1 H, *J* = 7.0, 1.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 0.0, 15.4, 15.7, 19.0, 23.2, 30.2, 33.8, 66.0, 85.5, 125.0, 144.2, 166.8, 174.2.

(2*R*,3*R*)-2′-(Trimethylsilyl)ethyl 2-Hydroxy-2,3-dimethyl-5(*E*)-ethylideneadipate (29). To a cold (0 °C) THF solution (2.5 mL) of **28** (37 mg, 0.124 mmol) and 30% H_2O_2 (0.7 mL, 6.2 mmol) was added an aqueous solution of LiOH. The mixture was stirred for 1 h at 0 °C and for 3 h at room temperature and was then acidified with 0.3 M HCl. The aqueous phase was extracted with $CHCl_3$, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude product by flash column chromatography (1:1–2:1 Et_2O–hexane) on silica gave 19 mg of **29** (64% based on recovered lactone) and 9 mg of **28**. A THF solution (0.8 mL) of **28** was treated with 0.1 M LiOH (0.4 mL) and H_2O_2 (0.1 mL) in THF (0.8 mL) as described above, to give a combined yield of 22.5 mg (57%) of **29**: mp (hexane/Et_2O) 111.5–113.0 °C; $[\alpha]^{21}_D$ −4.30° (*c* = 0.23, $CHCl_3$); IR (KBr) 3480, 3250–2500, 1715, 1675, 1630 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.06 (s, 9 H), 0.90 (d, 3 H, *J* = 6.7 Hz), 1.03–1.08 (m, 2 H), 1.37 (s, 3 H), 1.83 (d, 3 H, *J* = 7.2 Hz), 2.09–2.17 (m, 1 H), 2.20–2.36 (m, 2 H), 4.20–4.32 (m, 2 H), 7.07 (q, 1 H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.6, 12.6, 15.0, 17.2, 24.0, 28.0, 39.6, 64.4, 76.3, 130.9, 141.8, 173.1, 177.8. Anal. Calcd for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 56.78; H, 9.03.

(2*R*,3*R*)-2′-(Trimethylsilyl)ethyl 2-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dimethyl-5(*E*)-ethylideneadipate (30). To a cold (0 °C) CH_2Cl_2 (1 mL) solution of **29** (2 mg, 0.070 mmol) and 2,6-lutidine (0.08 mL, 0.69 mmol) was added neat *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.08 mL, 0.35 mmol). After 1 h water and Et_2O were added, the phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed sequentially with water, 0.3 M HCl, and brine and was dried ($MgSO_4$). The solvent was removed, and the crude material was dissolved in a mixture of THF (1.5 mL), HOAc (1.5 mL), and water (0.5 mL). The mixture was stirred for 8 h at room temperature. Brine and $CHCl_3$ were added, the phases were separated, and the organic phase was dried ($MgSO_4$). Removal of the solvent and purification of the crude product by flash column chromatography (1:5 EtOAc–hexane) on silica gave 26 mg (87%) of **30**: $[\alpha]^{20}_D$ +16.2° (*c* = 0.315, $CHCl_3$); IR (neat) 3500–2400, 1740, 1680, 1640 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.09 (s, 3 H), 0.17 (s, 3 H), 0.70–1.14 (m, 2 H), 0.81 (d, 3 H, *J* = 6.5 Hz), 0.92 (s, 9 H), 1.39 (s, 3 H), 1.80 (d, 3 H, *J* = 7.5 Hz), 2.25 (bs, 3 H), 4.07–4.29 (m, 2 H), 7.02 (q, 1 H, *J* = 7.5 Hz); ^{13}C NMR (80 MHz, $CDCl_3$ δ −2.9, −2.6, −1.5, 12.4, 14.8, 17.4, 18.7, 24.2, 25.7, 26.0, 27.8, 41.6, 63.2, 79.8, 131.6, 141.0, 173.0, 175.7.

9-(*tert*-Butyldimethylsilyl)retronecine (31). To a cold (0 °C) DMF solution (1.5 mL) of retronecine (**4**) (105 mg, 0.677 mmol) was added a DMF solution (0.5 mL) of *tert*-butyldimethylsilyl chloride (117 mg, 0.776 mmol) followed by Et_3N (0.27 mL, 1.94 mmol). After 5 h an aqueous solution (7 mL) of 0.5% NaOH was added, and the mixture was extracted with $CHCl_3$ (4 × 10 mL). The organic phase was dried (Na_2SO_4), the solvent was removed and the residue was purified by flash column chromatography (30:1 CH_2Cl_2 (saturated with NH_4OH)–MeOH) on silica to give 157 mg (86%) of **31** as a pale yellow oil. CH_2Cl_2 saturated with NH_4OH was prepared by shaking CH_2Cl_2 with 29% NH_4OH (5:1 ratio) and drying the organic layer quickly with anhydrous K_2CO_3. **31**: $[\alpha]^{21}_D$ +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, 3 H), 0.14 (s, 3 H), 0.93 (s, 9 H), 1.94 (m, 1 H), 2.03 (dd, 1 H, *J* = 12.9, 5.6 Hz), 2.74 (m, 1 H), 3.25 (t, 1 H, *J* = 7.9 Hz), 3.40–3.48 (m, 2 H), 3.87 (dd, 1 H, *J* = 15.6, 1.9 Hz), 4.15 (m, 2 H), 4.25 (t, 1 H, *J* = 3.6 Hz), 4.37 (d, 1 H, *J* = 11.1 Hz), 5.74 (bs, 1 H). Anal. Calcd for $C_{14}H_{27}SiNO_2$: C, 62.40; H, 10.10; N, 5.20. Found: C, 62.57; H, 10.02; N, 5.07.

Retronecine Ester (32). To a cold (0 °C) THF solution (1 mL) of **30** (25 mg, 0.058 mmol) were added Et_3N (0.03 mL, 0.20 mmol) and $(EtO)_2POCl$ (15 mg, 0.087 mmol). The mixture was stirred for 3 h at room temperature and filtered. To a cold (0 °C) THF solution (1 mL) of **31** (47 mg, 0.174 mmol) and 4-(dimethylamino)pyridine were added a hexane solution of *n*-BuLi (0.166 mL, 0.163 mmol) followed by the THF solution of the mixed anhydride of **30**. The mixture was stirred for 5 h at room temperature, and aqueous NH_4Cl and $CHCl_3$ were added. The organic phase was dried ($MgSO_4$), and the solvent was evaporated. Flash column chromatography of the crude product (1:20 MeOH–CH_2Cl_2) on silica gave 20 mg (51%) of **32**: $[\alpha]^{20}_D$ +27.1° (*c* = 0.49,

$CHCl_3$); IR (neat) 1740, 1705, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.06 (s, 9 H), 0.09 (s, 3 H), 0.16 (s, 3 H), 0.79 (d, 3 H, J = 7.0 Hz), 0.87 (s, 9 H), 0.92 (s, 9 H), 1.00–1.07 (m, 2 H), 1.37 (s, 3 H), 1.78 (d, 3 H, J = 7.2 Hz), 2.00–2.35 (m, 5 H), 2.96 (bs, 1 H), 3.69 (bd, 1 H, J = 14.0 Hz), 3.80 (bs, 1 H), 4.11–4.25 (m, 4 H), 4.31 (bd, 1 H, J = 14.0 Hz), 4.76 (bs, 1 H), 5.54 (bs, 1 H), 5.64 (d, 1 H, J = 1.3 Hz), 6.86 (q, 1 H, J = 7.2 Hz); HRMS calcd for $C_{35}H_{67}O_6NSi_3$ 681.4276, found 681.4277.

***O*-(*tert*-Butyldimethylsilyl)integerrimine (35).** To a MeOH solution (3 mL) of **32** (19 mg, 28 μmol) were added 1 mL of water and solid NH_4F (42 mg, 1.12 mmol). The mixture was maintained at 60–65 °C for 4 h, and the solvent was removed. $CHCl_3$ was added, and the solution was dried (Na_2SO_4). Removal of the solvent and purification of the crude product by flash column chromatography on silica (1:7–1:3 CH_2Cl_2–MeOH) gave 10.7 mg (67%) of **33**.

To a cold (0 °C) CH_2Cl_2 solution (1 mL) of **33** (6.6 mg, 0.012 mmol) was added a CH_2Cl_2 solution (2.3 mL) of $MeSO_2Cl$ (0.023 mmol). The mixture was stirred for 30 min at 0 °C and then added via syringe (syringe pump, 2 h) to a MeCN solution (4 mL) of n-Bu_4NF (0.17 mmol). After 30 min, aqueous NH_4Cl was added to the mixture, the MeCN was removed, and the aqueous residue was treated with 10% NaOH. The aqueous phase was extracted with Et_2O, and the organic phase was dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by flash column chromatography (1:60 MeOH–CH_2Cl_2 containing NH_3) on silica to give 3.9 mg (75%) of **35**: $[\alpha]^{23}_D$ 17.2° (c = 0.36, $CHCl_3$); IR ($CHCl_3$) 1740, 1710, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.19 (s, 3 H, 0.85 (d, 3 H, J = 6.7 Hz), 0.91 (s, 9 H), 1.34 (s, 3 H), 1.70–1.78 (m, 1 H), 1.73 (d, 1 H, J = 7.5 Hz), 1.96 (d, 1 H, J = 13.4 Hz), 2.15–2.25 (m, 2 H), 2.51–2.56 (m, 1 H), 2.63–2.68 (m, 1 H), 3.48–3.53 (m, 2 H), 4.00 (d, 1 H, J = 11.9 Hz), 4.14 (bd, 1 H, J = 16.2 Hz), 4.55 (bs, 1 H), 5.06 (bs, 1 H), 5.40 (d, 1 H, J = 11.9 Hz), 6.22 (d, 1 H, J = 1.2 Hz), 6.52 (q, 1 H, J = 7.1 Hz); HRMS calcd for $C_{24}H_{39}O_5NSi$ 449.2597, found 449.2639.

Integerrimine (1). A MeCN solution (0.5 mL) of **35** (3.6 mg, 0.0080 mmol) was added to an aqueous 48% solution (0.5 mL) of HF. After being stirred for 12 h at room temperature, the mixture was poured into an aqueous solution (5 mL) of Na_2CO_3 (2 g) and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), and the solvent was removed. Purification of the crude product by flash column chromatography on silica (1:10–1:5 MeOH–CH_2Cl_2) gave 1.8 mg (67%) of integerrimine (1) which was recrystallized from Me_2CO: $[\alpha]^{23}_D$ −18.3° (c = 0.12, $CHCl_3$) and +2.7° (c = 1.1, MeOH); IR ($CHCl_3$) 3685, 3535, 1715, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, 3 H, J = 6.9 Hz), 1.33 (s, 3 H), 1.75 (d, 3 H, J = 7.2 Hz), 1.99 (d, 1 H, J = 13.2 Hz), 2.05–2.14 (m, 1 H), 2.20 (dd, 1 H, J = 13.5, 10.2 Hz), 2.43 (dd, 1 H, J = 13.7, 6.1 Hz), 2.49–2.56 (m, 1 H), 3.16 (bs, 1 H), 3.94 (d, 1 H, J = 16.5 Hz), 3.24 (t, 1 H, J = 8.1 Hz), 3.40 (dd, 1 H, J = 15.1, 5.3 Hz), 4.11 (d, 1 H, J = 11.7 Hz), 4.31 (bs, 1 H), 5.01 (bs, 1 H), 5.42 (d, 1 H, J = 11.7 Hz), 6.22 (bs, 1 H), 6.52 (q, 1 H, J = 7.1 Hz); HRMS calcd for $C_{18}H_{25}O_5N$ 335.1736, found 335.1736.

(*R*)-(+)-Citronellol (36). HCl gas was bubbled through cold (−10 °C) neat (*R*)-(+)-pulegone (**38**) (27 g, 176 mmol) for 1 h, and the mixture was stirred overnight at room temperature. This solution and a solution (50 mL) of NaOH (18.6 mg, 465 mmol) were separately added dropwise to a mechanically stirred aqueous solution (73.5 mL) of NaOH (1.29 mg, 32.3 mmol) at 10–15 °C. After addition was complete (~45 min) the mixture was stirred overnight at room temperature and residual pulegone was extracted with Et_2O (3 × 50 mL). The aqueous phase was cooled to 0 °C, and 10 mL of H_2SO_4 was slowly added. The mixture was extracted with Et_2O (3 × 100 mL), and the organic phase was dried ($MgSO_4$). Evaporation of the solvent gave 16 g (53%) of citronellic acid (**39**) as a pale yellow oil and 11 g (40%) of pulegone (**38**). Citronellic acid (**39**) was used without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, 3 H, J = 6.6 Hz), 1.22 (m, 1 H), 1.26 (m, 1 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 2.0 (m, 3 H), 2.26 (dd, 1 H, J = 14.8, 8.2 Hz), 2.37 (dd, 1 H, J = 14.8, 5.8 Hz), 5.1 (m, 1 H), 10.8 (bs, 1 H).

To a cold (0 °C) stirred suspension of $LiAlH_4$ (4.6 g, 120.8 mmol) in Et_2O (150 mL) was added an Et_2O solution (30 mL) of **39** (13.7 g, 80.5 mmol) over a period of 1 h. To the mixture was added an aqueous solution (20 mL) of NaOH (0.69 mg, 16.7 mmol), and the mixture was stirred at room temperature for 10 min. The mixture was filtered, and the precipitate was washed with EtOAc (250 mL). The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine and was dried ($MgSO_4$). Evaporation of solvents in vacuo and purification of the crude product by flash column chromatography (1:5 EtOAc–hexane) on silica yielded 12.1 g (97%) of **36**: $[\alpha]^{21}_D$ +5.49° (neat), (lit.[19] $[\alpha]^{21}_D$ +5.47° (neat)); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3 H, J = 6.6 Hz), 1.19 (m, 1 H), 1.41 (m, 3 H), 1.56 (m, 2 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 2.01 (m, 2 H), 3.69 (m, 2 H), 5.11 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.6, 19.5, 25.4, 25.7, 29.1, 37.2, 39.7, 61.2, 124.7, 131.2.

(*R*)-(+)-Citronellal (40). To a stirred suspension of pyridinium chlorochromate (4.3 g, 19.8 mmol) and NaOAc (325 mg, 3.95 mmol) in CH_2Cl_2 (30 mL) was added a CH_2Cl_2 solution of **40** (2.1 g, 13.2 mmol). The mixture was stirred for 2 h and was diluted with Et_2O (50 mL). The supernatant was decanted from the black gummy residue which was washed thoroughly with Et_2O (3 × 40 mL). The organic phase was passed through a short pad of Florisil and was concentrated in vacuo. The crude product was purified by flash column chromatography (1:5 Et_2O–hexane) on silica to yield 1.43 g (70%) of **40** as a colorless oil: $[\alpha]^{20}_D$ +13.21° (neat) (lit.[19] $[\alpha]^{18}_D$ +13.09° (neat)); ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, 3 H, J = 6.7 Hz), 1.34 (m, 2 H), 1.60 (s, 3 H), 1.69 (s, 3 H), 2.02 (m, 3 H), 2.25 (m, 1 H), 2.39 (m, 1 H), 5.09 (m, 1 H), 9.76 (t, 1 H, J = 2.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.7, 19.9, 25.4, 25.7, 27.8, 37.0, 51.0, 124.0, 131.8, 203.0.

(*R*)-3,7-Dimethyl-2-methylene-6-octenal (41). To a stirred solution of i-Pr_2NH (0.36 mL, 2.56 mmol) in THF (1.5 mL) at −78 °C was added n-BuLi (1.61 mL, 2.45 mmol). The mixture was warmed to 0 °C for 15 min and was cooled to −78 °C. A THF solution (1.5 mL) of **40** (344 mg, 2.2 mmol) was added, and the mixture was stirred for 45 min at −78 °C. It was then added, via cannula, to a cold (−78 °C) stirred suspension of *N*,*N*-dimethylmethyleneammonium iodide (1.16 g, 6.3 mmol) in THF (3 mL). The mixture was stirred for 45 min at −78 °C and for 5 h at room temperature, an the solvent was evaporated in vacuo. The residue was taken up in cold (0 °C) MeOH (1.5 mL) to which was added neat MeI (0.43 mL, 6.7 mmol). The mixture was stirred overnight at 4 °C and at room temperature for an additional 5 h after which the solvent was removed in vacuo. The resultant red solid was dissolved in CH_2Cl_2 (2.5 mL), and the solution was stirred with 5% aqueous $NaHCO_3$ for 16 h at room temperature. The mixture was diluted with CH_2Cl_2 (3 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL). The organic phase was dried ($MgSO_4$), the solvent was removed, and the crude product was purified by flash column chromatography (1:5 Et_2O–hexane) on silica to yield 289 mg (78%) of **41** 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, 3 H, J = 7.4 Hz), 1.40 (m, 1 H), 1.54 (m, 1 H), 1.57 (s, 3 H), 1.67 (s, 3 H), 1.93 (m, 2 H), 2.71 (m, 1 H), 5.08 (m, 1 H), 5.99 (s, 1 H), 6.23 (s, 1 H), 9.53 (s, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.6, 19.6, 25.7, 25.8, 31.0, 35.6, 124.2, 131.6, 133.0, 155.5, 194.6. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.11; H, 10.72.

(3*R*)-3,7-Dimethyl-2-methylene-6-octen-1-ol (42). To a cold (0 °C) MeOH solution of **41** (12.8 g, 77 mmol) were added $CeCl_3 \cdot 6H_2O$ hexahydrate (27.5 g, 77 mmol) and solid $NaBH_4$ (3.8 g, 100 mmol). After 5–10 min saturated aqueous NH_4Cl was added, the solvent was removed, and water (550 mL) was added to the residue. The mixture was extracted with EtOAc (4 × 100 mL), the organic phase was dried, and the crude product was purified by flash column chromatography (1:1 Et_2O–hexane) on silica to yield 12.3 g (95%) of **42** 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, 3 H, J = 6.5 Hz), 1.37 (m, 1 H), 1.48 (m, 2 H), 1.59 (s, 3 H), 1.68 (d, 3 H, J = 1.0 Hz), 1.96 (m, 2 H), 2.16 (m, 1 H), 4.10 (bs, 2 H), 4.89 (s, 1 H), 5.05 (d, 1 H, J = 1.4 Hz), 5.09 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.7, 20.1, 25.7, 25.9, 35.8, 36.6, 64.5, 107.8, 124.5, 131.5, 153.9; HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1511. This compound was converted to its 4-phenylbenzoate. Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.71; H, 8.11. Found: C, 82.49; H, 8.25.

Oxiranes 43 and 44. To a stirred suspension of 3-Å molecular sieves (powder, 500 mg) in CH_2Cl_2 (35 mL) at room temperature

were added diisopropyl (−)-tartrate (0.34 mL, 1.62 mmol) and a CH_2Cl_2 solution of **42** (3.9 g, 23.2 mmol). The mixture was cooled to −5 °C, and Ti(O-*i*-Pr)$_4$ (0.39 mL, 1.29 mmol) was added. After 20 min cumene hydroperoxide (12 mL, 64.9 mmol) was added dropwise and the mixture was stirred for 8 h at −5 °C. After being stirred overnight at 4 °C, the mixture was cooled to −20 °C, $(MeO)_3P$ (4.4 mL, 37.1 mmol) was added and stirring was continued for 1.5 h. The mixture was filtered through Celite, extracted with brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo, and the crude product was purified by column chromatography (1:1 Et_2O–hexane) on silica to give 2.95 g (69%) of **43** and **44** as a 3:1 mixture: IR (neat) 3450 (broad), 2900, 1440, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97, 1.04 (d, 3 H, J = 7.1 Hz), 1.25 (m, 2 H), 1.56 (m, 2 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 2.04 (m, 2 H), 2.62 (d, 1 H, J = 4.7 Hz), 2.91 (d, J = 1.7 Hz) and 2.93 (d, J = 4.7 Hz), 3.70, 3.85 (m, 2 H), 5.07 (m, 1 H); HRMS calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1458.

The preparation of **44** from **42** was carried out in a manner similar to that described above using diisopropyl (+)-tartrate and gave a 96:4 ratio of **44** and **43** in 81% yield: $[\alpha]^{22}_D$ −2.15° (c = 41.74, $CHCl_3$); IR (neat) 3431 (broad), 2925, 1455, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 6.8 Hz), 1.26 (m, 1 H), 1.58 (m, 2 H), 1.60 (s, 3 H), 1.69 (s, 3 H), 2.07 (m, 2 H), 2.61 (d, 1 H, J = 4.8 Hz), 2.91 (d, 1 H, J = 4.8 Hz), 3.72 (dd, 1 H, J = 12.4, 9.5 Hz), 3.83 (dd, 1 H, J = 12.4, 3.6 Hz), 5.09 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.1, 17.7, 25.7, 25.8, 33.0, 35.8, 48.7, 60.2, 62.5, 124.1, 131.8.

3,5-Dinitrobenzoates 45 and 46. To a stirred suspension of 3,5-dinitrobenzoyl chloride (3.7 g, 16.1 mmol) in pyridine (40 mL) was added a pyridine solution (10 mL) of **43** and **44** (1.98 g, 10.7 mmol). After 4 h the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), was washed sequentially with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Flash column chromatography (1:3 EtOAc–hexane) of the crude product on silica gave 3.52 g (98%) of a mixture of **45** and **46**, which was separated by crystallization.

Compound **45**: mp (CH_2Cl_2–hexane) 56.5–57 °C; $[\alpha]^{22}_D$ −2.44° (c = 16.59, $CHCl_3$); IR (KBr) 2968, 1738, 1630, 1165, 984 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3 H, J = 6.7 Hz), 1.29 (m, 1 H), 1.56 (m, 2 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 2.03 (m, 2 H), 2.76 (d, 1 H, J = 4.5 Hz), 2.87 (d, 1 H, m, J = 4.5 Hz), 4.46 (d, 1 H, J = 12.1 Hz), 4.73 (d, 1 H, J = 12.1), 5.06 (m, 1 H), 9.14 (d, 2 H, J = 2.2 Hz), 9.24 (t, 1 H, J = 2.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.3, 17.8, 25.7, 25.8, 32.6, 36.3, 50.5, 59.8, 65.8, 122.6, 123.7, 129.5, 132.3, 133.4, 148.7, 162.2. 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 **46**: oil; $[\alpha]^{22}_D$ −1.44° (c = 7.28, $CHCl_3$); IR (neat) 2923, 1730, 1630, 1095, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, 3 H, J = 6.8 Hz), 1.34 (m, 1 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 1.73 (m, 2 H), 2.01 (m, 2 H), 2.75 (d, 1 H, J = 4.5 Hz), 2.84 (d, 1 H, J = 4.5 Hz), 4.44 (d, 1 H, J = 12.3 Hz), 4.76 (d, 1 H, J = 12.3 Hz), 5.10 (m, 1 H), 9.15 (d, 2 H, J = 2.1 Hz), 9.25 (t, 1 H, J = 2.1 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.3, 17.7, 25.7, 25.8, 33.2, 36.1, 49.5, 60.0, 66.0, 122.6, 123.7, 129.5, 132.2, 133.5, 148.8, 162.2. Anal. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.12; H, 5.86; N, 7.41. Found: C, 56.91; H, 5.99; N, 7.33.

(2*R*,3*R*)-2,3,7-Trimethyl-6-octene-1,2-diol (47). $LiAlH_4$ (81 mg, 2.1 mmol) was added to a THF solution (8 mL) of **45** (202 mg, 0.5 mmol) at room temperature. After 15 h, a cold (0 °C) solution of 5% HCl in MeOH (50 mL) was added, and the mixture was refluxed for 5–10 min. The gray solid was filtered and washed with MeOH, and the filtrate was concentrated in vacuo. EtOAc (50 mL) was added and the resultant solution was washed with brine and dried (Na_2SO_4). The solvent was removed, and the crude product was purified by flash column chromatography (1:1 EtOAc–hexane) on silica to give 81 mg (82%) of **47**: $[\alpha]^{21}_D$ +38.46° (c = 3.82, $CHCl_3$); IR (neat) 3400 (broad), 2900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3 H, J = 6.8 Hz), 1.05 (m, 1 H), 1.06 (s, 3 H), 1.61 (s, 3 H), 1.64 (m, 2 H), 1.69 (s, 3 H), 1.83 (s, 1 H), 1.94 (m, 2 H), 2.17 (m, 1 H), 3.43 (dd, 1 H, J = 10.7, 6.2 Hz), 3.55 (dd, 1 H, J = 10.7, 5.2 Hz), 5.13 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.5, 17.7, 19.1, 25.7, 26.5, 30.7, 39.3, 68.7, 75.3, 124.5, 131.7. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.64; H, 11.81.

(2*R*,3*R*)-2,3,7-Trimethyl-2-[(3,5-dinitrobenzoyl)oxy]-6-octenyl 3,5-Dinitrobenzoate (48). To a stirred suspension of 3,5-dinitrobenzoyl chloride (1.7 g, 7.3 mmol) in pyridine (15 mL) was added a pyridine solution (5 mL) of **47** (270 mg, 1.5 mmol). After 72 h, the solvent was removed and the residue was dissolved in CH_2Cl_2 (50 mL). The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ and brine and was dried (Na_2SO_4). Purification of the crude product by flash column chromatography (1:3 EtOAc–hexane) on silica gave 749 mg (87%) of **48**: $[\alpha]^{22}_D$ +7.90 (c = 6.49, $CHCl_3$); IR (neat) 2900, 1740, 1545, 1340, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3 H, J = 7.0 Hz), 1.30 (m, 1 H), 1.61 (s, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 2.06 (m, 1 H), 2.17 (m, 2 H), 2.55 (m, 1 H), 4.92 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 9.06 (d, 2 H, J = 2.2 Hz), 9.12 (t, 1 H, J = 2.2 Hz), 9.21 (d, 2 H, J = 2.1 Hz), 9.25 (t, 1 H, J = 2.1 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.3, 17.7, 18.0, 25.7, 26.0, 31.1, 37.5, 67.5, 88.9, 122.5, 122.7, 123.4, 129.2, 129.3, 132.9, 133.8, 134.6, 148.8, 148.8, 161.3, 162.1.

(4*R*,5*R*)-4,5-Dimethyl-5-(hydroxymethyl)-5-pentanolide (49). To a suspension of **48** (946 mg, 1.6 mmol) in a mixture of CCl_4 (3 mL), MeCN (3 mL), and water (4.5 mL) were added $NaIO_4$ (1.4 g, 6.8 mmol) and $RuCl_3 \cdot 3H_2O$ (9.5 mg). After 24 h CH_2Cl_2 (50 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic extract was dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was dissolved in Et_2O (50 mL) and filtered through a short Celite pad. The crude acid, obtained after evaporation of the solvents, was dissolved in MeOH (10 mL), and the solution was stirred with anhydrous K_2CO_3 (300 mg, 2 mmol) for 45 min. The solvent was removed, and the residue was treated with a mixture of $CHCl_3$ (30 mL) and 5% HCl (12 mL) for 24 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried an concentrated, and the crude product was chromatographed (4:1 EtOAc–hexane) on silica to provide 143 mg (55%) of **49** as a colorless solid: mp 87–88 °C (CH_2Cl_2–hexane) (lit.[6d] mp 85–86 °C); $[\alpha]^{22}_D$ +42.87° (c = 1.17, $CHCl_3$); IR (KBr) 3400 (broad), 2950, 1730, 1340 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3 H, J = 6.72 Hz), 1.22 (s, 3 H), 1.77 (m, 3 H), 2.23 (m, 1 H), 2.47–2.67 (m, 2 H), 3.58 (d, 1 H, J = 12.4 Hz), 3.64 (d, 1 H, J = 12.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.1, 17.4, 24.4, 29.7, 30.5, 67.5, 88.1, 171.5. Anal. Calcd for $C_8H_{14}O_3$: C, 60.72; H, 8.93. Found: C, 60.72; H, 9.16.

(4*R*,5*R*)-5-Carbomethoxy-4,5-dimethyl-2(*E*)-ethylidene-5-pentanolide (52). To a cold (−78 °C) THF solution (1 mL) of *i*-Pr_2NH (0.033 mL, 0.24 mmol) was added a hexane solution of *n*-BuLi (0.15 mL, 0.22 mmol). The mixture was warmed to 0 °C, stirred for 15 min, and cooled to −78 °C. A THF solution of **24** (26.0 mg, 0.14 mmol) was added, and the resultant solution was stirred at −78 °C for 1 h. HMPA (0.10 mL, 0.56 mmol) was added followed, after 10 min, by freshly distilled acetaldehyde (0.04 mL, 0.7 mmol). The mixture was stirred at −78 °C for 10 min and at −45 °C for 3 h. Saturated aqueous NH_4Cl and Et_2O were added, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed. The crude product was dissolved in CH_2Cl_2 (2 mL) and was stirred overnight with Ac_2O (0.06 mL, 0.6 mmol), Et_3N (0.08 mL, 0.57 mmol) and a catalytic amount of 4-(dimethylamino)pyridine. To this mixture was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.05 mL, 0.33 mmol), and after a further 24 h, the reaction mixture was diluted with Et_2O and washed with 1% HCl and brine. The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo. Purification of the crude product by flash column chromatography (1:2 EtOAc–hexane) on silica gave 14.8 mg (50%) of **52** as a colorless solid: mp 91–92 °C (pentane–Et_2O), (lit.[6d] mp 92.5–94 °C); $[\alpha]^{22}_D$ +46.43° (c = 0.14, $CHCl_3$) (lit.[6d] $[\alpha]^{21}_D$ +47.3°); IR (KBr) 2958, 1745, 1725, 1638, 1255, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (d, 3 H, J = 6.8 Hz), 1.54 (s, 3 H), 1.78 (d, 3 H, J = 7.2 Hz), 2.36 (m, 3 H), 3.77 (s, 3 H), 7.24 (m, 1 H); HRMS calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1049.

(4*R*,5*S*)-5-(Hydroxymethyl)-4-methyl-5-[[(3,5-dinitrobenzoyl)oxy]methyl]-5-pentanolide (54). To a stirred suspension of **46** (125.7 mg, 0.33 mmol) in a mixture of CCl_4 (1.5 mL), MeCN (1.5 mL), and water (2.3 mL) were added $NaIO_4$ (292 mg, 1.4 mmol) and $RuCl_3 \cdot 3H_2O$ (1.9 mg). After 4 h the reaction mixture was diluted with CH_2Cl_2 (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the organic phase was dried ($MgSO_4$). The solvent was removed, the residue was

dissolved in Et_2O (30 mL), and the solution was passed through a short pad of Celite. Removal of the solvent gave crude **53** which was dissolved in THF (3 mL) and refluxed with camphorsulfonic acid (92 mg, 0.13 mmol) for 6 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and was washed sequentially with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Flash column chromatography (1:1 EtOAc–hexane to 3:2 EtOAc–hexane) of the crude product on silica provided 25.2 mg of **54** and 28.3 mg of a mixture of **54** and **55** (4:1) as thick oils.

Compound **54**: $[\alpha]^{22}_D$ +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, 3 H, J = 6.8 Hz), 1.88–2.09 (m, 2 H), 2.24 (m, 1 H), 2.51–2.75 (m, 2 H), 3.20 (bs, 1 H), 3.84 (d, 1 H, J = 12.5 Hz), 3.99 (d, 1 H, J = 12.5 Hz), 4.57 (d, 1 H, J = 12.1 Hz), 4.69 (d, 1 H, J = 12.1 Hz), 9.10–9.25 (m, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.6, 25.0, 29.4, 31.0, 62.4, 66.7, 86.4, 122.8, 129.5, 133.2, 148.8, 162.3, 171.1. Anal. Calcd for $C_{15}H_{16}N_2O_9$: C, 48.92; H, 4.38; N, 7.61. Found: C, 48.58; H, 4.50; N, 7.39.

(4*R*,5*R*)-5-(Iodomethyl)-4-methyl-5-[[(3,5-dinitrobenzoyl)oxy]methyl]-5-pentanolide (56). To a C_6H_6 solution (4.5 mL) of **54** (49 mg, 0.13 mmol) were added sequentially Ph_3P (30 mg, 0.31 mmol), imidazole (41 mg, 0.6 mmol), and I_2 (74 mg, 2.2 mmol) and the mixture was refluxed for 1.5 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatographic purification (1:1 EtOAc–hexane) of the crude product on silica yielded 51 mg (82%) of **56** 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, 3 H, J = 7.2 Hz), 1.94 (m, 1 H), 2.12 (m, 1 H), 2.44 (m, 1 H), 2.66 (m, 2 H), 3.39 (d, 1 H, J = 11.1 Hz), 3.58 (d, 1 H, J = 11.1 Hz), 4.74 (d, 1 H, J = 12.1 Hz), 4.79 (d, 1 H, J = 12.1 Hz), 9.13–9.27 (m, 3 H). Due to its instability compound **56** was used without further purification.

Ester 57. To a MeOH solution (1 mL) of **56** (43 mg, 0.09 mmol) was added anhydrous K_2CO_3 (5 mg). After 30 min the mixture was diluted with EtOAc and washed with brine, and the organic phase was dried ($MgSO_4$). Purification of the crude product by flash column chromatography (1:1 EtOAc–hexane) on silica gave 13 mg (79%) of **57**: $[\alpha]^{22}_D$ +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, 3 H, J = 7.2 Hz), 1.49–1.86 (m, 4 H), 2.37 (m, 2 H), 2.66 (d, 1 H, J = 4.8 Hz), 2.92 (d, 1 H, J = 4.8 Hz), 3.68 (s, 3 H), 3.68–3.84 (m, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.1, 27.3, 32.2, 35.6, 49.41, 51.7, 60.3, 61.9, 173.9. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.61; H, 8.28.

(2*S*)-2-[(1*R*)-1,5-Dimethyl-4-hexenyl]-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]oxirane (58). To a DMF solution (1.5 mL) of **44** (1.5 g, 8.2 mmol) were added sequentially imidazole (1.4 g, 20.4 mmol), *tert*-butyldiphenylsilyl chloride (2.8 mL, 10.6 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The reaction mixture was stirred for 5 h, diluted with Et_2O (200 mL), and washed with water (75 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL), and the organic phase was dried (Na_2SO_4). The crude product was purified by flash column chromatography (1:6 Et_2O–hexane) on silica to provide 3.1 g (90%) of **58** 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, 3 H, J = 6.9 Hz), 1.04 (s, 9 H), 1.10 (m, 1 H), 1.54 (m, 1 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 1.69 (m, 1 H), 1.94 (m, 2 H), 2.57 (d, 1 H, J = 5.1 Hz), 2.78 (d, 1 H, J = 5.1 Hz), 3.74 (d, 1 H, J = 11.7 Hz), 3.78 (d, 1 H, J = 11.7 Hz), 5.05 (m, 1 H), 7.37–7.76 (m, 10 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.3, 17.7, 19.3, 25.7, 25.9, 26.8, 33.0, 35.3, 48.8, 62.5, 63.6, 124.3, 127.7, 129.7, 129.8, 131.8, 133.1, 133.2, 135.6, 135.7.

Oxirane 59. O_3 was passed through a cold (−78 °C) CH_2Cl_2 solution (10 mL) of **58** (3.03 g, 7.2 mmol) until a blue color persisted. The mixture was stirred for 45 min at −78 °C, an the excess O_3 was removed with a stream of N_2. The solvent was removed, the resultant oil was dissolved in cold (−10 °C) Me_3CO, and Jones' reagent was added until the reaction mixture was orange in color. The mixture was stirred for 45 min and was treated with excess *i*-PrOH and filtered through a Celite pad. The filtrate was concentrated in vacuo, the residue was dissolved in Et_2O (50 mL), and the solution was treated with CH_2N_2. After 5 h the solvent was removed and the crude product was purified by flash column chromatography (1:7 EtOAc–hexane) on silica to yield 1.38 g (45%) of **59** 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, 3 H, J = 6.9 Hz), 1.04 (s, 9 H), 1.60 (m, 2 H), 1.85 (m, 1 H), 2.35 (m, 2 H), 2.54 (d, 1 H, J = 5.0 Hz), 2.75 (d, 1 H, J = 5.0 Hz), 3.64 (s, 3 H), 3.73 (d, 1 H, J = 11.7 Hz), 3.78 (d, 1 H, J = 11.7 Hz), 7.37–7.68 (m, 10 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.5, 19.2, 26.8, 28.2, 32.1, 35.8, 48.9, 51.5, 61.93, 63.6, 127.7, 129.7, 129.8, 133.1, 133.2, 135.6, 135.7, 174.0. Anal. Calcd for $C_{25}H_{34}SiO_4$: C, 70.39; H, 8.04. Found: C, 70.07; H, 7.99.

(4*R*,5*S*)-5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-(hydroxymethyl)-4-methyl-5-pentanolide (60). To a cold (−10 °C) $CHCl_3$ solution (1 mL) of **59** (35 mg, 0.08 mmol) was added CF_3CO_2H (0.03 mL, 0.39 mmol), and the mixture was allowed to warm to 0 °C over a period of 1 h. The reaction mixture was diluted with C_6H_6 (1 mL), and the solvent was removed in vacuo. Purification of the crude product by flash column chromatography (1:1 EtOAc–hexane) on silica yielded 16.8 mg (50%) of **60**: $[\alpha]^{22}_D$ +13.14° (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, 3 H, J = 6.9 Hz), 1.05 (s, 9 H), 1.85 (m, 2 H), 2.31 (bs, 1 H), 2.45 (m, 2 H), 2.65 (m, 1 H), 3.70 (m, 2 H), 3.64 (d, 1 H, J = 11.0 Hz), 3.71 (d, 1 H, J = 11.0 Hz), 7.36–7.66 (m, 10 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.3, 19.3, 25.2, 26.8, 29.5, 29.6, 63.4, 65.3, 88.2, 127.9, 123.0, 132.5, 132.8, 135.6, 135.7, 171.5. Anal. Calcd for $C_{24}H_{32}SiO_4$: C, 69.87; H, 7.84. Found: C, 69.49; H, 7.67.

(4*R*,5*R*)-5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-(iodomethyl)-4-methyl-5-pentanolide (61). To a C_6H_6 solution (1.5 mL) of **60** (17 mg, 0.04 mmol) were added Ph_3P (24 mg, 0.09 mmol), imidazole (13 mg, 0.18 mmol), and I_2 (22 mg, 0.09 mmol), and the mixture was refluxed for 1.5 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by flash column chromatography (1:3 EtOAc–hexane) on silica yielded 18.8 mg (90%) of **61**: $[\alpha]^{22}_D$ −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, 9 H), 1.05 (d, 3 H, J = 7 Hz), 1.40–1.80 (m, 3 H), 2.40 (m, 2 H), 3.25 (d, 1 H, J = 11 Hz), 3.55 (d, 1 H, J = 11 Hz), 3.80 (bs, 2 H), 7.30–7.80 (m, 10 H).

(2*S*,3*R*)-3,7-Dimethyl-2-hydroxy-2-(hydroxymethyl)-6-octenyl Pivalate (63). To a C_6H_6 solution (6 mL) of **44** (119.2 mg, 0.64 mmol) and pivalic acid (100 mg, 0.96 mmol) was added neat $Ti(O\text{-}i\text{-}Pr)_4$ (0.28 mL, 0.96 mmol). After 20 min, the C_6H_6 was evaporated and the residue was dissolved in Et_2O (100 mL). Saturated aqueous Na_2SO_4 (0.5 mL) was added, and the mixture was stirred vigorously for 4 h. The colloidal suspension was filtered through a short Celite pad, and the filtrate was dried ($MgSO_4$). The solvent was removed, and the crude product was purified by flash column chromatography (1:1 EtOAc–hexane) on silica to provide 93.2 mg (51%) of **63** 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, 3 H, J = 6.9 Hz), 1.12–1.26 (m, 3 H), 1.22 (s, 9 H), 1.61 (s, 3 H), 1.65 (m, 2 H), 1.68 (s, 3 H), 1.92 (m, 1 H), 2.12 (m, 1 H), 3.54 (q, 2 H, J = 11.7, 3.6 Hz, AB), 4.09 (d, 1 H, J = 11.7 Hz), 4.26 (d, 1 H, J = 11.7 Hz), 5.08 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.3, 17.7, 25.7, 26.2, 27.2, 30.6, 36.8, 39.0, 64.1, 65.6, 75.5, 124.2, 131.9, 179.3. Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.84; H, 10.66.

(4*S*)-2,2-Dimethyl-4-[1(1*R*)-1,5-dimethyl-4-hexenyl]-4-[(pivalyloxy)methyl]-1,3-dioxolane (64). To a CH_2Cl_2 solution (6 mL) of **63** (94.5 mg, 0.33 mmol) were added 2,2-dimethoxypropane (0.4 mL, 3 mmol) and camphorsulfonic acid (10 mg). After 5 h, solid $NaHCO_3$ was added and the mixture was stirred for 15 min. The solvent was removed, and the crude product was purified by flash column chromatography (1:10 EtOAc–hexane) on silica to yield 105 mg (98%) of **64**: $[\alpha]^{22}_D$ +5.98° (c = 3.59, $CHCl_3$); IR (neat) 2978, 1734, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3 H, J = 6.8 Hz), 1.16 (m, 1 H), 1.21 (s, 9 H), 1.39 (s, 3 H), 1.41 (m, 1 H), 1.43 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.76 (m, 1 H), 1.90 (m, 1 H), 2.15 (m, 1 H), 3.83 (d, 1 H, J = 8.8 Hz), 3.90 (d, 1 H, J = 8.8 Hz), 3.97 (d, 1 H, J = 11.6 Hz), 4.16 (d, 1 H, J = 11.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 17.7, 25.7, 26.4, 26.6, 27.2, 27.2, 32.1, 38.6, 28.9, 65.0, 69.4, 84.5, 109.7, 124.1, 131.9, 178.4.

(4*R*)-2,2-Dimethyl-4-[1(1*R*)-1,5-dimethyl-4-hexenyl]-4-(hydroxymethyl)-1,3-dioxolane (65). To a suspension of $LiAlH_4$

(20 mg, 0.45 mmol) in Et_2O (5 mL) was added an Et_2O solution of **64** (105 mg, 0.30 mmol), and the mixture was refluxed for 1 h. Water (0.02 mL) was cautiously added at 0 °C, followed by 0.2 mL of 15% NaOH and a further 0.6 mL of water. The mixture was stirred for 10 min at room temperature, the solution was filtered, and the precipitate was washed with EtOAc. The combined organic phase was dried ($MgSO_4$), the solvent was removed, and the crude product was purified by flash column chromatography (1:3 EtOAc–hexane) on silica to give 65.3 mg (90%) of **65**: $[\alpha]^{22}_D$ +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, 3 H, J = 7.0 Hz), 1.07 (m, 1 H), 1.38 (m, 1 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.88 (m, 3 H), 2.15 (m, 1 H), 3.47 (dd, 1 H, J = 11.4, 6.7 Hz), 3.66 (dd, 1 H, J = 11.4, 5.8 Hz), 3.85 (q, 2 H, J = 8.7, 4.2 Hz, AB), 5.08 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.2, 17.7, 25.7, 26.4, 26.8, 27.3, 31.8, 37.8, 62.7, 68.8, 86.4, 109.5, 124.1, 131.9. Anal. Calcd for $C_{14}H_{26}O_3$: O, 69.37; H, 10.82. Found: C, 69.34; H, 11.08.

(4*S*)-4-Carbomethoxy-2,2-dimethyl-4-[(1*R*)-1,5-dimethyl-4-hexenyl]-1,3-dioxolane (66). To a DMF solution (6 mL) of **65** (559 mg, 2.3 mmol) at room temperature was added solid pyridinium dichromate (3.5 g, 9.2 mmol). After 30 h the reaction mixture was poured into 60 mL of water and extracted with Et_2O (4 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 395 mg (67%) of the acid as an oil: IR (neat) 3200 (broad), 2932, 1721, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3 H, J = 6.7 Hz), 1.26 (m, 2 H), 1.42 (m, 1 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.88 (m, 1 H), 2.07 (m, 1 H), 3.98 (d, 1 H, J = 9.3 Hz), 4.36 (d, 1 H, J = 9.3 Hz), 5.05 (m, 1 H).

The acid (395 mg, 1.54 mmol) was dissolved in Et_2O and treated with excess CH_2N_2. The solvent was removed, and the crude product was purified by column chromatography (1:7 EtOAc–hexane) on silica to provide 412 mg (99%) of **66** 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, 3 H, J = 6.8 Hz), 1.20 (m, 1 H), 1.38 (m, 1 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.89–2.10 (m, 3 H), 3.77 (s, 3 H), 3.89 (d, 1 H, J = 8.9 Hz), 4.33 (d, 1 H, J = 8.9 Hz), 5.05 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.7, 17.7, 25.6, 25.7, 25.9, 26.1, 31.7, 38.5, 52.2, 69.9, 87.6, 110.9, 1234,0, 131.9, 174.1. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.81; H, 9.47.

(4*S*)-2,2-Dimethyl-4-[(1*R*)-1,5-dimethyl-4-hexenyl]-4-[[2-(trimethylsilyl)ethoxy]carbonyl]-1,3-dioxolane (67). To a solution of **66** (723 mg, 2.7 mmol) in 2-(trimethylsilyl)ethanol (7.7 mL) was added neat $Ti(OEt)_4$ (0.84 mL, 4.0 mmol), and the mixture was stirred at 100 °C. After 36 h the MeOH was removed in vacuo, a further quantity of 2-(trimethylsilyl)ethanol (3 mL) was added, and the reaction mixture was stirred for another 24 h at 100 °C. The mixture was cooled to room temperature, and the solvent was removed. The residue was dissolved in Et_2O (150 mL) and stirred vigorously with saturated aqueous Na_2SO_4 (1 mL) for 2 h. The precipitate was removed by filtration through a short Celite pad, the filtrate was concentrated, and the crude product was purified by flash column chromatography (1:10 EtOAc–hexane) on silica to yield 861 mg (93%) of **67** 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, 9 H), 0.95 (d, 3 H, J = 6.7 Hz), 1.04 (t, 2 H, J = 8.6 Hz), 1.20 (m, 1 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.43 (m, 1 H), 1.59 (s, 3 H), 1.68 (s, 3 H), 1.90 (m, 2 H), 2.06 (m, 1 H), 3.88 (d, 1 H, J = 9.0 Hz), 4.24 (m, 2 H), 4.31 (d, 1 H, J = 9.0 Hz), 5.06 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.6, 13.6, 17.6, 17.7, 25.7, 25.8, 25.9, 26.1, 31.7, 38.3, 63.5, 69.8, 87.5, 110.7, 124.0, 131.8, 173.7. Anal. Calcd for $C_{19}H_{36}SiO_4$: C, 64.00; H, 10.19. Found: C, 64.21; H, 10.48.

(4*R*)-4-[(4*S*)-2,2-Dimethyl-4-[[2-(trimethylsilyl)ethoxy]carbonyl]-1,2-dioxolanyl]pentanoic Acid (69). O_3 was passed through a cold (−78 °C) CH_2Cl_2 solution (4 mL) of **67** (251 mg, 0.70 mmol) until a blue color persisted. The mixture was stirred for 45 min at −78 °C, and excess O_3 was removed by passing a stream of N_2 through the solution. Me_2S (0.31 mL, 4.2 mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 7 h. The mixture was washed with brine, the organic phase was dried ($MgSO_4$), and the solvent was removed to yield 226 mg (98%) of crude aldehyde. The aldehyde was dissolved in a mixture of CCl_4 (1.6 mL), MeCN (1.6 mL), and phosphate buffer (pH 7, 2.4 mL) and was stirred with $NaIO_4$ (220 mg, 1.02 mmol) and $RuCl_3 \cdot 3H_2O$ (2%) for 20 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The organic phase was dried ($MgSO_4$), the solvent was evaporated and the crude product was purified by column chromatography (1:1–2:1 EtOAc–hexane) on silica to provide 160 mg (67%) of **69** 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, 9 H), 0.97 (d, 3 H, J = 6.7 Hz), 1.05 (bt, 2 H, J = 8.8 Hz), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.47 (m, 1 H), 1.81 (m, 1 H), 1.98 (m, 1 H), 2.32 (m, 1 H), 2.47 (m, 1 H), 3.94 (d, 1 H, J = 9.15 Hz), 4.27 (m, 2 H), 4.31 (d, 1 H, J = 9.15 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.6, 13.5, 17.6, 25.5, 26.1, 26.7, 31.9, 38.1, 63.9, 69.8, 87.0, 111.1, 173.6, 179.4; HRMS calcd for $C_{15}H_{27}SiO_6$ (M^+ − 15) 331.1577, found 331.1577.

(4*R*,5*S*)-5-[[2-(Trimethylsilyl)ethoxy]carbonyl]-5-(hydroxymethyl)-4-methyl-5-pentanolide (70). An HOAc–water (4:1) solution (2 mL) of **68** (72 mg, 0.208 mmol) was heated at 75 °C for 8 h. The solvent was evaporated, and water was removed by azeotropic distillation with toluene to give 61 mg (96%) of **69** which was used without further purification: $[\alpha]^{24}_D$ +1.8° (c = 3.74, $CHCl_3$); IR (neat) 3628-2719 (bs), 3462, 2957, 1716, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (s, 9 H), 0.86–1.50 (m, 5 H with d, J = 6.8 Hz), 1.45–1.70 (m, 2 H), 1.90 (m, 1 H), 2.60–2.70 (m, 2 H), 3.70 (dd, 2 H, J = 4.7, 9.5 Hz), 4.30 (m, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ −1.6, 12.9, 17.5, 26.2, 31.4, 36.8, 65.1, 66.3, 81.0, 175.4, 178.3.

To a cold (0 °C) MeCN solution (2 mL) of crude **69** (31 mg, 0.1 mmol) were added 2-chloro-1-methylpyridinium iodide (67.5 mg, 0.3 mmol) and 4-(dimethylamino)pyridine (61 mg, 0.5 mmol). The mixture was stirred for 3 h at 0 °C and for 10 h at room temperature before being filtered through a pad of Celite and silica gel. Evaporation of the solvent from the filtrate, followed by flash column chromatography (50:50:1 EtOAc–hexane–HOAc) of the crude product on silica, gave 21 mg (74%) of **70**: $[\alpha]^{24}_D$ +36.4° (c = 0.11, $CHCl_3$); IR (neat) 3467 (bs), 2955, 1749, 1285, 1252, 1213, 1150, 1108, 1077, 1039, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 1.30 (m, 5 H; with D_2O, d, J = 7.2 Hz), 1.72 (m, 1 H), 1.87 (m, 1 H), 2.40 (m, 1 H), 2.58 (m, 2 H), 3.89 (m, 2 H), 4.33 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 12.9, 17.5, 24.7, 25.4, 29.4, 65.0, 65.3, 88.8, 169.5, 171.7. Anal. Calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found: C, 54.42; H, 8.41.

MOM Ether 71. To a cold (0 °C) THF solution (2 mL) of **70** (300 mg, 1.04 mmol) and $(i\text{-}Pr)_2NEt$ (2.7 mL, 15.0 mmol) was added $ClCH_2OMe$ (1.0 mL, 12 mmol). After 15 h at 50 °C, water was added and the mixture was extracted with Et_2O. The organic phase was washed with cold (0 °C) aqueous 5% HCl, saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$), the solvent was removed and the crude product was purified by column chromatography (1:1 EtOAc–hexane) on silica to give 315 mg (91%) of **71**: $[\alpha]^{24}_D$ −54.2° (c = 0.24, $CHCl_3$); IR (neat) 2959, 2895, 1752, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 1.05 (m, 5 H; with D_2O, d, J = 6.9 Hz), 1.71 (m, 1 H), 1.87 (m, 1 H), 2.36 (m, 1 H), 2.57 (dd, 2 H, J = 5.5, 8.9 Hz), 3.40 (s, 3 H), 3.80 (d, 1 H, J = 10.6 Hz), 3.88 (d, 1 H, J = 10.8 Hz), 4.31 (m, 2 H), 4.63 (dd, 2 H, J = 6.6, 19.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.7, 13.0, 17.4, 24.6, 25.3, 30.2, 55.4, 64.6, 69.8, 87.9, 96.7, 169.2, 170.9. Anal. Calcd for $C_{15}H_{28}O_6Si$: C, 54.19; H, 8.49. Found: C, 53.99; H, 8.57.

Ethylidene Lactone 72. To a cold (−60 °C) THF solution (1.5 mL) of *N*-isopropylcyclohexylamine (234 mg, 1.66 mmol) was added a hexane solution (1.03 mL) of *n*-BuLi (1.60 mmol). After 20 min a THF solution (1.5 mL) of **71** (345 mg, 1.04 mmol) was added, and the temperature was maintained between −50 and −60 °C for 45 min. Freshly distilled acetaldehyde (0.10 mL, 1.79 mmol) was added, and the mixture was stirred for 45 min at −60 °C followed by warming to −20 °C and stirring for a further 10 min. The mixture was added to a solution (1:1) of aqueous 1 M HCl and saturated aqueous NH_4Cl and was extracted with Et_2O. The organic phase was washed with aqueous 0.5 M HCl, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), the solvent was removed, and the crude product was purified by column chromatography (1:1 EtOAc–hexane) on silica to yield 35 mg (10%) of recovered **71** and 332 mg (94% based on recovered **71**) of a mixture of the four stereoisomeric β-hydroxy δ-lactones.

To a cold (0 °C) CH_2Cl_2 solution (15 mL) of the latter material (332 mg) were added Et_3N (1.9 mL, 13.6 mmol), Ac_2O (1.0 mL, 10 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. After 6 h the solution was cooled to 0 °C, MeOH (1 mL) was added, and stirring was continued for a further 1 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with Et_2O. The organic phase was washed with cold (0 °C) 0.5 M HCl, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), and the solvent was removed to afford a mixture of stereoisomeric acetates. A cold (4 °C) CH_2Cl_2 solution (15 mL) of the latter material and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.375 mL, 2.5 mmol) was stirred for 15 h, Et_2O (150 mL) was added, and the mixture was washed with cold (0 °C) 0.5 M HCl, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), the solvent was removed, and the crude product was purified by column chromatography (1:2 EtOAc–hexane) on silica to give 250 mg (75%) of **72**: $[\alpha]^{20}_D$ +25.7° (c = 1.4, $CHCl_3$); IR (neat) 2953, 2897, 1749, 1729, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.4 (s, 9 H), 1.00 (m, 5 H; with D_2O, d, J = 7.1 Hz), 1.76 (d, 3 H, J = 7.1 Hz), 2.35 (bs, 1 H), 2.50 (m, 1 H), 3.36 (s, 3 H), 3.81 (d, 1 H, J = 10.5 Hz), 3.91 (d, 1 H, J = 10.3 Hz), 4.30 (m, 2 H), 4.62 (d, 1 H, J = 6.6 Hz), 4.68 (d, 1 H, J = 6.6 Hz), 7.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6, 14.0, 17.4, 28.8, 30.4, 55.5, 64.6, 70.5, 86.5, 96.8, 97.0, 123.1, 142.9, 164.6, 170.8.

δ-Lactone 73. A THF solution (6 mL) of **72** (145 mL, 0.405 mmol) and 3 M aqueous HCl (13 mL) was stirred for 1 h at room temperature and was heated to 35 °C for an additional 10 h. The mixture was cooled to 0 °C neutralized with 0.5 M aqueous NaOH, and extracted with Et_2O. The organic phase was washed with brine and was dried ($MgSO_4$). The solvent was removed, and the crude product was purified by column chromatography (1:1 EtOAc–hexane) on silica to give 114 mg (90%) of **73**: $[\alpha]^{20}_D$ +20.0° (c = 0.80, $CHCl_3$); IR (neat) 3400 (bs), 2953, 1750, 1729, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 1.00 (m, 5 H; with D_2O, d, J = 7.1 Hz), 1.77 (d, 3 H, J = 7.3 Hz), 2.20 (bs, 1 H), 2.35 (s, 2 H), 2.53 (m, 1 H), 3.86 (d, 1 H, J = 11.8 Hz), 3.94 (d, 1 H, J = 11.8 Hz), 4.31 (m, 2 H), 7.25 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6, 13.9, 14.1, 17.4, 28.9, 29.6, 54.9, 65.9, 87.2, 123.1, 143.4, 164.7, 171.4. Anal. Calcd for $C_{15}H_{26}O_5Si$: C, 57.29; H, 8.34. Found: C, 57.50; H, 8.39.

Hydroxy Acid 74. To a cold (0 °C) THF solution (2.5 mL) of **73** (220 mg, 0.70 mmol) were added water (0.4 mL), $RuCl_3 \cdot 3H_2O$ (133 mg, 0.79 mmol), and an aqueous 30% solution of H_2O_2. The mixture was stirred at 0 °C for 0.5 h and at room temperature for a further 2 h. The solution was acidified to pH 1 with 0.5 M aqueous HCl and was extracted with Et_2O and dried (Na_2SO_4). Removal of the solvent and purification of the crude product by column chromatography (200:100:3 EtOAc–hexane–HOAc) gave 139 mg (60%) of **74**: $[\alpha]^{20}_D$ -22.5° (c = 0.15, $CHCl_3$); IR (neat) 3457, 3451, 2956, 2897, 1723, 1686, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.86 (d, 3 H, J = 6.5 Hz), 1.10 (m, 2 H), 1.83 (d, 3 H, J = 7.2 Hz), 2.21–2.33 (m, 3 H), 3.70 (s, 3 H), 4.30 (m, 2 H), 7.1 (q, 1 H, J = 7.2, 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.7, 12.8, 14.9, 17.2, 27.7, 36.6, 64.9, 66.4, 80.5, 130.2, 142.0, 172.4, 175.5. Anal. Calcd for $C_{15}H_{28}O_6Si$: C, 54.19; H, 8.49. Found: C, 53.90; H, 8.46.

Acetonide 75. To a cold (0 °C) $CHCl_3$ solution (10 mL) of **74** (49 mg, 0.148 mmol) were added dimethoxypropane (2.5 mL) and camphorsulfonic acid (2 mg). After the solution was stirred for 12 h at room temperature water was added and the aqueous phase was extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), the solvent was removed, and the crude product was purified by column chromatography (50:50:1 EtOAc–hexane–HOAc) to give 50 mg (91%) of **75**: $[\alpha]^{20}_D$ +2.0° (c = 0.41, $CHCl_3$); IR (neat) 3500–2800 (b), 2986, 2956, 1749, 1724, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.86 (d, 3 H, J = 6.6 Hz), 1.01 (m, 2 H), 1.43 (d, 6 H, J = 12.1 Hz), 1.83 (d, 3 H, J = 7.2 Hz), 2.28 (m, 4 H), 4.03 (d, 1 H, J = 8.9 Hz), 4.28 (dd, 2 H, J = 9.1, 19.0 Hz), 7.10 (q, 1 H, J = 7.2, 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6, 13.2, 14.9, 17.5, 25.4, 26.0, 28.1, 38.4, 63.7, 70.1, 86.9, 111.0, 130.5, 142.0, 172.3, 173.5. Anal. Calcd for $C_{18}H_{32}O_6Si$: C, 58.03; H, 8.66. Found: C, 57.77; H, 8.91.

9-*O*-(*tert*-Butyldimethylsilyl)retronecine Ester 77. A CH_2Cl_2 solution of **69** (46.3 mg, 0.13 mmol) and 1,3-dicyclohexylcarbodiimide (16.6 mg, 0.08 mmol) was stirred at room temperature for 6 h. The solvent was evaporated in vacuo to afford the crude anhydride **76** which was used without further purification. In a separate flask, n-BuLi (0.16 mL, 0.23 mmol) was added to a THF solution of **31** (63.6 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (5 mg) in THF at 0 °C. After 10 min, the THF solution of **76** was added to this mixture via cannula. After the solution was stirred overnight at room temperature, saturated aqueous NH_4Cl was added and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography on neutral alumina (Brockmann Activity III, 1:2 to 2:1 EtOAc–hexane) to provide 24.8 mg (64%) of **77** 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, 9 H), 0.92 (d, 3 H, J = 6.8 Hz), 1.04 (bt, 2 H, J = 5.8 Hz), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.70–2.10 (m, 5 H), 2.20–2.45 (m, 2 H), 2.65 (m, 1 H), 3.32 (m, 2 H), 3.90 (d, 1 H, J = 8.9 Hz), 3.93 (m, 1 H), 4.20 (q, 2 H, AB, J = 9.2 Hz), 4.25 (m, 3 H), 4.32 (d, 1 H, J = 8.9 Hz), 5.27 (bt, 1 H, J = 2.9 Hz), 5.64 (bd, 1 H, J = 1.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.6, 13.5, 17.6, 18.3, 25.6, 25.9, 26.1, 26.8, 32.4, 34.6, 38.3, 53.6, 60.6, 62.8, 63.8, 69.8, 69.7, 73.8, 75.4, 87.0, 110.9, 123.2, 138.6, 172.4, 173.5; HRMS calcd for $C_{26}H_{46}NSi_2O_7$ (M^+ - 57) 540.2813, found 540.2814.

Retronecine Ester 78. A THF solution (0.5 mL) of **77** (12 mg, 0.02 mmol) was stirred with 5% HF in THF at room temperature for 9 h. The reation mixture was diluted with CH_2Cl_2 and poured into 15% aqueous Na_2CO_3 (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica (20:1 CH_2Cl_2 saturated with NH_4OH–MeOH) yielded 5.4 mg (56%) of **78**: $[\alpha]^{24}_D$ +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, 3 H, J = 7.0 Hz), 1.04 (bt, 2 H, J = 5.8 Hz), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.78 (m, 1 H), 1.94 (m, 1 H), 2.09 (m, 2 H), 2.24 (m, 1 H), 2.36 (m, 1 H), 2.71 (m, 2 H), 3.38 (m, 2 H), 3.90 (d, 1 H, J = 8.9 Hz), 3.99 (d, 1 H, J = 14.7 Hz), 4.17 (bs, 1 H), 4.28 (bt, 2 H, J = 5.8 Hz), 4.32 (d, 1 H, J = 8.9 Hz), 4.36 (bs, 2 H), 5.32 (bs, 1 H), 5.68 (bd, 1 H, J = 1.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ -1.6, 13.5, 17.6, 25.5, 26.1, 26.9, 32.5, 34.5, 37.9, 53.3, 59.9, 62.9, 64.0, 69.4, 74.3, 75.9, 86.9, 111.0, 123.4, 139.0, 172.8, 173.6; HRMS calcd for $C_{24}H_{41}SiNO_7$ 483.2652, found 483.2658.

Chloride 79. To a cold (0 °C) CH_2Cl_2 solution (0.5 mL) of **78** (4.2 mg, 0.009 mmol) were added $MeSO_2Cl$ (1.3 μL, 0.016 mmol) and Et_3N (3.0 μL, 0.02 mmol), and the mixture was stirred for 1 h. To a separate flask was added a THF solution (0.13 mL) of n-Bu_4NF (0.13 mmol), and the solvent was evaporated in vacuo. The residue was dried (vacuum pump) for 1.5 h and was taken up in MeCN. To this solution was added over a period of 2–3 h the previously prepared CH_2Cl_2 solution of **78**. After a further 1.5 h saturated aqueous NH_4Cl was added. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (5 mL) and was poured into 15% aqueous Na_2CO_3. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica (35:1 CH_2Cl_2 saturated with NH_4OH–MeOH) to give 1 mg (45%) of **79**: IR (neat) 2955, 1738, 1172, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3 H, J = 6.9 Hz), 1.02 (m, 2 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 2.85 (m, 1 H), 3.56 (m, 2 H), 3.90 (d, 1 H, J = 9.2 Hz), 4.10 (q, 2 H, AB, J = 13.4 Hz), 4.26 (m, 3 H), 4.31 (d, 1 H, J = 9.2 Hz), 5.49 (bs, 1 H), 5.88 (bs, 1 H).

Desethylideneusaramine Acetonide (80). To an MeCN solution of **79** (1 mg, 1.9 μmol) was added a THF solution (0.1 mL) of n-Bu_4NF. The reaction mixture was stirred for 2 h at 50 °C, and saturated aqueous NH_4Cl was added. The solvents were evaporated, the residue was dissolved in CH_2Cl_2, and the solution was poured into 15% aqueous Na_2CO_3. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica (30:1 CH_2Cl_2 saturated with NH_4Cl–MeOH) gave 0.5 mg (70%) of **80**: IR (neat) 2961, 1742, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, 3 H, J = 6.5 Hz), 1.45 (s, 3 H), 1.46 (s, 3 H), 2.45 (m, 2 H), 4.04 (d, 1 H, J = 12.4 Hz), 4.11

(m, 3 H), 4.59 (m, 1 H), 5.02 (bs, 1 H), 5.52 (d, 1 H, J = 12.4 Hz), 6.26 (bs, 1 H); HRMS calcd for $C_{19}H_{27}NO_6$ 365.1838, found 365.1838.

9-*O*-(*tert*-Butyldimethylsilyl)retronecine–Borane (82). To a THF solution (1 mL) of **31** (60 mg, 0.387 mmol) at room temperature was added dropwise a THF solution of BH_3·THF (0.387 mL, 0.387 mmol). After 10 min, water (0.3 mL) and CH_2Cl_2 were added and the two-phase mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried (Na_2SO_4). Removal of the solvent and purification of the crude product by column chromatography (1:1 EtOAc–hexane) on silica gave 56 mg (86%) of **82**: $[\alpha]^{24}_D$ +59.7° (c = 3.93, $CHCl_3$); mp 49–50 °C; IR (KBr) 3459 (b), 2954, 2890, 2271, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6 H), 0.92 (s, 9 H), J = 13.3 Hz), 2.03 (dd, 1 H, J = 5.3 Hz), 2.30 (m, 1 H), 3.16 (m, 1 H), 3.51 (dd, 1 H, J = 7.4, 9.5 Hz), 3.74 (dd, 1 H, J = 2.8, 14.5 Hz), 4.16 (m, 2 H), 4.25 (bs, 1 H), 4.34 (d, 1 H, J = 11.2 Hz), 4.38 (t, 1 H, J = 4.1 Hz), 5.64 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 25.7, 33.7, 60.1, 63.2, 71.4, 71.5, 89.18, 124.9, 134.52. Anal. Calcd for $C_{14}H_{30}BNO_2$: C, 59.53; H, 10.71; N, 4.96. Found: C, 59.59; H, 10.98; H, 5.13.

Retronecine–Borane Ester 83. To a cold (0 °C) THF solution (1.0 mL) of **75** (50 mg, 0.134 mmol) and Et_3N (0.063 mL, 0.469 mmol) was added $(EtO)_2POCl$ (29 mL, 0.202 mmol). The cooling bath was removed, and the solution was stirred for 3 h. The suspension was filtered through a cotton plug and was added to a separate flask containing a cold (0 °C) THF solution (1 mL) of **82** (114 mg, 0.402 mmol) and a catalytic quantity of 4-(dimethylamino)pyridine to which had been added a hexane solution of n-BuLi (0.245 mL, 0.375 mmol) prepared 0.5 h in advance. The mixture was stirred for 8 h at room temperature. Aqueous saturated NH_4Cl and CH_2Cl_2 were added, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), the solvent was removed, and the crude product was purified by column chromatography (EtOAc–hexane) on silica to give 50 mg (55%) of **83**: $[\alpha]^{23}_D$ +6.7° (c = 1.65, $CHCl_3$); IR (neat) 3415, 2957, 2931, 2858, 2273, 1717, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (t, 9 H, J = 3.8 Hz), 0.06 (d, 6 H, J = 3.8 Hz), 1.41 (d, 3 H, J = 16.0 Hz), 1.75 (d, 3 H, J = 7.2 Hz), 2.00–2.10 (m, 1 H), 2.20–2.30 (m, 3 H), 2.47 (m, 1 H), 3.10 (m, 1 H), 3.60 (dd, 1 H, J = 7.1, 9.5 Hz), 3.80 (m, 1 H), 3.90 (d, 1 H, J = 9.0 Hz), 2.40 (bs, 2 H), 4.24–4.30 (m, 4 H; with D_2O, d, J = 8.9 Hz), 4.40 (bs, 1 H), 5.50 (t, 1 H, J = 4.1 Hz), 5.60 (bs, 1 H), 6.90 (q, 1 H, J = 7.2, 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.6, -5.5, -1.6, 13.1, 14.8, 17.6, 18.3, 25.3, 25.8, 26.1, 28.1, 33.5, 38.2, 59.9, 62.9, 63.8, 71.9, 73.6, 84.6, 86.8, 110.9, 119.6, 130.8, 137.1, 140.5, 166.0, 173.6; HRMS calcd for $C_{32}H_{60}BNO_7Si_2$ 636.404, found 636.403.

Hydroxy Ester 84. To a MeOH solution (1.1 mL) of **83** (12.0 mg, 17.6 mmol) were added water (0.5 mL) and solid NH_4F (13 mg, 0.351 mmol). The mixture was heated at 60–65 °C for 6 h, and the solvent was removed. CH_2Cl_2 was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), the solvent was removed, and the crude product was purified by column chromatography (EtOAc–hexane) on silica to give 6.0 mg (65%) of **84**: $[\alpha]^{24}_D$ +12.8° (c = 0.46, $CHCl_3$); IR (neat) 3509 (bs), 2954, 2272, 1714, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, 9 H, J = 2.8 Hz), 0.81 (d, 3 H, J = 6.8 Hz), 1.05 (m, 2 H), 1.25 (m, 3 H), 1.43 (d, 6 H, J = 18.9 Hz), 1.81 (d, 3 H, J = 7.2 Hz), 2.10–2.53 (m, 6 H), 3.25 (m, 1 H), 3.86 (m, 1 H), 3.99 (d, 1 H, J = 8.9 Hz), 4.18–4.30 (m, 4 H; with D_2O, d, J = 8.8 Hz), 4.44 (bs, 1 H), 5.40 (m, 1 H), 5.60 (bs, 1 H), 6.93 (q, 1 H, J = 7.2, 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6, 13.2, 14.8, 17.6, 25.3, 26, 27.9, 33.3, 37.9, 59.5, 62.7, 63.9, 69.3, 71.9, 74.2, 84.8, 86.6, 110.9, 120.6, 130.81, 137.3, 140.9, 166.6, 173.7; HRMS calcd for $C_{26}H_{46}BNO_7Si$ 522.317, found 522.317.

Usaramine Acetonide–Borane (85). To a CH_2Cl_2 solution (5 mL) of **84** (23 mg, 43.9 mmol) was added $MeSO_2Cl$ (16.1 mL, 79 mmol) and Et_3N (13.4 mL, 97 mmol). After 2 h at room temperature the mixture was added to a warm (30 °C) MeCN solution (14 mL) of n-Bu_4NF (0.614 mmol) over a period of 2 h. After the addition was complete, the temperature was raised and maintained at 50 °C for 1.5 h. The solvent was removed, and the crude product was purified by column chromatography (EtOAc–hexane) on silica to give 13 mg (75%) of **85**: $[\alpha]^{24}_D$ +16.3° (c = 0.21, $CHCl_3$); mp 167–168 °C; IR (KBr) 2928, 2274, 1751, 1716, 1657, 1457, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.6 Hz), 1.25 (m, 2 H), 1.48 (s, 3 H), 1.55 (s, 3 H), 1.76 (d, 3 H, J = 7.0 Hz), 1.90 (m, 1 H), 2.14 (d, 1 H, J = 13.9 Hz), 2.23 (m, 1 H), 2.48 (m, 2 H), 2.96 (m, 1 H), 3.55 (m, 1 H), 3.74 (bd, 1 H, J = 13.3 Hz), 4.00 (m, 3 H; with D_2O, d, J = 5.1 Hz), 4.09 (d, 1 H, J = 12.1 Hz), 4.20 (bd, 1 H, J = 15.5 Hz), 4.39 (m, 1 H), 5.20 (m, 1 H), 5.38 (d, 1 H, J = 12.2 Hz), 6.20 (s, 1 H), 6.60 (q, 1 H, J = 7.1, 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 14.1, 14.2, 24.9, 25.8, 29.7, 32.5, 37.5, 59.6, 61.9, 71.4, 74.9, 85.4, 86.6, 99.9, 111.7, 129.9, 132.7, 132.9, 137.1, 168.2, 173.4. Anal. Calcd for $C_{21}H_{32}BNO_6$: C, 62.24; H, 7.98; N, 3.46. Found: C, 62.37; H, 7.94; N, 3.40.

(+)-Usaramine (2). An EtOH solution (1 mL) of **85** (7 mg, 17.3 μmol) was heated to reflux for 1.5 h, and the solvent was removed. A mixture of THF (0.5 mL) and aqueous 1 M HCl (0.5 mL) was added to the residue, and the solution was heated at 35–40 °C for 1 h. Most of the THF was removed by evaporation, and the remaining solution was neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 and was dried (Na_2SO_4). Removal of the solvent and purification of the crude product by column chromatography (MeOH–CH_2Cl_2 saturated with NH_4OH) gave 4.1 mg (67%) of **2**: $[\alpha]^{24}_D$ +6.8° (c = 0.31, EtOH); mp 180–181 °C; IR (KBr) 3496, 3481, 2972, 2958, 1733, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3 H, J = 6.8 Hz), 1.40 (bs, 2 H), 1.74 (d, 3 H, J = 7.1 Hz), 1.79 (m, 1 H), 1.98–2.20 (m, 3 H), 2.50 (m, 2 H), 3.25 (t, 1 H, J = 8.3 Hz), 3.40 (dd, 1 H, J = 4.8, 15.6 Hz), 3.75 (ABq, 2 H, J = 11.2, 3.8 Hz), 3.94 (d, 1 H, J = 16.5 Hz), 4.17 (d, 1 H, J = 11.7 Hz), 4.31 (bs, 1 H), 5.00 (bs, 1 H), 5.44 (d, 1 H, J = 11.8 Hz), 6.24 (s, 1 H), 6.53 (q, 1 H, J = 7.4, 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.1, 29.1, 33.6, 36.7, 52.9, 61.4, 62.5, 66.8, 75.6, 80.9, 99.9, 131.4, 133.3, 135.6, 137.0, 168.8, 175.6; HRMS calcd for $C_{18}H_{25}NO_6$ 351.168, found 351.168.

Acknowledgment. We are grateful to Dr. C. C. J. Culvenor, Animal Health Research Laboratory, Melbourne, Australia, for a sample of natural usaramine, to Professor Koichi Narasaka, University of Tokyo, for IR and NMR spectra of (±)-**24**, to Dr. John Blout and Louis Todaro, Hoffmann-LaRoche, Inc., Nutley, NJ, for the X-ray crystal structure of **49**, and to Dr. Fraser F. Fleming for assistance in the preparation of this manuscript. Financial support was provided by the National Institute for Environmental Health Sciences (ES 03334).

Supplementary Material Available: ORTEP representation of **49** and NMR spectra of new compounds (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.