Daphniphyllum Alkaloids. 17. A Possibly Biomimetic Transformation of the Secodaphnane to the Daphnane Skeleton[1]

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An investigation of conversion of the secodaphnane to the daphnane skeleton has been carried out. Treatment of oxaziridine **16** with various Lewis acids resulted in rearrangements involving migration of the C15–C16 bond. However, oxazolidine **28**, in which the N–O bond is constrained to be roughly antiperiplanar to the C12–C16 bond, ionizes with predominant cleavage of this C–C bond when treated with a variety of trialkylaluminum reagents. The preferred reagent for simple cleavage of the C12–C16 bond is trimethylaluminum, which converts **28** into unsaturated imines **30-32** in approximately 90% yield. The major isomer of this fragmentation process, compound **30**, was converted by the process summarized in Scheme 10 into (±)-daphnan-23-ol (**43**), which has previously been converted into (±)-methyl homodaphniphyllate (**44**). Remarkably, conditions were also found that convert **28** *directly* into the daphnane skeleton. For example, **28** reacts with diisobutylaluminum hydride in toluene to give daphnanes **34** and **35** in approximately 80% yield.

Introduction

We have pointed out that *Daphniphyllum* alkaloids having the the secodaphnane skeleton (e.g., **1**), although generally less abundant than those having the daphnane skeleton (e.g., **4**), must occur earlier in the biosynthetic pathway because the precursor squalenoid skeleton is still intact within the pentacyclic, nitrogen-containing core.[2] The intriguing question remains of how compounds of type **1** are converted into compounds of type **4** (Scheme 1). It has been proposed that this conversion might occur by way of the ring-opened intermediate **3**,[3] and the feasibility of this proposal was demonstrated by preparation of a compound having the ring-opened skeleton of **3** and conversion of this material into methyl homodaphniphyllate (**4**, R = $CH_2CH_2CO_2Me$).[2] This synthesis utilized a secodaphnane having a tertiary ether suitably positioned to undergo Grob-Eschenmoser fragmentation to imine **2**, which was reduced *in situ* to provide **3** (Scheme 1, fragmentation mode A). Although it is possible that fragmentation mode A mimics the biosynthetic conversion of the secodaphnane to the daphnane skeleton, one must also consider the alternative fragmentation mode B, in which initial oxidation of the secodaphnane skeleton occurs on nitrogen and fragmentation occurs with the electrons moving "in the opposite direction", leading to the same imine.

Results

The most simple test of the foregoing hypothesis would be oxidation of a secodaphnane on nitrogen and investigation of the behavior of the resulting hydroxylamine derivative under various solvolytic conditions. However, it was already known that oxidation of methyl homosecodaphniphyllate (**5**) by lead tetraacetate provides the bridgehead imine **6**.[4] Reinvestigation of this reaction with (±)-methyl homosecodaphniphyllate[5] showed that the oxidation does indeed provide imine **6** in 81% yield and revealed the formation of an isomer, the skeletal rearrangement product **7**, which was obtained in 14% yield (Scheme 2). The structure of **7** was elucidated by mass spectrometry and a variety of NMR experiments (DEPT, COSY, HETCOR, and inverse long-range heteronuclear correlation). Details are provided in the supplementary material. The presence of a double bond in **7** was also shown by catalytic hydrogenation of the compound to give **8**, a dihydro product of undefined ring fusion stereochemistry.

The insert in Scheme 2 shows a reasonable mechanistic interpretation of the oxidative rearrangement of **5** to the minor product **7**. It is reasonable to postulate that the triacetoxylead group occupies the position indicated in **9** so as to avoid a serious *syn*-pentane interaction between isopropyl and lead. From this intermediate, heterolysis of the Pb–N bond could be accompanied by simultaneous 1,2-migration, leading to secondary carbocation **10**. Further 1,2-rearrangement of **10** would provide the tertiary carbocation **11**, which can deprotonate to give **7**.

Scheme 2 suggests that there may be two problems in realizing the desired oxidative fragmentation of **1** to **2**. First, there is the intrinsic propensity of **5** to undergo elimination to the bridgehead imine **6**. Second, the conformational preference of the leaving group results in migration of the anti C–C bond, leading to cation **10**. The first problem could be remedied by installation of a non-hydrogen group at the bridgehead position. Attempts to prepare **12** or **13** by addition of methanol or acetic acid to **6** were unsuccessful, but we were able to prepare amino nitrile **14** as reported by Hirata and coworkers.[4] However, treatment of **14** with either lead tetraacetate or mercuric acetate gave only small amounts of imine **6**, resulting from base-catalyzed elimination of HCN (Scheme 3).

⊗ Abstract published in *Advance ACS Abstracts*, February 1, 1995.

(1) For part 16, see Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, XXXX.

(2) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585.

(3) (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Chem. Lett.* **1976**, 1381. (c) Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289.

(4) (a) Toda, M.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1597. (b) Hirata, Y.; Toda, M.; Yamamura, Y. *Tetrahedron* **1972**, *28*, 1477.

(5) (a) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734. (b) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544.

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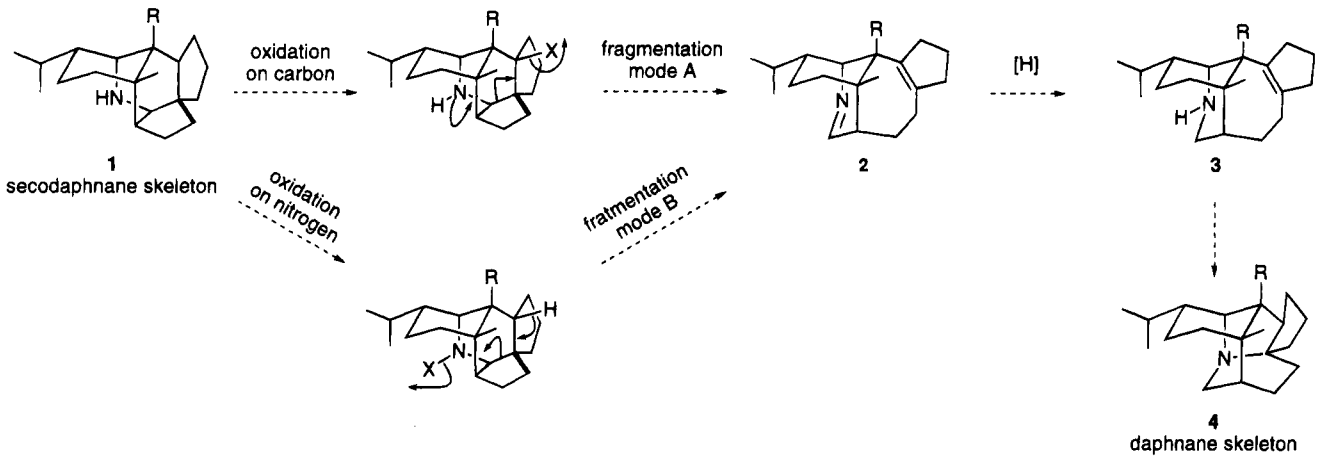
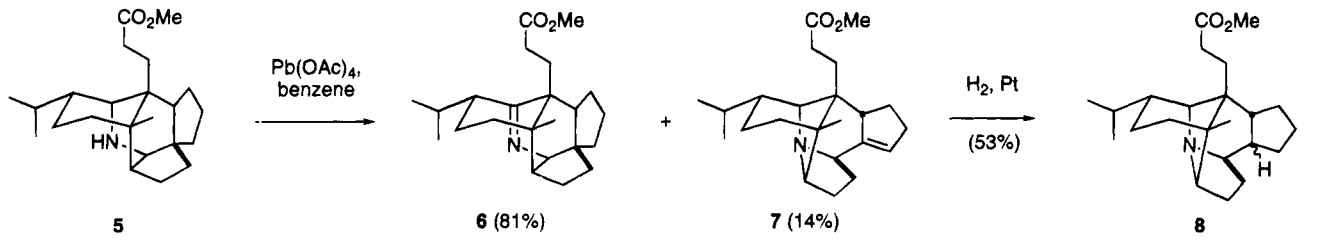
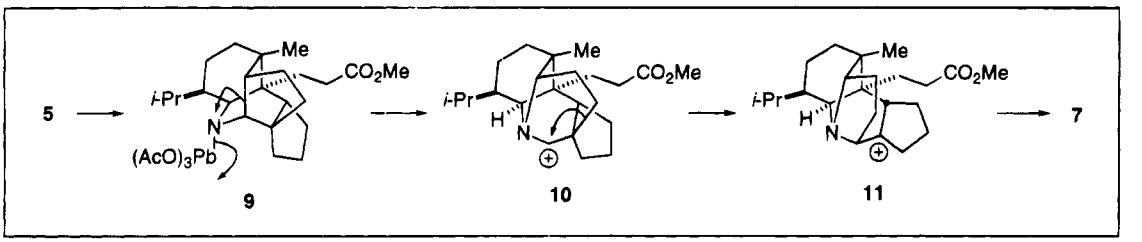
Scheme 1

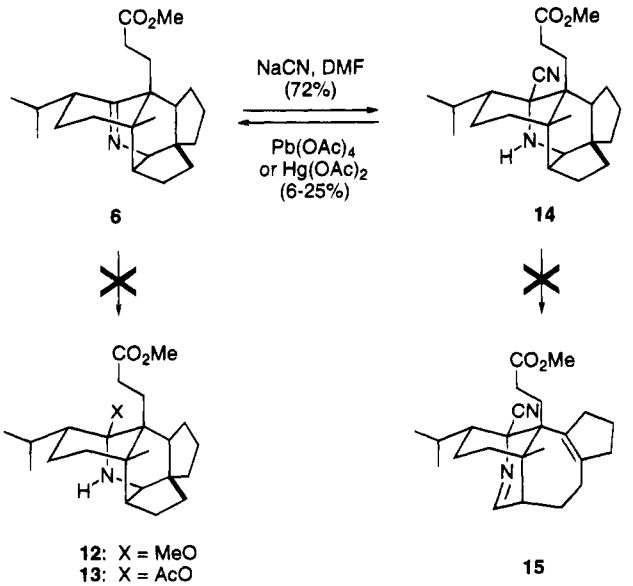


Scheme 2

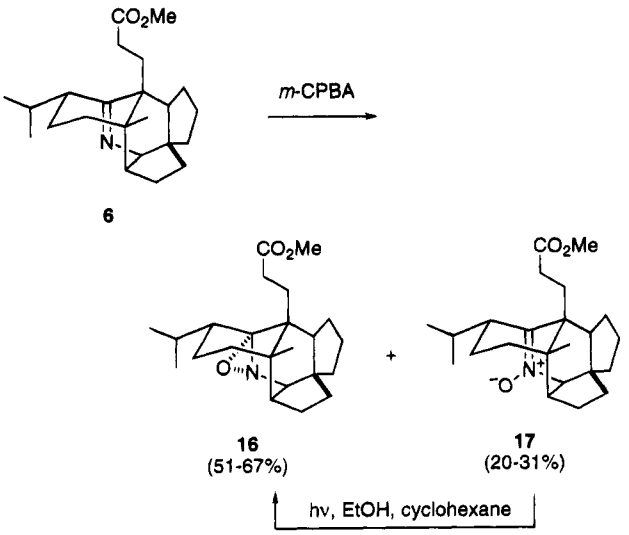




Scheme 3



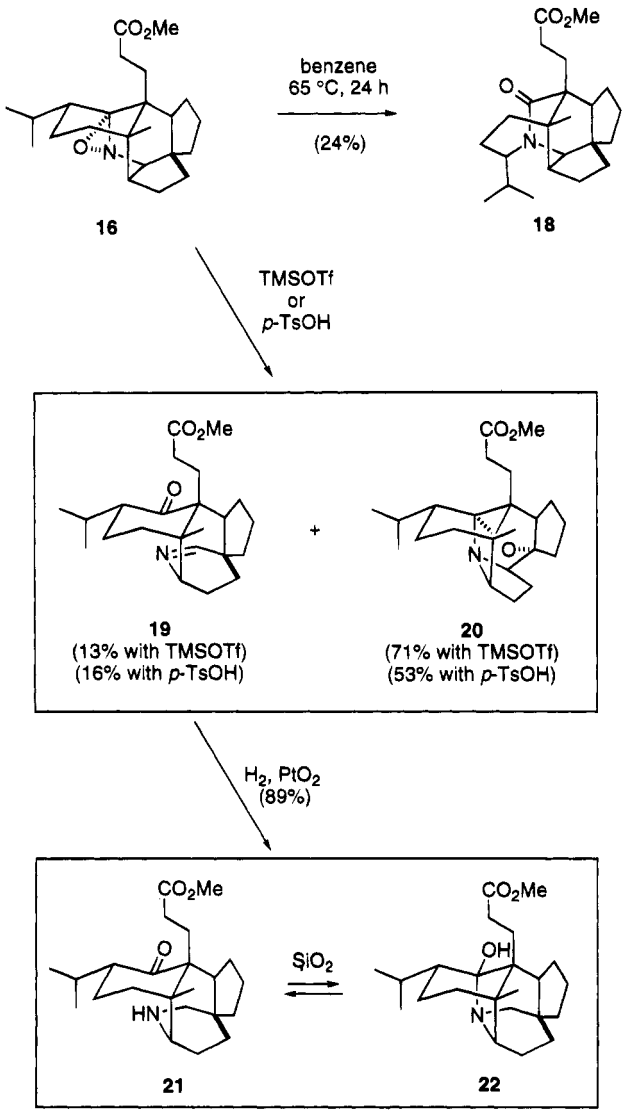
Scheme 4



We reasoned that compound **16**, the oxaziridine derived from **6**, might be a good candidate for fragmentation. Heterolysis of the weak O–N bond would give a nascent nitrenium ion that is blocked from elimination to the bridgehead imine by the oxygen. Oxaziridine **16** was obtained in 51–67% yield by the treatment of **6** with *m*-chloroperoxybenzoic acid (Scheme 4).[6] The oxidation also afforded isomeric nitrone **17** as a byproduct in 20–31% yield. The structures of **16** and **17** were assigned on the basis of spectral analysis (see supplementary material). The presence of the oxaziridine ring in **16** and the nitrone group in **17** was further verified by chemical means. As expected, hydrogenation of **16** over Adams'

(6) (a) Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5769. (b) Pews, R. G. *J. Org. Chem.* **1967**, *32*, 1628.

Scheme 5

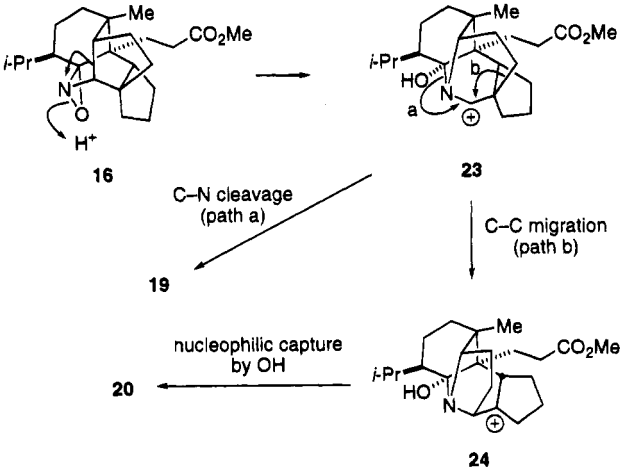


catalyst in methanol for 1 h yielded imine **6** and (±)-methyl homosecodaphniphyllate (**5**). Irradiation of nitrone **17** in 1:1 ethanol:cyclohexane at 254 nm for 2.5 h resulted in partial isomerization to oxaziridine **16**. Photochemical isomerizations of nitrones to oxaziridines are precedented.[7]

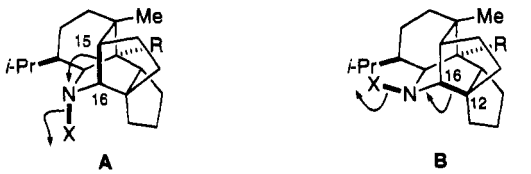
Oxaziridine **16** is partially converted into lactam **18** upon being heated in benzene at 65 °C for 24 h (Scheme 5); similar thermal rearrangements of oxaziridines to amides have been reported by Emmons.[6a] Treatment of oxaziridine **16** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) or *p*-toluenesulfonic acid (*p*-TsOH) produced a mixture of keto imine **19** and the isomeric amino ether **20**. The total yield of this conversion was high, especially with TMSOTf (in addition to 13% of pure **19** and 71% of pure **20**, also obtained was 12% of a mixed fraction), and isomeric amino ether **20** was the major product in both reactions. The structures of **19** and **20** were elucidated by analysis of their spectra (see supplementary material). Catalytic hydrogenation of **19** provided an amino ketone (**21**), which was partially converted into a carbinolamine (**22**) by chromatography on silica gel. A reasonable mechanism for formation of **19** and **20** is set forth in Scheme 6.

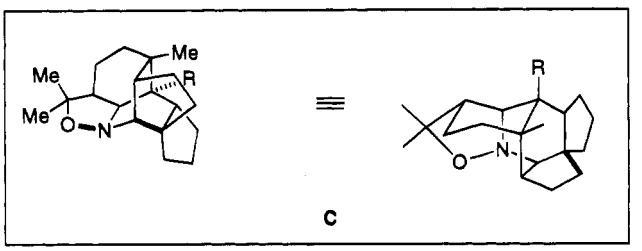
(7) Butler, B. C.; Challis, B. C. *J. Chem. Soc. (B)* **1971**, 778.

Scheme 6



Consideration of the lead tetraacetate oxidation of **5** (Scheme 2) and the acid-catalyzed rearrangment of **16** (Scheme 6) reveals a consistent pattern of involvement of the C15–C16 bond when a leaving group departs from nitrogen, probably because of the configuration at the nitrogen atom. That is, when the N-leaving group is directed away from the isopropyl group, synchronous migraton of the C15–C16 bond is expected because this bond is more-or-less syn-coplanar with the leaving group (see structure **A**, below). What is clearly needed is a way to force the N-leaving group to occupy the other position (see structure **B**, below). One way that this might be accomplished is to tie the leaving group to the isopropyl group; for example, as in the isoxazolidine **C**.

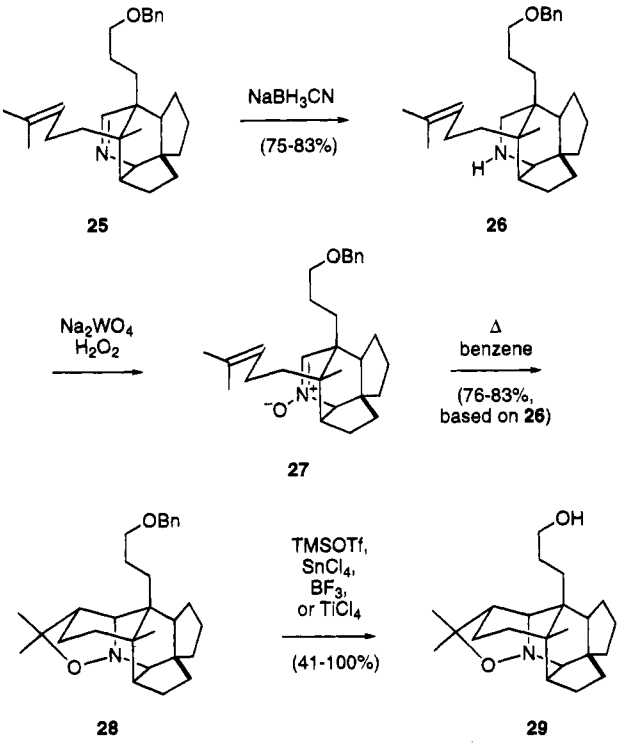




A compound of this structure was easily prepared as shown in Scheme 7. Tetracyclic imine **25**, prepared as previously reported,[5] was reduced by sodium cyanoborohydride[8] to obtain unsaturated amine **26**. Oxidation of **26** with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate dihydrate[9] afforded nitrone **27**, accompanied by a small amount (<5%) of a byproduct, presumed to be the epoxide produced by overoxidation of **27**. Although nitrone could be purified at this stage by careful chromatography, it was found to be more convenient to simply heat a benzene solution of the crude oxidation product, whereupon isoxazolidine **28** was obtained in 76–83% overall yield, based on amine **26**.

(8) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(9) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.

Scheme 7



Initial attempts to bring about rearrangement of oxaziridine **28** were unproductive; treatment with titanium isopropoxide, aluminum chloride, or aluminum isopropoxide gave no reaction. Treatment of **28** with TMSOTf in toluene–methylene chloride gave only alcohol **29** (100% yield). Several other Lewis acids ($SnCl_4$, BF_3, $TiCl_4$) in toluene or toluene–methylene chloride mixtures also gave the debenzylation product **29**, along with smaller amounts of unidentified products. The most promising of these reagents was $TiCl_4$. In addition to 41% of **29**, this reaction gave an inseparable mixture of two products that showed spectral evidence of the imine functional group. However, both were debenzylated. To avoid debenzylation, we examined Lewis acids with less nucleophilic ligands. Treatment of **28** with trimethylaluminum in toluene at 0–25 °C gave a relatively clean mixture of products (Scheme 8), from which compound **30** could be isolated in 50% yield (Table 1). Also obtained in 20–28% yield were the inseparable alkene regioisomers **31** and **32**. Triethylaluminum gave these fragmentation products, along with modest amounts of **33**, obtained as one stereoisomer of undefined stereochemistry, and ether **34**, an isomer of **28** having the daphnane skeleton.

The structure of the major product, unsaturated imine **30**, was established by a combination of spectroscopic analysis and conversion to a compound of known structure. A definitive placement of the double bond was made possible by the DQF-COSY[10] spectrum, which showed the following vicinal couplings: C13-H and C14-H, C14-H and C15-H, C15-H and C16-H. The assignment was reinforced by the HMBC[11] spectrum of **30**, which showed a distinct three-bond coupling between C13-H and C15. Treatment of **30** with trifluoroacetic acid caused isomerization of the C–C double bond to the more stable tetrasubstituted position, providing **31** in 45% yield, along with a similar amount of two unidentified isomers (Scheme 9). Catalytic hydrogenation of **30** gave the pentacyclic amino alcohol **36** in 75% yield. We have no precedent for this remarkable transformation, in which a 1,5-diene system undergoes reductive cyclization under conditions of catalytic hydrogenation.

The skeleton of **30** (and therefore of **31**) was firmly established by converting it into methyl homodaphniphyllate, as shown in Scheme 10. Reduction of the C=N proceeded smoothly upon treatment with sodium cyanoborohydride.[8] The resulting unsaturated amino alcohol **39** was cyclized by the procedure previously developed for creation of the daphnane skeleton.[2,12] Thus, treatment of **39** successively with phenyl isocyanate, hot formic acid, and methanolic KOH provided daphnane **35**. Dehydration of the tertiary alcohol was accomplished by treatment of **35** with thionyl chloride in pyridine;[13] this treatment gave a mixture of tertiary chloride **40** and alkenes **41** and **42**. Catalytic hydrogenation of the minor alkene provided the known daphnan-23-ol (**43**), identified by comparison of its spectral properties with those of an authentic sample.[2] Amino alcohol **43** has previously been converted by Jones oxidation and Fischer esterification into (±)-methyl homodaphniphyllate (**44**).[2,12]

A mechanism that partly accounts for the products seen with trimethylaluminum and triethylaluminum is presented in Scheme 11. It is proposed that **28** coordinates with the Lewis acid to provide **45**, which undergoes the fragmentation depicted by the arrows in Scheme 11 to give tertiary carbocation **46**. It is proposed that a second molecule of the trialkylaluminum compound can coordinate with the imine nitrogen, providing cation **47**. Cations **46** and **47** can eliminate a proton to give **30-32** or be reduced to **33** if the trialkylaluminum reagent has β-hydrogens. In addition, cation **46** can cyclize to give the secondary carbocation **48**, which can cyclize to amino ether **34**. We think that the difference in product ratios seen with trimethylaluminum and triethylaluminum (Table 1) might arise if the smaller Lewis acid trimethylaluminum is more effective at coordinating the imine, thus eliminating the possible cyclization to give **48**. In addition, trimethylaluminum is incapable of the reduction leading to **33**.

With the foregoing mechanistic working hypothesis, we carried out the additional rearrangements shown in Table 1. The use of triisobutylaluminum (*i*-Bu_3Al) resulted in a further reduction in the amount of alkenes **30-32**. With this reagent, the amino ether **34** is the major product (41%) and two new products **35** and **36** are obtained. These results can be understood in terms of the more bulky *i*-Bu_3Al being even less capable of coordinating with the imine nitrogen, thus encouraging cyclization to **48**. Compound **35**, the second most abundant product under these conditions, would result from reduction of **48**. Compound **36** is rather uninteresting, respresenting simple reduction of the N–O bond in **45** without skeletal fragmentation. Not surprisingly, diisobutylaluminum hydride (*i*-Bu_2AlH) gave somewhat greater amounts of **35**, the product of reduction of **48**. Thus, with *i*-Bu_3Al and *i*-Bu_2AlH cyclization of cation **46** is by far the preferred reaction path, giving rise to 71 and 100% of the observed products, respectively.

(10) DQF-COSY = double-quantum-filtered correlated spectrosopy; see Derome, A. E.; Williamson, M. P. *J. Mag. Reson.* **1990**, *88*, 177.
(11) HMBC = heteronuclear multiple-bond connectivity; see Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(12) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714.
(13) Mehta, G.; Murthy, N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443.

Scheme 8

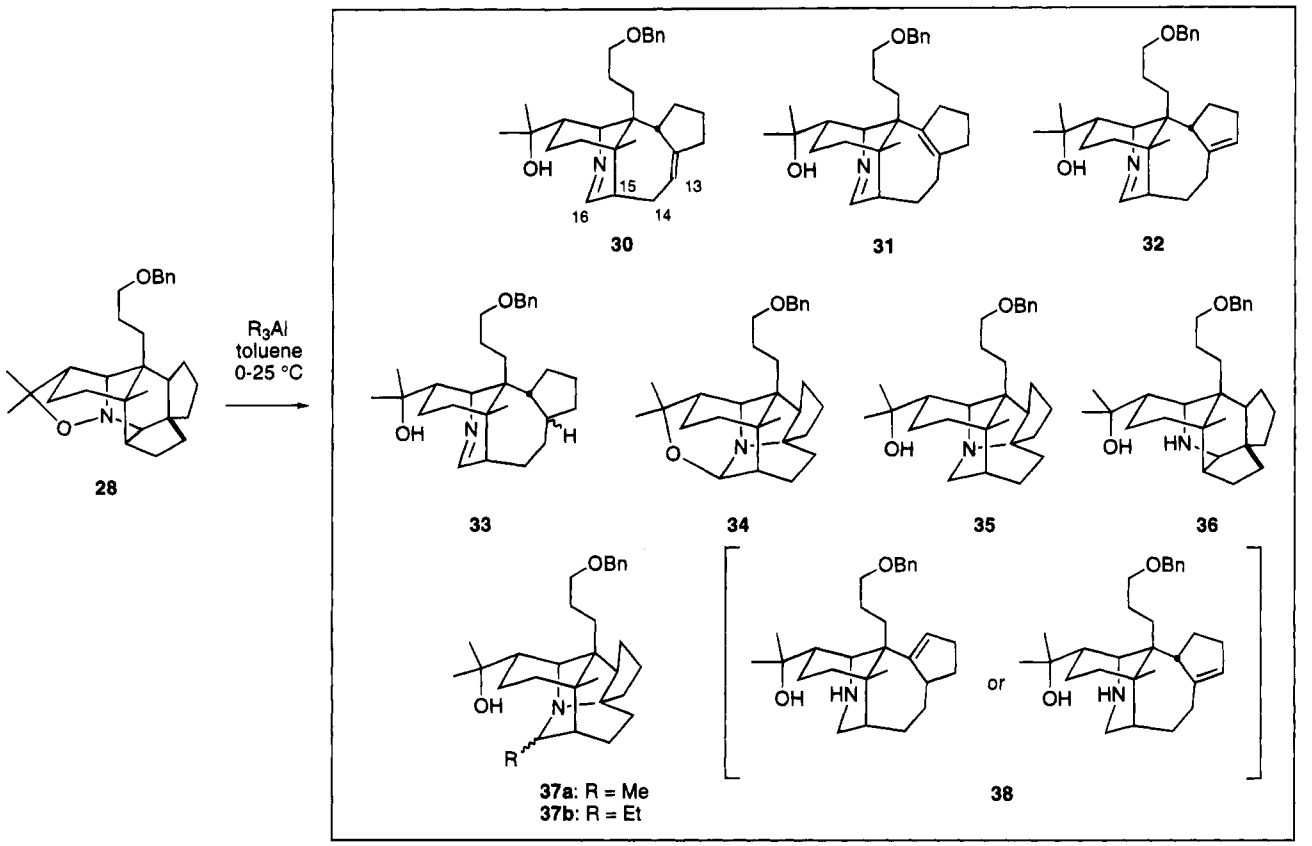
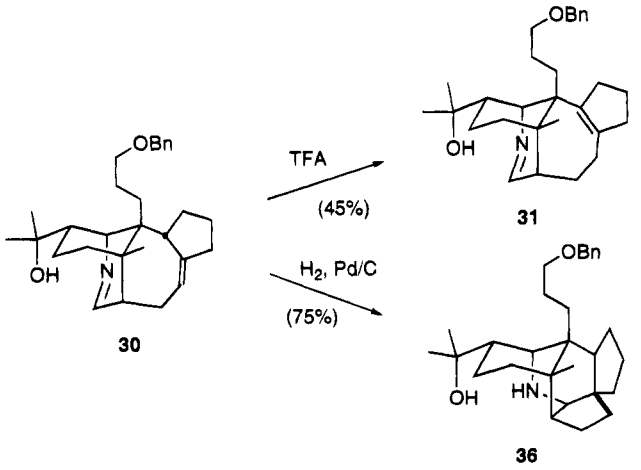


Table 1. Reactions of Oxaziridine 28 with Alkylaluminum Reagents (Scheme 8)

		product yield, %							
Lewis acid	temp, °C	**30**	**31 + 32**	**33**	**34**	**35**	**36**	**37**	**38**
Me_3Al	0	60–68	20–28	0	0	0	0	0	0
Me_3Al	25	50	20	0	0	0	0	0	0
Et_3Al	25	41	7–14	23–32	0–14	0	0	0	0
i-Bu_3Al	25	---------- 19 ----------			41	26	8	0	0
i-Bu_2AlH	25	---------- 0 ----------			32–42	25–44	0	0	0
Me_3Al + *i*-Pr_2NEt	25	---------- 5–22 ----------			37–44	0	0	34–46	0
Et_3Al + *i*-Pr_2NEt	25	---------- 0 ----------			29	5	17–28	12–20	9–23

Scheme 9



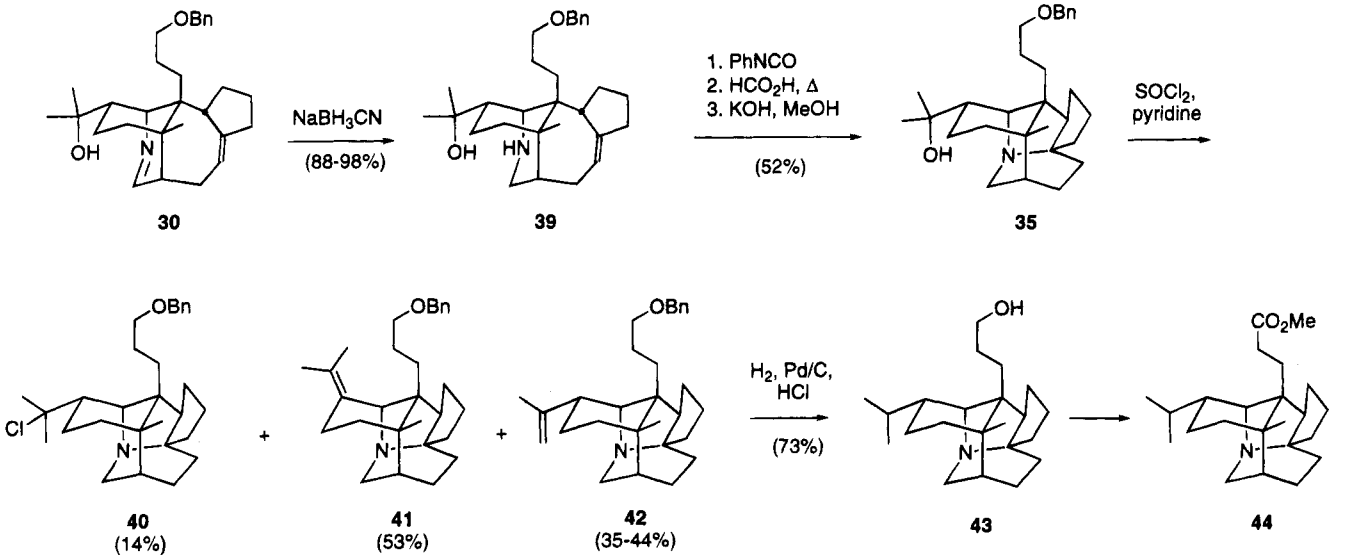
The foregoing analysis led us to try the reaction in the presence of an external tertiary amine, which might serve as a kind of buffer, thus shifting the equilibrium between **46** and **47** in the direction of uncoordinated imine. We thought that this might have the same effect as using a more sterically-demanding alane. The results are seen in the last two rows of Table 1. The fragmentation is much slower in the presence of Hünig's base (diisopropylethylamine), but, as expected, the amount of simple elimination to give alkenes **30-32** is greatly reduced with trimethylaluminum and triethylaluminum. Cyclization of **46** to the daphnane skeleton represents the major pathway with both alanes, although there is now a new reaction mode—transfer of an alkyl group to **48**, giving rise to the alkylated products **37a** and **37b**. Finally, the reaction with triethylaluminum and Hünig's base also gives rise to a modest amount of a product that appears on the basis of its NMR spectra to have structure **38**, in which the exact placement of the double bond is not fully defined.

Control experiments were carried out to ascertain whether amino ether **34** might be an intermediate in the formation of reduction product **35** or alkylation products **37**. However, treatment of **34** with Me_3Al (either alone or in the presence of Hünig's base), Et_3Al, *i*-Bu_2AlH, or *i*-Bu_3Al under the normal reaction conditions gave no detectable reaction.

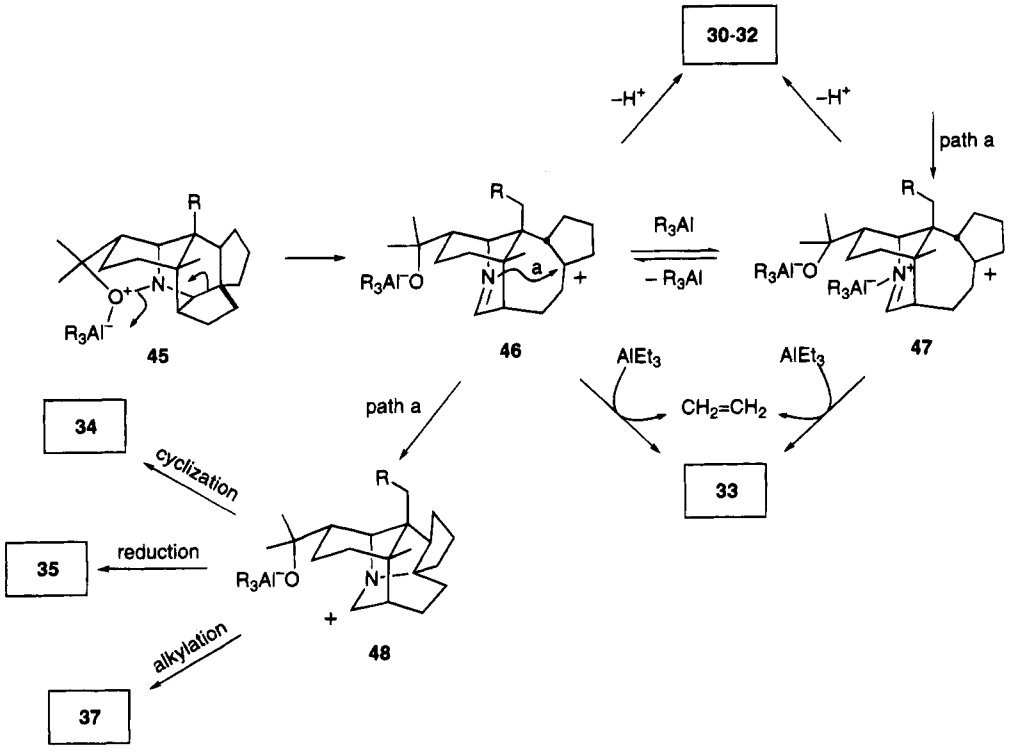
Discussion

This investigation has shown that fragmentation of the secodaphnane skeleton using mode B in Scheme 1 is

Scheme 10



Scheme 11



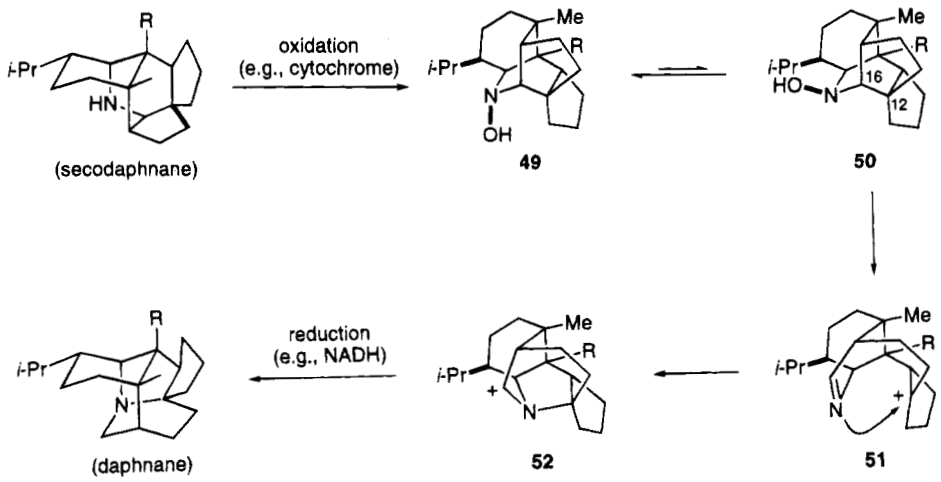
feasible provided the nitrogen leaving group is constrained to occupy the thermodynamically less preferred position anti to the C12–C16 bond. In this study, the nitrogen leaving group has been artificially constrained by incorporation into an isoxazolidine ring. It is possible that this conformational distortion is achieved *in vivo* by an enzyme that preferentially binds the less stable conformer **50** of a biosynthetic intermediate in which the secondary nitrogen of the secodaphnane skeleton has been hydroxylated (Scheme 12).

The *direct* formation of the daphnane skeleton in some of the reactions studied (e.g., **34** and **35**) is intriguing and might have biosynthetic relevance. Thus, one can imagine the initially-formed secodaphnane skeleton being oxidized on nitrogen by cytochrome P_{450} system, giving rise to hydroxylamine **49**, in equilibrium with a small amount of the less stable conformer **50**. If conformer **50** is bound by an enzyme that then delivers a proton to the OH group, fragmentation might occur to give **51**, which could cyclize to provide **52**. If the fragmenting and cyclizing enzyme also binds a reducing cofactor like NADH, cation **52** could be reduced to provide the daphnane skeleton.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Benzene, toluene, triethylamine, *N,N*-diisopropylethylamine, and CH_2Cl_2 were distilled from CaH_2 prior to use. Ether and tetrahydrofuran (THF) were distilled from Na/benzophenone or K before use. Dry THF was degassed by four freeze-pump-thaw cycles, and the resulting dry degassed THF was generally transferred by a cannula, not a syringe. Pyridine and *N,N'*-dimethylformamide (DMF) were distilled from

Scheme 12



CaH_2 and stored over molecular seives. All reactions involving oxygen- or moisture-sensitive compounds were conducted under a nitrogen atmosphere. When reactions were worked-up by extraction, organic solutions were dried with Na_2SO_4 and filtered unless otherwise indicated. A rotary evaporator was used for solvent removal. IR spectra were measured as thin films on NaCl plates unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$. J values are in hertz. In some cases, a DEPT spectrum was used to assign the carbon resonances as 3(CH_3), 2(CH_2), 1(CH), 0(C). Mass spectra were determined using the electron-impact method; data are reported as m/z (relative intensity).

Reaction of (±)-Methyl Homosecodaphniphyllate (5) with $Pb(OAc)_4$. To a solution of 200 mg (0.556 mmol) of (±)-methyl homosecodaphniphyllate (**5**) in 2 mL of dry benzene was added 275 mg (0.589 mmol) of $Pb(OAc)_4$. The resulting yellow precipitate became white after a few min. The mixture was stirred for 45 min and quenched with 1 mL of ethylene glycol. The resultant two-phase mixture was partitioned between ether (10 mL) and 1 M NaOH (10 mL), and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried, and concentrated to give 200 mg of a tan oil. Flash chromatography on 13 g of silica gel using 1:1 hexanes/EtOAc and then 7:3 EtOAc/MeOH gave, in order of elution, 162 mg (81%) of imine **6** as a colorless oil and 28 mg (14%) of amino alkene **7** as a white solid. Imine **6** became a white solid within a colorless oil after continued evaporation *in vacuo*.

(±)-12,15-Cyclo-1,12-secodaphnan-23-oic Acid, 1,2-Didehydro-, Methyl Ester (6). Mp 69–71 °C. IR: 1745, 1605 cm^{-1}. ^1H NMR (500 MHz): δ 0.89 (d, 3, J = 6.7), 0.92 (d, 3, J = 6.3), 0.92 (s, 3), 0.98 (dd, 1, J = 6.1, 14.7), 1.04–1.20 (m, 2), 1.35 (m, 1), 1.45–1.80 (m, 10), 1.93 (m, 1), 2.02 (m, 1), 2.20 (m, 3), 2.45–2.58 (m, 3), 3.73 (s, 3), 4.22 (d, 1, J = 4.2). ^{13}C NMR (125 MHz): δ 19.18 (3), 21.67 (3), 22.17 (3), 22.84 (2), 25.19 (2), 25.77 (2), 27.64 (1), 31.35 (2), 33.12 (2), 37.44 (2), 37.92 (2), 40.18 (2), 40.59 (2), 49.64 (0), 50.03 (1), 50.70 (0), 50.89 (1), 51.11 (0), 51.30 (1), 51.62 (3), 72.82 (1), 174.43 (0), 192.76 (0). [Literature[4] (enantiomerically pure compound) mp 96–8 °C. IR ($CHCl_3$): 1736, 1600 cm^{-1}. ^1H NMR (60 MHz): δ 0.88 (d, 3, J = 6), 0.92 (d, 3, J = 6), 0.93 (s, 3), 3.73 (s, 3), 4.24 (d, 1, J = 3.5)]. Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.09; H, 10.12; N, 3.79.

(±)-Amino Alkene 7. Mp 140 °C dec. IR: 1745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ passed through alumina): δ 0.86 (t, 6, J = 6.3), 1.04 (s, 3), 1.25 (m, 3), 1.66–1.76 (m, 7), 2.01–2.20 (m, 5), 2.25 (m, 1), 2.32 (ddd, 1, J = 3.2, 11.2, 16.0), 2.48 (ddd, 1, J = 7.0, 11.5, 18.6), 2.95 (br s, 2), 3.37 (br s, 1), 3.69 (s, 3), 4.10 (br s, 1), 5.57 (br s, 1). ^{13}C NMR (100 MHz): δ 19.10 (3), 20.71 (3), 21.24 (3), 23.71 (2), 23.98 (2), 26.73 (2), 30.15 (2), 30.32 (1), 31.34 (2), 32.09 (2), 33.44 (2), 35.95 (2), 40.42 (1), 45.52 (0), 48.32 (0), 48.83 (1), 51.73 (3), 65.54 (1), 66.01 (1), 71.05 (1), 127.81 (1), 174.14 (0). MS: 357 M^+ (10.37), 270 (5.02), 135 base (100). HRMS: calcd for $C_{23}H_{35}NO_2$ 357.2670, found 357.2659. Satisfactory analytical data could not be obtained for this compound.

(±)-Amino Ester 8. To a solution of 12 mg (0.03 mmol) of amino alkene **7** in 1 mL of MeOH was added 2 mg of PtO_2. The mixture was stirred under H_2(1 atm) for 2.25 h and filtered through Celite. The filtrate was concentrated to give 10 mg of a colorless oil. Flash chromatography on 3 g of silica gel using 7:3 EtOAc/MeOH and then 20:1:1 hexanes/EtOAc/triethylamine gave 6 mg (53%) of **8** as a colorless oil. IR: 1745 cm^{-1}. ^1H NMR (500 MHz): δ 0.84 (d, 3, J = 6.7), 0.88 (d, 3, J = 6.6), 0.95 (s, 3), 1.14–1.32 (m, 5), 1.41 (m, 1), 1.50 (m, 2), 1.59 (m, 2), 1.66–1.80 (m, 6), 1.86–1.96 (m, 2), 2.03 (ddd, 1, J = 6.4; 12.1, 18.4), 2.25 (m, 2), 2.40 (ddd, 1, J = 6.4, 12.4, 18.7), 2.91 (d, 1, J = 2.0), 3.04 (t, 1, J = 3.7), 3.19 (m, 1), 3.68 (s, 3). ^{13}C NMR (125 MHz): δ 19.13 (3), 20.71 (3), 21.12 (3), 24.04 (2), 25.79 (2), 25.97 (2), 26.51, (2), 29.06 (2), 31.16 (1), 32.01 (2), 34.79 (2), 36.71 (2), 37.24 (2), 39.18 (1), 40.34 (1), 41.96 (1), 44.71 (0), 45.20 (0), 51.59 (3), 61.11 (1), 67.81 (1), 68.45 (1), 174.84 (0). MS: 359 M^+ (9.50), 272 base (100). HRMS: calcd for $C_{23}H_{37}NO_2$ 359.2826, found 359.2814. Satisfactory analytical data could not be obtained for this compound with the small amount available.

(±)-Homosecodaphniphyllic Acid, 2-Cyano-, Methyl Ester (14).[4] To a solution of 110 mg (0.308 mmol) of imine **6** in 2.2 mL of dry DMF was added 110 mg (2.24 mmol) of NaCN. The solution was heated to 90–110 °C, stirred for 3 h, allowed to cool to rt, and partitioned between ether (3 mL) and H_2O (3 mL). The aqueous layer was extracted with ether (9 × 3 mL). The combined organic layers were dried and concentrated to give 130 mg of a yellow oil. Flash chromatography on 10 g of silica gel using a gradient of 7:1 and then 1:1 hexanes/EtOAc gave 85 mg (72%) of **14** as a colorless oil which solidified on standing to give a white solid, mp 97–9 °C. IR ($CHCl_3$): 2240, 1735 cm^{-1}. ^1H NMR (400 MHz): δ 0.88 (s, 3), 0.95 (d, 3, J = 6.9), 0.97 (d, 3, J = 7.0), 1.24 (m, 1), 1.44 (m, 3), 1.55–1.84 (m, 9), 1.86–1.95 (m, 4), 2.11 (m, 2), 2.34–2.65 (m, 4), 2.67 (d, 1, J = 4.6), 3.69 (s, 3). ^{13}C NMR (125 MHz): δ 15.67, 18.12, 22.46, 23.24, 23.83, 25.63, 26.81, 28.43, 29.12, 31.34, 36.34, 38.53, 38.95, 40.27, 45.21, 48.10, 49.50, 50.90, 51.69, 58.60, 61.79, 123.98, 174.04. [Lit.[4] (enantiomerically pure compound) IR ($CHCl_3$) 2240, 1735 cm^{-1}]. Anal. Calcd for $C_{24}H_{36}N_2O_2$: C, 74.95; H, 9.44; N, 7.28. Found: C, 75.11; H, 9.52; N, 6.97.

Reaction of Imine 6 with *m*-Chloroperoxybenzoic Acid. *m*-Chloroperoxybenzoic acid (MCPBA) was purified by dissolving in CH_2Cl_2, washing with pH 6 buffer solution, and concentrating to give a white solid. To a solution of 160 mg (0.448 mmol) of imine **6** in 4.5 mL of dry CH_2Cl_2 at 0 °C was added portionwise, over 8 min, 92 mg (0.48 mmol) of purified MCPBA. The solution was stirred for 4 h, during which time a white precipitate formed. The suspension was filtered, and the filtrate was washed with 25% Na_2SO_3 (10 mL). The aqueous layer was back extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were sequentially washed with 20% Na_2CO_3 (10 mL) and H_2O (10 mL), dried (Na_2CO_3), and

concentrated to give 192 mg of a pale yellow oil. Flash chromatography on 15 g of silica gel using 7:1 hexanes/EtOAc, EtOAc, and then 9:1 EtOAc/MeOH gave, in order of elution, 85 mg (51%) of oxaziridine **16** as a colorless oil and 52 mg (31%) of nitrone **17** as a white solid. Oxaziridine **16** solidifed after continued evaporation *in vacuo* to give a white solid.

(±)-Oxaziridine 16. Mp 74–6 °C. IR ($CHCl_3$): 1735 cm^{-1}. ^1H NMR (500 MHz): δ 0.76 (d, 3, J = 6.8), 0.91 (d, 3, J = 5.4), 0.90 (s, 3), 1.25–1.38 (m, 3), 1.41–1.83 (m, 13), 1.98–2.13 (m, 3), 2.22 (m, 1), 2.48 (m, 1), 2.67 (ddd, 1, J = 6.3, 11.9, 18.0), 3.47 (d, 1, J = 4.6), 3.70 (s, 3). ^{13}C NMR (125 MHz): δ 19.46 (3), 20.74 (3), 23.27 (2), 23.93 (3), 25.00 (1), 26.23 (2), 27.20 (2), 27.43 (2), 30.11 (2), 32.55 (2), 36.09 (2), 37.93 (2), 41.44 (2), 42.58 (1), 42.71 (0), 43.68 (0), 48.09 (1), 51.41 (0), 51.68 (3), 52.60 (1), 65.55 (1), 84.30 (0), 174.52 (0). TLC R_f 0.4 (7:1 hexanes/EtOAc). MS: 373 M^+ (30.62), 330 (92.34), 300 base (100), 105 (60.27), 91 (83.91), 79 (53.59), 55 (76.55). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.59; H, 9.22; N, 3.64.

(±)-Nitrone 17. Mp 170 °C dec. IR ($CHCl_3$): 1735, 1550 cm^{-1}. UV λ_{max}: 270 nm. ^1H NMR (400 MHz): δ 0.85 (d, 3, J = 6.6), 0.94 (s, 3), 1.02 (d, 3, J = 6.6), 1.12 (m, 1), 1.22–1.44 (m, 2), 1.54–1.90 (m, 11), 1.96–2.06 (m, 2), 2.13–2.30 (m, 3), 2.47 (m, 1), 2.60 (m, 1), 2.87 (m, 1), 3.73 (s, 3), 4.00 (d, 1, J = 4.8). ^{13}C NMR (400 MHz): δ 20.49 (3), 20.94 (3), 22.66 (2), 23.19 (3), 25.67 (2), 26.16 (2), 26.93 (2), 31.44 (2), 31.49 (1), 33.32 (2), 36.89 (2), 38.84 (2), 38.90 (2), 48.78 (1), 50.79 (0), 51.46 (0), 51.81 (3), 52.36 (0), 52.46 (1), 52.82 (1), 84.10 (1), 156.95 (0), 174.02 (0). TLC R_f 0.25 (9:1 EtOAc/MeOH). MS: 373 M^+ (1.82), 357 (69.26), 342 (52.86), 314 (62.10), 284 (98.23), 260 (54.31), 234 (64.17), 194 base (100). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.79; H, 9.49; N, 3.65.

Thermal Rearrangement of Oxaziridine 16. A solution of 17 mg (0.05 mmol) of oxaziridine **16** in 1 mL of dry benzene was stirred at 65 °C for 24 h and concentrated to give 17 mg of an oil. Flash chromatography on 2 g of silica gel using a gradient of 7:1 and then 4:1 hexanes/EtOAc gave 11 mg (65%) of starting oxaziridine **16** and 4 mg (24%) of amide **18** as a colorless oil.

(±)-Amide 18. IR: 1740, 1690 cm^{-1}. ^1H NMR (500 MHz): δ 0.89 (d, 3, J = 6.6), 0.96 (d, 3, J = 6.5), 0.96 (s, 3), 1.08–1.17 (m, 2), 1.33–1.44 (m, 2), 1.51 (m, 2), 1.56–1.88 (m, 11), 1.94 (ddd, 1, J = 4.6, 12.7, 17.2), 2.11 (dt, 1, J = 2.2, 6.5), 2.40 (m, 1), 2.69 (ddd, 1, J = 4.9, 12.7, 17.5), 3.18 (d, 1, J = 6.3), 3.67 (s, 3), 3.84 (m, 1). ^{13}C NMR (125 MHz): δ 19.48 (3), 19.92 (3), 21.56 (3), 21.64 (2), 23.52 (2), 25.58 (2), 30.42 (2), 30.97 (1), 31.49 (2), 31.67 (2), 32.71 (2), 35.36 (2), 38.31 (2), 39.60 (0), 41.01 (1), 47.85 (1), 51.53 (3), 52.48 (0), 54.49 (0), 59.43 (1), 66.86 (1), 174.47 (0), 186.29 (0). MS: 373 M^+ (22.50), 330 base (100), 300 (99.89). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.94; H, 9.41; N, 3.60.

(±)-Keto Imine 19 and (±)-Oxazolidine 20. Method A. To a solution of 85 mg (0.23 mmol) of oxaziridine **16** in 4 mL of dry CH_2Cl_2 at −78 °C was added 100 mg (88 μL, 0.46 mmol) of trimethylsilyl trifluoromethanesulfonate over 5 min. The solution was stirred for 1 h, allowed to warm to 0 °C, stirred for an additional 45 min, allowed to warm to rt, and stirred for an additional 2.5 h. The reaction solution was then quenched with a few drops of saturated $NaHCO_3$, diluted with CH_2Cl_2 (5 mL), and washed with saturated $NaHCO_3$ (5 mL). The aqueous layer was back extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL), dried, and concentrated to give 95 mg of a pale yellow oil. Flash chromatography on 5 g of silica gel using 1:2 hexanes/EtOAc and then 4:1 EtOAc/MeOH gave, in order of elution, 11 mg (13%) of keto imine **19** as a white solid, 10 mg (12%) of a mixture of keto imine **19** and oxazolidine **20**, and 60 mg (71%) of oxazolidine **20** as a colorless oil. Oxazolidine **20** solidified after continued evaporation *in vacuo* to give a white solid.

Method B. To a solution of 45 mg (0.13 mmol) of oxaziridine **16** in 1 mL of toluene was added 95 mg (0.50 mmol) of p-TsOH·H_2O. The resulting mixture was stirred for 5 h and partitioned between EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed sequentially with H_2O (10 mL) and brine (5 mL), dried, and concentrated to give 40 mg of an oil. Flash chromatography on 4.5 g of silica gel using a gradient of 19:1 and then 4:1 EtOAc/MeOH gave, in order of elution, 7 mg (16%) of keto imine **19** and 24 mg (53%) of oxazolidine **20** as oils. Both **19** and **20** solidified after continued evaporation *in vacuo* to give white solids.

(±)-Keto Imine 19. Mp 110–11 °C. IR ($CHCl_3$): 1735, 1695, 1635 cm^{-1}. ^1H NMR (500 MHz): δ 0.86 (d, 3, J = 6.8), 0.90 (d, 3, J = 6.9), 1.05 (s, 3), 1.32 (dt, 1, J = 4.7, 12.2), 1.46 (m, 2), 1.62–1.80 (m, 7), 1.83–1.96 (m, 4), 2.03–2.30 (m, 6), 2.38 (m, 1), 3.65 (s, 3), 3.74 (d, 1, J = 6.7), 7.60 (s, 1). ^{13}C NMR (125 MHz): δ 17.97 (3), 20.56 (2), 21.12 (3), 22.18 (2), 22.99 (3), 25.47 (2), 25.72 (1), 30.24 (2), 30.31 (2), 31.52 (2), 35.10 (2), 38.88 (2), 40.08 (2), 46.34 (0), 47.49 (0), 51.71 (3), 54.45 (1), 54.54 (0), 55.52 (1), 67.71 (1), 173.90 (0), 181.47 (1), 216.54 (0). MS: 373 M^+ (23.93), 330 (27.99), 300 base (100), 286 (38.67), 262 (76.56), 119 (62.43), 91 (85.16), 69 (54.56), 55 (82.81). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.97; H, 9.41; N, 3.71.

(±)-Oxazolidine 20. Mp 74–6 °C. IR ($CHCl_3$): 1740 cm^{-1}. ^1H NMR (400 MHz): δ 0.87 (d, 3, J = 6.8), 1.01 (s, 3), 1.04 (d, 3, J = 6.5), 1.21 (m, 1), 1.37 (m, 1), 1.55–1.82 (m, 7), 1.86–2.15 (m, 10), 2.23 (m, 1), 2.45 (ddd, 1, J = 6.6, 11.5, 17.9), 3.10 (m, 1), 3.47 (d, 1, J = 7.5), 3.68 (s, 3). ^{13}C NMR (125 MHz): δ 20.15 (3), 21.22 (3), 21.40 (2), 23.46 (3), 24.15 (2), 24.83 (2), 26.36 (2), 27.86 (2), 28.04 (2), 28.20 (2), 29.00 (1), 30.41 (2), 36.26 (2), 40.12 (1), 46.04 (0), 46.40 (1), 51.59 (3), 60.19 (0), 70.53 (1), 70.63 (1), 99.48 (0), 111.36 (0), 174.27 (0). MS m/e 373 M^+ (17.79), 330 (9.12), 286 base (100), 91 (56.17). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.64; H, 9.27; N, 3.37.

(±)-Amino Ketone 21 and (±)-Hemiaminal 22. To a solution of 9 mg (20 μmol) of keto imine **19** in 1 mL of MeOH was added 5 mg of PtO_2. The mixture was stirred under H_2 for 3.7 h and filtered through Celite. The filtrate was concentrated to give 10 mg of crude keto amine **21** as a colorless oil. IR: 1740, 1690 cm^{-1}. Flash chromatography on 3 g of silica gel using 2:1 hexanes/EtOAc, 1:1 hexanes/EtOAc, EtOAc, 19:1 EtOAc/MeOH, and then 1:1 EtOAc/MeOH gave 8 mg (89%) of a mixture of amino ketone **21** and its isomeric hemiaminal **22** as a white foam. IR: 3650–2400, 1740, 1670, 1660 cm^{-1}. ^1H NMR (400 MHz): δ 0.90 (d, 3, J = 6.5), 1.01 (d, 3, J = 7.7), 1.02 (s, 3), 1.33 (m, 1), 1.40–1.54 (m, 4), 1.66–2.00 (m, 12), 2.02 (br s, 1), 2.22–2.35 (m, 2), 2.40–2.54 (m, 2), 2.74 (d, 1, J = 10.5), 3.30 (br s, 1), 3.43 (br s, 1), 3.68 (s, 3). MS m/e 375 M^+ (6.78), 332 (6.10), 302 (69.03), 288 (12.12), 137 base (100), 108 (66.27), 56 (99.12). HRMS: calcd for $C_{23}H_{37}NO_3$ 375.2775, found 375.2774. Satisfactory ^{13}C NMR and analytical data could not be obtained for this mixture.

(3α,3aβ,6α,6aα,9a*R,10*S**)-(±)-Decahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-[3-(phenylmethoxy)propyl]-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (26).** To a solution of 570 mg (1.36 mmol) of imine **25**[5] in 7.0 mL of MeOH was added 71 μL (71 μmol) of 1 N HCl, followed by portionwise addition of 280 mg (4.23 mmol) of $NaBH_3CN$. The solution was stirred for 2 h and quenched with 2 N HCl (2 mL) until pH ≈ 2. The reaction solution should be cooled to 0 °C during the addition of acid. The resulting cloudy solution was diluted with benzene (5 mL) and concentrated. The residue was partitioned between ether (20 mL) and 2 N NaOH (15 mL), and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried (K_2CO_3), decanted, and concentrated to give 560 mg of a cloudy oil. Flash chromatography on 25 g of silica gel using a gradient of 95:4.5:0.5 and then 90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH gave 10 mg (2%) of pentacyclic amine[5] as a colorless oil and 430 mg (75%) of **26** as a colorless oil which solidified upon standing to give a white solid, mp 97–9 °C. IR: 2950, 740 cm^{-1}. ^1H NMR (400 MHz): δ 0.79 (s, 3), 1.03 (ddd, 1, J = 4.4, 13.0, 17.3), 1.23 (ddd, 1, J = 4.8, 12.4, 17.1), 1.39–1.76 (m, 16), 1.62 (s, 3), 1.68 (d, 3, J = 0.9), 1.90–2.00 (m, 3), 2.59 (d, 1, J = 5.3), 2.65 (s, 2), 3.35 (t, 2, J = 6.7), 4.47 (s, 2), 5.14 (tt, 1, J = 1.4, 7.0), 7.25–7.36 (m, 5). ^{13}C NMR (100 MHz): δ 17.73 (3), 18.09 (3), 21.55 (2), 22.98 (2), 25.49 (2), 25.72 (3), 26.42 (2), 28.92 (2), 29.21 (2), 34.71 (2), 37.74 (0), 38.35 (2), 38.50 (2), 40.01 (0), 40.86 (2), 44.24 (1), 49.47 (1), 50.44 (0),

58.86 (1), 71.68 (2), 72.81 (2), 125.51 (1), 127.46 (1), 127.51 (1), 127.56 (1), 128.31 (1), 130.84 (0), 138.60 (0). TLC: R_f 0.2 (7:3 EtOAc/MeOH). Anal. Calcd for $C_{29}H_{43}NO$: C, 82.61; H, 10.28; N, 3.32. Found: C, 82.33; H, 10.49; N, 3.20.

(±)-Isoxazolidine 28. An ethereal solution of amine **26** was washed with 1 N NaOH, dried (K_2CO_3), decanted, and concentrated to assure that the amine was fully deprotonated. To a mixture of 170 mg (0.403 mmol) of **26**, 13.6 mg (0.041 mmol) of $Na_2WO_4{\cdot}2H_2O$, and 21.1 mg (0.053 mmol) of Aliquot 336 in 3.5 mL of CH_2Cl_2 at 0 °C was added 0.41 mL (4.0 mmol) of H_2O_2 (30 wt % solution in H_2O). The two-phase mixture was allowed to warm to rt and an additional 2.2 mg (6.7 μmol) of $Na_2WO_4{\cdot}2H_2O$, 9.4 mg (0.02 mmol) of Aliquot 336, and 50 μL (0.49 mmol) of H_2O_2 (30 wt % solution in H_2O) was added portionwise during the following 21 h, until TLC analysis (90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH) indicated the reaction was complete and only a minor amount (<5%) of overoxidation had occurred to give a mixture of epoxy nitrones. The mixture was then cooled to 0 °C, quenched by the slow addition of 5 M $NaHSO_3$ (0.92 mL), and partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried and concentrated to give 210 mg of nitrone **27** as a colorless oil, which was typically used directly in the next step. A pure sample was prepared by flash chromatography using 95:4.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH to give **27** as a colorless oil which slowly cyclized upon standing at rt. IR: 1595 cm^{-1}. ^1H NMR (500 MHz): δ 0.90 (s, 3), 1.03 (m, 1), 1.16 (m, 1), 1.29–1.39 (m, 1), 1.44 (m, 1), 1.57 (s, 3), 1.57–1.95 (m, 15), 1.64 (s, 3), 2.29 (t, 1, J = 5.7), 3.46 (t, 2, J = 5.6), 3.95 (dd, 1, J = 1.4, 5.1), 4.51 (s, 2), 4.98 (t, 1, J = 1.3), 7.11 (s, 1), 7.28–7.37 (m, 5). ^{13}C NMR (100 MHz): δ 17.05 (3), 17.59 (3), 22.00 (3), 22.72 (2), 25.35 (2), 25.51 (3), 26.44 (2), 27.36 (2), 32.38 (2), 35.45 (2), 36.47 (2), 38.60 (3), 43.07 (1), 46.36 (0), 48.33 (0), 54.33 (0), 54.63 (1), 70.67 (2), 72.85 (2), 79.17 (1), 127.04 (1), 127.44 (1), 127.48 (1), 128.27 (1), 131.44 (0), 138.28 (0), 139.66 (1). TLC: R_f 0.3 (39:1 $CHCl_3$/MeOH). Anal. Calcd for $C_{29}H_{41}NO_2$: C, 79.95; H, 9.49; N, 3.22. Found: C, 80.11; H, 9.76; N, 3.45.

A solution of 210 mg of crude nitrone **27** in 5 mL of benzene was stirred at 80 °C for 20 h and concentrated to give 210 mg of a colorless oil. Flash chromatography on 11.5 g of silica gel using 7:1 hexanes/EtOAc gave 145 mg (83%) of **28** as a colorless oil which solidified after continued evaporation *in vacuo* and storage at 0 °C to give a white solid, mp 84–5 °C. IR: 2950, 1110 cm^{-1}. ^1H NMR (500 MHz): δ 0.85 (s, 3), 1.18 (m, 1), 1.24 (s, 3), 1.29 (m, 1), 1.30 (s, 3), 1.39 (m, 2), 1.47–1.78 (m, 14), 1.90 (m, 1), 2.09 (m, 2), 2.90 (d, 1, J = 3.7), 3.41 (t, 2, J = 6.6), 3.46 (d, 1, J = 5.3), 4.51 (s, 2), 7.27–7.37 (m, 5). ^{13}C NMR (125 MHz): δ 20.01 (2), 20.57 (3), 21.81 (3), 23.37 (2), 26.23 (3), 26.28 (2), 28.89 (2), 29.53 (2), 35.55 (2), 35.93 (0), 36.53 (2), 36.75 (0), 39.09 (2), 40.79 (1), 44.30 (1), 51.57 (0), 52.81 (1), 60.67 (1), 68.42 (1), 71.49 (2), 72.86 (2), 80.10 (0), 127.45 (1), 127.53 (1), 128.28 (1), 138.46 (0). TLC: R_f 0.5 (3:1 hexanes/EtOAc). MS: 435 M^+ (59.62), 344 (23.21), 286 (7.51), 91 base (100). Anal. Calcd for $C_{29}H_{41}NO_2$: C, 79.95; H, 9.49; N, 3.22. Found: C, 79.68; H, 9.58; N, 3.10. Other lower R_f materials were not characterized.

(±)-Debenzylated Isoxazolidine 29. Solutions of $SnCl_4$ and $TiCl_4$ were prepared by combining the purified Lewis acid (distilled from CaH_2) with dry CH_2Cl_2. The Lewis acid was added portionwise to a solution of 20–30 mg (0.050–0.075 mmol) of **28** in 2 mL of dry toluene over the reaction time period: 1 h at −78 °C for TMSOTf; 12 h at 80 °C for $SnCl_4$; 20 h at 60 °C for BF_3; 45 min at 0 °C for $TiCl_4$.

The reaction mixture at rt was quenched with a few drops of 1 M NaOH and partitioned between CH_2Cl_2 (5 mL) and 1 M NaOH (5–10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine, dried, and concentrated. Flash chromatography on 2–3 g of silica gel using a gradient ranging from 5:1 hexanes/EtOAc to 7:3 EtOAc/MeOH gave **29** as an off-white solid, mp 107.0–9.5 °C. IR: 3650–3100 cm^{-1}. ^1H NMR (400 MHz): δ 0.86 (s, 3), 1.20 (m, 1), 1.25 (s, 3), 1.31 (s, 3), 1.35–1.82 (m, 18), 1.92 (m, 1), 2.10 (m, 2), 2.90 (d, 1, J = 3.7), 3.47 (d, 1, J = 5.3), 3.60 (t, 2, J = 6.2). ^{13}C NMR (100 MHz): δ 20.06 (2), 20.62 (3), 21.91 (3), 23.42 (2), 26.28 (3), 26.32 (2), 28.92 (2), 29.24 (2), 29.30 (2), 35.62 (2), 36.01 (0), 36.58 (2), 36.82 (0), 39.14 (2), 40.86 (1), 44.38 (1), 51.66 (0), 52.79 (1), 60.83 (1), 64.06 (2), 68.48 (1), 80.20 (0). TLC: R_f 0.25 (2:1 hexanes/EtOAc). Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21; N, 4.05. Found: C, 76.40; H, 10.46; N, 3.86.

When using $TiCl_4$, the reaction mixture at 0 °C was quenched with 2 mL of 20% K_2CO_3, allowed to warm to rt, stirred for 3 h, and extracted with 1:1 ether/ethyl acetate (4 × 5 mL). The combined organic layers were washed with brine, dried, and concentrated. Flash chromatography on 4 g of silica gel using 1:1 hexanes/EtOAc and then 19:1 EtOAc/MeOH gave **29** as a colorless oil which solidified after continued evaporation *in vacuo* to give an off-white solid. An inseparable mixture of two debenzylated imines was also produced with this Lewis acid.

Experimental Procedures for the Reactions Summarized in Schemes 8 and 9. A. Reaction of Isoxazolidine 28 with Et_3Al. To a solution of 42.7 mg (0.098 mmol) of isoxazolidine **28** in 2.0 mL of dry toluene was added dropwise 0.52 mL (0.98 mmol) of Et_3Al (1.9 M solution in toluene). The solution was stirred for 1 h, cooled to 0 °C, quenched by slow addition of 1 N NaOH (2 mL), and partitioned between ether (5 mL) and 1 N NaOH (3 mL). The aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried, and concentrated to give 44.8 mg of a cloudy heterogeneous mixture. Flash chromatography on 5 g of silica gel using 4:1 hexanes/EtOAc, 1:1 hexanes/EtOAc, and then 19:1 EtOAc/MeOH gave, in order of elution, 6 mg (14%) of amino ether **34**, 10 mg (23%) of imine **33**, 14 mg of a 20:1 mixture of imine **30** and other imines (believed to be mainly **32** and **31**), and 8 mg of a 1:2 mixture of imine **30** and other imines (believed to be mainly **32** and **31**), all as colorless oils (41% total yield of **30**). Ratios were determined by ^1H NMR and are approximate. A pure sample of **30** was obtained by additional flash chromatography using 1:1 hexanes/EtOAc to give a colorless oil.

B. Reaction of Isoxazolidine 28 with Me_3Al. To a solution of 89 mg (0.21 mmol) of isoxazolidine **28** in 4.0 mL of dry toluene at 0 °C was added 1.0 mL (2.0 mmol) of Me_3Al (2 M solution in toluene) over 2 min. The solution was stirred for 1 h and quenched by slow adition of 1 N NaOH (1 mL). A gas vent needle should be added to the reaction vessel during the quench due to initial vigorous bubbling. The resulting mixture was partitioned between ether (5 mL) and 1 N NaOH (5 mL), and the aqueous layer was extracted with ether (2 × 5mL). The combined organic layers were washed with brine, dried, and concentrated to give 90 mg of a cloudy heterogeneous mixture. Flash chromatography of the crude material on 8 g of silica gel using a gradient of 5:1 and then 1:1 hexanes/EtOAc gave, in order of elution, 47 mg of a 10:1 mixture of **30** and other imines (believed to be mainly **32** and **31**) and 25 mg of a 1:3 mixture of **30** and other imines (believed to be mainly **32** and **31**), both as colorless oils (60% total yield of **30**). Ratios were determined by ^1H NMR and are approximate.

C. Reaction of Imine 30 with Trifluoroacetic Acid. A solution of 11 mg (25 μmol) of a 20:1 mixture of imine **30** and other imines (believed mainly to be **32** and **31**) in 0.5 mL of trifluoroacetic acid was stirred overnight, diluted with CH_2Cl_2, transferred to 2 N NaOH at 0 °C, and basified with 6 N NaOH. The two-phase mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried and concentrated to give 10 mg of an oil. After ^1H NMR spectroscopic analysis indicated the reaction was incomplete, the oil was resubmitted to the above reaction conditions to give 10 mg of an oil. Flash chromatography on 1 g of silica gel using a gradient of 95:4.5:0.5 and then 90:4.5:0.5 CH_2Cl_2:MeOH:27% NH_4OH gave 5 mg (45%) of imine **31**.

D. Hydrogenation of Imine 30 with Pd/C. A mixture of 10 mg (23 μmol) of imine **30**, contaminated with approximately 5% of another imine, and 10 mg of 10% Pd/C in 1 mL of absolute EtOH was stirred under H_2 (1 atm) for 3 h and filtered through Celite. The filtrate was concentrated to give 10.5 mg of an oil. Flash chromomatography on 1 g of silica gel using a gradient of 95:4.5:0.5 and then 90:9.5:0.5 CH_2Cl_2/

MeOH/27% NH_4OH gave, in order of elution, 2 mg (20%) of a mixture of imines (believed mainly to be **31**), and 7.5 mg (75%) of amino alcohol **36** as a colorless oil. Additional chromatography of **36** on alumina using 97.5:2.3:0.2 CH_2Cl_2/MeOH/27% NH_4OH gave a white solid.

E. Reaction of Isoxazolidine 28 with Me_3Al and *N,N*-Diisopropylethylamine. To a solution of 48 mg (0.11 mmol) of isoxazolidine **28** in 1.8 mL of dry toluene was added 0.19 mL (1.1 mmol) of *N,N*-diisopropylethylamine, followed by dropwise addtion of 0.55 mL (1.1 mmol) of Me_3Al (2 M solution in toluene) over 8 min. The resulting yellow solution, which became orange after 16 h, was cooled to 0 °C and quenched by slow addition of 1 N NaOH (1 mL). After initial vigorous bubbling, the resultant mixture was partitioned between ether (5 mL) and 1 N NaOH (5 mL), and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried and concentrated to give 58 mg of an orange oil. Chromatography on 9 g of alumina using 20:1 hexanes/EtOAc, 3:1 hexanes/EtOAc, 2:1 hexanes/EtOAc, EtOAc, 19:1 EtOAc/MeOH, and then 7:3 EtOAc/MeOH gave, in order of elution, 18.6 mg (37%) of amino ether **34** as a colorless oil, 10.5 mg (22%) of a 1:1 mixture of imine **30** and other imines(believed to be mainly **32** and **31**) as a yellow oil, and 19.1 mg (39%) of amino alcohol **37a** as a pale yellow oil. Ratios were determined by ^1H NMR and are approximate. Additional chromatography of **37a** on silica gel using 10:10:1 hexanes/EtOAc/Et_3N gave material of slightly greater purity.

F. Reaction of Isoxazolidine 28 with Et_3Al and *N,N*-Diisopropylethylamine. To a solution of 20.8 mg (0.048 mmol) of isoxazolidine **28** in 0.8 mL of dry touene was added 83 μL (0.48 mmol) of *N,N*-diisopropylethylamine, followed by dropwise addition of 250 μL (0.48 mmol) of Et_3Al (1.9 M solution in toluene) over 2 min. The solution was stirred for 12 h, cooled to 0 °C, quenched by slow addition of 1 N NaOH (0.5 mL), and partitioned between ether (3 mL) and 1 N NaOH (3 mL). The aqueous layer was extracted with ether (2 × 3 mL). The combined organic layers were washed with brine (3 mL), dried, and concentrated to give 21 mg of an oil. Chromatography on 4 g of alumina using CH_2Cl_2, 97.5:2.3:0.2 CH_2Cl_2/MeOH/27% NH_4OH, 90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH, and then 7:3 EtOAc:MeOH gave, in order of elution, 6 mg (29%) of amino ether **34** as a colorless oil, 7 mg (28%) of amino alcohol **36** contaminated with approximately 5% of a mixture of imines, and 6.5 mg of a mixture of compounds. Additional chromatography of the mixture of compounds on 2 g of alumina using a gradient of 0, 2, 5, and then 30% MeOH/EtOAc gave, in order of elution, 3.6 mg (16%) of amino alcohol **37b** as a colorless oil and 1.1 mg (5%) of amino alcohol **35**.

G. Reaction of Isoxazolidine 28 with *i*-Bu_3Al. To a solution of 99 mg (0.23 mmol) of isoxazolidine **28** in 3.0 mL of dry toluene was added dropwise 2.3 mL (2.3 mmol) of *i*-Bu_3Al (1 M solution in toluene) over 1 min. After initial fuming and slight evolution of heat, the reaction solution was stirred for 3 h, cooled to 0 °C, and quenched by slow addition of 1 N NaOH (1 mL). The resulting mixture was partitioned between ether (5 mL) and 1 N NaOH (5 mL), and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried and concentrated to give 102 mg of a heterogeneous mixture. Chromatography on 10 g of alumina using 10:1 hexanes/EtOAc, 1:1 hexanes/EtOAc, EtOAc, 19:1 EtOAc/MeOH, and then 7:3 EtOAc/MeOH gave, in order of elution, 40.8 mg (41%) of amino ether **34** as a colorless oil, 27 mg of a mixture of compounds as an oil, and 26 mg (26%) of amino alcohol **35** as a colorless oil. Flash chromatography of the mixture of compounds on 2 g of silica gel using 95:4.5:0.5 and then 90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH gave, in order of elution, 18.4 mg (19%) of a 1:1 mixture of imine **30** and other imines (believed to be **33**, **32**, and **31**) as an oil and 7.9 mg (8%) of amino alcohol **36** as a colorless oil. Ratios were determined by ^1H NMR and are approximate.

H. Reaction of Isoxazolidine 28 with Diisobutylaluminum Hydride. To a solution of 28.5 mg (0.065 mmol) of isoxazolidine **28** in 1.0 mL of dry toluene was added dropwise 220 μL (0.325 mmol) of diisobutylaluminum hydride (1.5 M solution in toluene) over 30 s. The solution was stirred for 1 h, cooled to 0 °C, and quenched by slow addition of 1 N NaOH (1 mL). After initial vigorous bubbling, the resulting mixture was partitioned between ether (3 mL) and 1 N NaOH (3 mL), and the aqueous layer was extracted with ether (2 × 3 mL). The combined organic layers were washed with brine (3 mL), dried, and concentrated to give 40 mg of a heterogeneous mixture. Chromatography on 5 g of alumina using 20:1 hexanes/EtOAc, 10:1 hexanes/EtOAc, 5:1 hexanes/EtOAc, 1:1 hexanes/EtOAc, EtOAc, 19:1 EtOAc/MeOH, and then 7:3 EtOAc/MeOH gave, in order of elution, 9 mg (32%) of amino ether **34** as a colorless oil, 6.5 mg (23%) of a compound believed to be amine **38** (position of double bond not defined) as an oil, and 12.5 mg (44%) of amino alcohol **35** as a tan oil, which solidified after storage at 0 °C to give an off-white solid, mp 71.0–3.5 °C.

Characterization of the Products of the Reactions Shown in Schemes 8 and 9 (foregoing procedures A–H). (±)-1,12,13,16-Tetradehydro-17-hydroxy-23-(phenylmethoxy)-1,12-secodaphnane (30). IR: 3600–3150, 1670 cm^{-1}. ^1H NMR (500 MHz): δ 1.00 (s, 3), 1.10 (s, 3,), 1.19 (ddd, 1, J = 1.7, 5.4, 14.0), 1.34–1.50 (m, 3), 1.43 (s, 3), 1.55–1.69 (m, 4), 1.70–1.92 (m, 5), 2.13 (br s, 1), 2.24 (m, 2), 2.34–2.48 (m, 3), 3.44 (m, 2), 3.68 (br s, 1), 4.26 (d, 1, J = 2.2), 4.52 (s, 2), 5.20 (d, 1, J = 7.1), 7.27–7.37 (m, 5), 7.60 (d, 1, J = 0.8). ^{13}C NMR (100 MHz): δ 16.52 (2), 22.46 (3), 22.47 (2), 26.10 (2), 27.70 (3), 28.85 (2), 29.87 (3), 30.23 (2), 32.08 (2), 35.30 (2), 37.00 (0), 39.59 (2), 39.71 (0), 43.65 (1), 49.02 (1), 49.42 (1), 128.21 (1), 138.42 (0), 146.54 (0), 170.76 (1). TLC: R_f 0.15 (1:1 hexanes/EtOAc). MS (FAB): 436.4 MH^+ base (100). Anal. Calcd for $C_{29}H_{41}NO_2$: C, 79.95; H, 9.49; N, 3.22. Found: C, 80.03; H, 9.29; N, 3.05.

(±)-1,8,12,16-Tetradehydro-17-hydroxy-23-(phenylmethoxy)-1,12-secodaphnane (31). IR: 3600–3100, 1660 cm^{-1}. ^1H NMR (500 MHz): δ 1.11 (s, 3), 1.13 (s, 3), 1.19–1.42 (m, 3), 1.40 (s, 3), 1.47–1.60 (m, 3), 1.65–1.80 (m, 4), 1.85 (dq, 1, J = 11.4, 5.2), 1.92 (m, 2), 2.02 (m, 1), 2.16–2.30 (m, 4), 2.40 (m, 1), 3.43 (t, 2, J = 6.7), 3.63 (br s, 1), 4.06 (s, 1), 4.50 (s, 2), 7.28 (m, 1), 7.26–7.36 (m, 5), 7.83 (s, 1). Satisfactory analytical and ^{13}C NMR spectroscopic data could not be obtained for this compound with the small amount available.

(±)-1,16-Didehydro-17-hydroxy-23-(phenylmethoxy)-1,12-secodaphnane (33). IR: 3360 (br), 1665 cm^{-1}. ^1H NMR (500 MHz): δ 1.05 (s, 3), 1.09 (s, 3), 1.11 (m, 2), 1.25 (m, 5), 1.38 (m, 4), 1.43 (s, 3), 1.49–1.87 (m, 19), 1.97 (m, 1), 2.31 (m, 1), 3.46 (m, 2), 3.98 (br s, 1), 4.29 (s, 1), 4.53 (s, 2), 7.29 (m, 1), 7.35 (m, 4), 7.84 (d, 1, J = 1.4). ^{13}C NMR (100 MHz): δ 16.88 (2), 19.36 (2), 23.41 (2), 23.52 (3), 27.30 (2), 27.75 (3), 28.82 (2), 29.64 (2), 29.91 (3), 33.59 (2), 34.16 (2), 38.05 (0), 40.99 (1), 41.12 (2), 42.46 (0), 43.59 (1), 49.87 (1), 53.32 (1), 60.08 (1), 71.17 (2), 71.79 (0), 72.89 (2), 127.52 (1), 127.54 (1), 128.34 (1), 138.53 (0), 170.13 (1). MS (FAB): 438.3 M^+ base (100), 420.3 (24), 288.2 (7). Satisfactory analytical data could not be obtained for this compound with the small amount available.

(±)-Amino Ether 34. IR (CCl_4): 2960, 1115 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ passed through alumina): δ 0.91 (s, 3), 1.18 (s, 3), 1.22 (m, 1), 1.32 (m, 1), 1.38–1.82 (m, 15), 1.62 (s, 3), 1.88 (m, 2), 2.05 (m, 2), 3.42 (m, 3), 4.51 (s, 2), 4.84 (s, 1), 7.26–7.37 (m, 5). ^{13}C NMR (100 MHz): δ 21.13 (2), 22.22 (2), 24.63 (3), 25.44 (2), 27.22 (2), 27.88 (2), 28.82 (2), 28.93 (3), 29.94 (2), 31.60 (3), 35.98 (2), 36.84 (0), 37.46 (1), 42.16 (2), 47.33 (0), 48.37 (1), 54.24 (1), 55.85 (1), 71.37 (0), 71.42 (2), 71.53 (0), 72.89 (2), 85.90 (1), 127.46 (1), 127.49 (1), 128.32 (1), 138.61 (0). TLC: R_f 0.3 (5:1 hexanes/EtOAc). MS (FAB): 436.2 MH^+ base (100), 344.1 (6). Anal. Calcd for $C_{29}H_{41}NO_2$: C, 79.95; H, 9.49; N, 3.22. Found: C, 79.65; H, 9.32; N, 3.24.

(±)-17-Hydroxy-23-(phenylmethoxy)daphnane (35). IR: 3600–3120 cm^{-1}. ^1H NMR (400 MHz): δ 0.79 (t, 1, J = 11.0), 0.90 (s, 3), 1.15 (s, 3), 1.25–1.95 (m, 18), 1.31 (s, 3), 2.03–2.18 (m, 2), 2.63 (d, 1, J = 14.6), 2.84 (d, 1, J = 3.1), 3.37 (m, 2), 3.67 (br d, 1, J = 12.7), 4.07 (br s, 1), 4.50 (s, 2), 7.26–7.35 (m, 5). ^{13}C NMR (100 MHz): δ 22.46 (2), 23.07 (2), 25.34 (2), 25.52 (3), 26.67 (3), 28.01 (2), 28.03 (2), 28.98 (2), 29.00 (2), 30.35 (3), 36.41 (2), 37.13 (0), 39.77 (1), 41.59 (2), 41.91 (1), 46.55 (2), 48.37 (0), 51.09 (1), 62.16 (1), 71.61 (2), 72.39 (0), 72.77 (2), 73.17 (0), 127.41 (1), 127.48 (1), 128.25 (1), 138.51 (0). TLC: R_f 0.3 (95:4.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH alumina).

MS (FAB): 438.3 MH^+ base (100), 288.2 (24). Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.59; H, 9.90; N, 3.20. Found: C, 79.28; H, 10.01; N, 3.06.

(±)-17-Hydroxy-23-(phenylmethoxy)-12,16-cyclo-1,12-secodaphnane (36). Mp 114–6 °C. IR: 3500–3000 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ passed through alumina): δ 0.79 (s, 3), 1.09 (dd, 1, J = 1.8, 3.9), 1.13 (s, 3), 1.23 (m, 1), 1.24 (s, 3), 1.31 (m, 2), 1.39–1.81 (m, 17), 1.98–2.10 (m, 2), 2.51 (d, 1, J = 4.4), 3.34 (s, 1), 3.39 (dt, 2, J = 0.9, 6.4), 4.49 (s, 2), 7.26–7.36 (m, 5). ^{13}C NMR (100 MHz): δ 16.54 (2), 20.90 (3), 23.26 (2), 25.17 (2), 26.50 (2), 28.82 (3), 29.26 (2), 29.72 (3), 30.08 (2), 36.11 (2), 36.32 (0), 36.52 (0), 38.04 (2), 40.16 (2), 41.52 (1), 46.00 (1), 48.60 (1), 50.23 (0), 53.91 (1), 58.83 (1), 71.26 (2), 72.60 (0), 72.85 (2), 127.52 (1), 128.34 (1), 138.58 (0). TLC: R_f 0.25 (90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH). Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.59; H, 9.90; N, 3.20. Found: C, 79.54; H, 10.04; N, 3.12. This material was recrystallized from diisopropyl ether by being allowed to stand at rt for a few days to give X-ray quality tan tinted crystals.

(±)-17-Hydroxy-16-methyl-23-(phenylmethoxy)daphnane (37a). IR: 3420 (br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ passed through alumina): δ 0.79 (m, 1), 0.93 (s, 3), 1.11 (d, 3, J = 7.0), 1.14 (s, 3), 1.24–1.42 (m, 4), 1.32 (s, 3), 1.47 (m, 2), 1.60–1.93 (m, 12), 2.04–2.14 (m, 2), 2.91 (d, 1, J = 4.1), 3.38 (dt, 2, J = 2.0, 6.5), 3.94 (m, 2), 4.50 (s, 2), 7.26 (7.37, m, 5). ^{13}C NMR (100 MHz, $CDCl_3$ passed through alumina): δ 17.88 (2), 21.30 (3), 23.33 (2), 25.15 (2), 26.02 (3), 26.44 (3), 28.04 (2), 28.23 (2), 28.92 (2), 29.89 (2), 30.62 (3), 36.36 (2), 38.41 (0), 39.27 (1), 42.18 (2), 47.35 (1), 47.87 (0), 49.25 (1), 51.99 (1), 64.43 (1), 71.75 (2), 72.69 (0), 72.87 (2), 73.28 (0), 127.51 (1), 127.59 (1), 128.34 (1), 138.63 (0). MS (FAB): 452.4 MH^+ base (100). Anal. Calcd for $C_{30}H_{45}NO_2$: C, 79.77; H, 10.04; N, 3.10. Found: C, 79.91; H, 10.09; N, 3.16.

(±)-16-Ethyl-17-hydroxy-23-(phenylmethoxy)daphnane (37b). IR: 3600–3100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ passed through alumina): δ 0.80 (m, 1), 0.85 (t, 3, J = 7.5), 0.94 (s, 3), 1.13 (s, 3), 1.25–1.93 (m, 20), 1.32 (s, 3), 2.12 (m, 2), 2.93 (br s, 1), 3.38 (dt, 2, J = 1.6, 6.7), 3.63 (m, 1), 3.88 (br s, 1), 4.50 (s, 2), 7.26–7.36 (m, 5). ^{13}C NMR (100 MHz, $CDCl_3$ passed through alumina): δ 12.53 (3), 17.70 (2), 23.36 (2), 25.06 (2), 26.03 (3), 26.38 (3), 27.92 (2), 28.21 (2), 28.51 (2), 28.85 (2), 30.38 (2), 30.58 (3), 36.32 (2), 38.17 (0), 39.28 (1), 41.95 (2), 44.17 (1), 48.17 (0), 51.74 (1), 56.05 (1), 64.41 (1), 71.63 (2), 72.44 (0), 72.76 (0), 72.86 (2), 127.42 (1), 127.49 (1), 128.25 (1), 138.50 (0). TLC: R_f 0.5 (49:1 EtOAc/MeOH, alumina). MS (FAB): 466.6 MH^+ base (100), 374.5 (6), 316.5 (41). Anal. Calcd for $C_{31}H_{47}NO_2$: C, 79.95; H, 10.17; N, 3.01. Found: C, 79.78; H, 10.04; N, 2.97.

(±)-12,13-Didehydro-17-hydroxy-23-(phenylmethoxy)-1,12-secodaphnane (39). To a solution of 43 mg (99 μmol) of imine **30**, contaminated with approximately 4% of another imine, in 0.6 mL of MeOH was added 100 μL (100 μmol) of 1 N HCl, followed by 49 mg (0.64 mmol) of $NaBH_3CN$. After the solution was stirred for 18 h and TLC analysis (90:9.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH) indicated the reaction was incomplete, an additional 90 μL (90 μmol) of 1 N HCl and 3.8 mg (0.06 mmol) of $NaBH_3CN$ were added portionwise over 3 h. The solution was then quenched with 1 N HCl (100 μL) until pH ≈ 2, diluted with benzene (1 mL), and concentrated. The residue was partitioned between ether (5 mL) and 1 N NaOH (10 mL), and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were dried and concentrated to give 43 mg of a colorless oil. Flash chromatography on 4 g of silica gel using 95:4.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH gave, in order of elution, 3 mg (7%) of an unidentified amine as a colorless oil and 38 mg (88%) of amino alcohol **39** as a colorless oil. IR: 3200 (br) cm^{-1}. ^1H NMR (500 MHz): δ 0.91 (m, 1), 1.07 (s, 3), 1.11 (s, 3), 1.27 (s, 3), 1.38–1.50 (m, 4), 1.55–1.97 (m, 10), 2.04 (m, 1), 2.13 (m, 1), 2.29 (m, 1), 2.43 (dd, 1, J = 7.0, 15.6), 2.52 (m, 2), 2.86 (m, 1), 3.20 (br s, 1), 3.41 (m, 2), 3.55 (m, 1), 4.51 (s, 2), 5.58 (d, 1, J = 6.2), 7.27–7.37 (m, 5). ^{13}C NMR (100 MHz, $CDCl_3$ passed through alumina): δ 22.15 (2), 24.60 (2), 25.94 (3), 26.96 (2), 27.90 (3), 30.00 (3), 30.17 (2), 32.89 (2), 33.36 (2), 36.81 (2), 38.30 (0), 39.61 (2), 40.03 (1), 41.90 (0), 42.17 (1), 46.34 (1), 47.71 (2), 54.14 (1), 71.38 (2), 72.61 (0), 72.91 (2), 118.77 (1), 124.25 (1), 127.55 (1), 128.34 (1), 138.52 (0), 147.21 (0). Anal. Calcd for $C_{29}H_{43}NO_2$: C, 79.59; H, 9.90; N, 3.20. Found: C, 79.43; H, 9.74; N, 3.15.

(±)-23-Phenylmethoxydaphnan-17-ol (35). To a solution of 16.5 mg (0.038 mmol) of amino alcohol **39**, contaminated with approximately 7% of another amino alcohol, in 1.0 mL of dry CH_2Cl_2 was added dropwise 12.3 μL (0.114 mmol) of phenyl isocyanate which had been freshly distilled from P_2O_5. The solution was stirred for 1 h, and an additional 3.0 μL (0.03 mmol) of phenyl isocyanate was added. The solution was stirred for 1 h and concentrated. A solution of the residue in 1.0 mL of 97% formic acid was heated at reflux for 2 h 15 min, and a stream of N_2 was passed over the reaction mixture, while it was heated, to evaporate the solvent. A solution of the resulting tan residue in 1 mL of 2 N methanolic KOH was heated at reflux for 3 h, allowed to cool to rt, diluted with benzene, and concentrated. The residue was partitioned between ether (5 mL), and H_2O (5 mL) and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried and concentrated to give 23 mg of a tan oil. Chromatography on 4 g of alumina using 4:1 hexanes/EtOAc, 1:1 hexanes/EtOAc, EtOAc, 49:1 EtOAc/MeOH, 19:1 EtOAc/MeOH, and then 7:3 EtOAc/MeOH gave 8.5 mg (52%) of amino alcohol **35**, identified by comparison of its NMR spectra with the sample obtained in foregoing procedures G and H.

Reaction of Amino Alcohol 35 with $SOCl_2$. To a pale yellow solution of 25.0 mg (0.057 mmol) of amino alcohol **35** in 250 μL of dry pyridine at 0 °C was added 4.4 μL (0.06 mmol) of $SOCl_2$, freshly distilled from 10 wt % triphenyl phosphite. The solution was stirred for 1 h, quenched with 1 drop of H_2O, and partitioned between CH_2Cl_2 (0.5 mL) and H_2O (0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 0.5 mL), and the combined organic layers were washed with 1 N NaOH (1 mL). The aqueous layer was back extracted with CH_2Cl_2 (3 × 0.5 mL), and the combined organic layers were dried and concentrated to give 22 mg of an oil. Chromatography on 4 g of alumina using 1:1 hexanes/EtOAc, EtOAc, 49:1 EtOAc/MeOH, 19:1 EtOAc/MeOH, and then 7:3 EtOAc/MeOH gave, in order of elution, 4.0 mg (14%) of chloroamine **40** as an oil, 8.7 mg (35%) of amino alkene **42** as a pale yellow oil, and 13.0 mg (53%) of amino alkene **41** as a colorless oil.

(±)-17-Chloro-23-(phenylmethoxy)daphnane (40). IR: 2930, 1110 cm^{-1}. ^1H NMR (400 MHz): δ 0.80 (m, 1), 0.91 (s, 3), 1.24–2.14 (m, 20), 1.72 (s, 6), 2.62 (d, 1, J = 14.6), 2.77 (d, 1, J = 3.3), 3.38 (m, 3), 4.51 (s, 2), 7.26–7.36 (m, 5). ^{13}C NMR (100 MHz): δ 22.69 (2), 23.66 (2), 25.36 (2), 25.85 (3), 28.22 (2), 28.43 (2), 28.89 (2), 29.13 (2), 29.96 (3), 32.18 (3), 36.47 (2), 37.36 (0), 41.97 (2), 42.10 (1), 44.48 (1), 46.72 (2), 49.33 (0), 51.18 (1), 63.18 (1), 71.69 (2), 72.56 (0), 72.91 (2), 75.58 (0), 127.52 (1), 127.62 (1), 128.36 (1), 138.5 (0). TLC: R_f 0.4 (5:1 hexanes/EtOAc, alumina). MS (FAB): 456.5 MH^+ (37), 420.4 base (100). Satisfactory analytical data could not be obtained for this compound with the small amount available.

(±)-3,17-Didehydro-23-(phenylmethoxy)daphnane (41). IR: 2940, 740 cm^{-1}. ^1H NMR (400 MHz): δ 0.93 (m, 1), 0.93 (s, 3), 1.30 (m, 3), 1.41–1.94 (m, 13), 1.64 (s, 3), 1.78 (s, 3), 2.20 (dd, 1, J = 7.4, 10.7), 2.43 (m, 2), 2.73 (d, 1, J = 13.6), 3.00 (d, 1, J = 13.8), 3.35 (t, 2, J = 6.8), 3.57 (s, 1), 4.48 (s, 2), 7.32 (m, 5). ^{13}C NMR (100 MHz): δ 20.19 (3), 20.30 (3), 22.66 (2), 25.47 (2), 25.63 (3), 25.70 (2), 27.65 (2), 27.73 (2), 28.88 (2), 29.10 (2), 36.16 (2), 37.52 (0), 41.86 (2), 42.48 (1), 46.30 (2), 48.25 (0), 52.02 (1), 64.02 (1), 71.68 (2), 72.37 (0), 72.77 (2), 124.28 (0), 127.43 (1), 127.52 (1), 128.29 (1), 131.39 (0), 138.64 (0). TLC: R_f 0.55 (95:4.5:0.5 CH_2Cl_2/MeOH/27% NH_4-OH, alumina). MS (FAB): 420.3 MH^+ base (100), 328.2 (11), 270.2 (9). Satisfactory analytical data could not be obtained for this compound due to its decomposition.

(±)-17,19-Didehydro-23-(phenylmethoxy)daphnane (42). IR: 1645 cm^{-1}. ^1H NMR (400 MHz): δ 0.91 (m, 1), 0.92 (s, 3), 1.21–1.57 (m, 7), 1.65–1.87 (m, 9), 1.87 (s, 3), 1.94 (m, 1), 2.17 (m, 2), 2.35 (m, 1), 2.63 (d, 1, J = 14.4), 2.86 (d, 1, J = 14.7), 3.17 (d, 1, J = 14.2), 3.39 (m, 2), 4.51 (s, 2), 4.89 (s, 1), 4.90 (s, 1), 7.26–7.36 (m, 5). ^{13}C NMR (100 MHz): δ 22.77 (3), 22.62 (2), 24.86 (2), 25.42 (2), 25.89 (3), 28.17 (2), 28.24 (2), 28.70 (2), 29.05 (2), 36.43 (2), 37.21 (1), 37.42 (0), 41.28 (1), 42.12 (2), 46.73 (2), 48.40 (0), 51.80 (1), 63.63 (1), 71.76 (2), 72.09

(0), 72.88 (2), 109.56 (2), 127.46 (1), 127.55 (1), 128.31 (1), 138.63 (0), 146.51 (0). TLC: R_f 0.25 (97.5:2.3:0.2 CH_2Cl_2/MeOH/27% NH_4OH, alumina). Anal. Calcd for $C_{29}H_{41}NO$: C, 83.00; H, 9.85; N, 3.34. Found: C, 82.69; H, 10.07; N, 3.37.

(±)-Daphnan-23-ol (43). A mixture of 13.8 mg (0.033 mmol) of amino alkene **42** and 12.0 mg of 10% Pd/C in 1 mL of absolute EtOH was stirred under H_2 (1 atm) for 1.5 h and opened to the atmosphere. After 1 drop of 12 N HCl was added, the mixture was stirred under H_2 (1 atm) for another 1.5 h and filtered through Celite. The filtrate was concentrated, and the residue was partitioned between CH_2Cl_2 (1 mL) and 1 N NaOH (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 1 mL), and the combined organic layers were dried and concentrated to give 13 mg of a white solid. Chromatography on 2 g of alumina using 95:4.5:0.5 CH_2Cl_2/MeOH/27% NH_4OH gave 8 mg (73%) of **43**, mp 164–7 °C. IR: 3500–2900 cm^{-1}. ^1H NMR (400 MHz): δ 0.85 (m, 1), 0.90 (d, 3, J = 6.6), 0.92 (s, 3), 1.00 (d, 3, J = 6.4), 1.25–1.43 (m, 7), 1.51–1.93 (m, 14), 2.18 (dd, 1, J = 7.4, 10.4), 2.70 (d, 1, J = 4.9), 2.74 (d, 1, J = 14.3), 3.24 (br d, 1, J = 147), 3.56 (m, 2). ^{13}C NMR (100 MHz): δ 21.10, 21.51, 22.84, 25.47, 26.01, 27.21, 27.82, 28.73, 29.00, 31.06, 31.22, 36.85, 37.17, 38.18, 41.77, 41.91, 47.36, 48.18, 51.72, 63.10, 64.31, 72.18. [Lit.[2] mp 168–71 °C. IR: 3250 (s). ^1H NMR (250 MHz): δ 0.90 (d, 3, J = 6.6), 0.91 (s, 3), 1.00 (d, 3, J = 6.4), 1.23–2.00 (m, 22), 2.15–2.22 (m, 1), 2.69 (d, 1, J = 5.0), 2.73 (d, 1, J = 14.2), 3.24 (br d, 1, J = 14.2), 3.54–3.59 (m, 2). ^{13}C NMR (50 MHz): δ 21.05, 21.47, 22.71, 25.37, 25.91, 27.09, 27.74, 28.65, 28.87, 30.90, 31.11, 36.71, 37.02, 38.07, 41.57, 41.77, 47.15, 48.03, 51.57, 62.92, 63.85, 72.05].

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Supplementary Material Available: Complete ^1H NMR and ^{13}C NMR peak assignments of known compounds **6** and **44**; details for the structure elucidation of compounds **7**, **16**, **17**, **18**, **19**, **20**, **30**, **31**, **33**, **34**, **37a**, **37b**, and **39** (25 pages). This material is contained in 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.

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