Supplementary Material Available: General experimental procedure for the hydrogenation of **22**; experimental procedure for the cyclization of **20**; ^{1}H NMR spectra of compounds **23**, **24**, **26**, and **32**; ^{1}H NMR spectrum of unpurified **25**/**26** mixture (4:1) from diimide reduction of **22**; ^{1}H NMR spectrum of unpurified alcohol **35**; ^{1}H NMR and IR spectra of synthetic and natural bukittinggine; ^{1}H NMR spectra of expanded region (0.6–4.8 ppm) of synthetic and natural bukittinggine; and the ^{1}H NMR spectrum of aldehyde **13** (15 pages). This material is found in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Daphniphyllum Alkaloids. 15. Total Syntheses of (±)-Methyl Homodaphniphyllate and (±)-Daphnilactone A[1]

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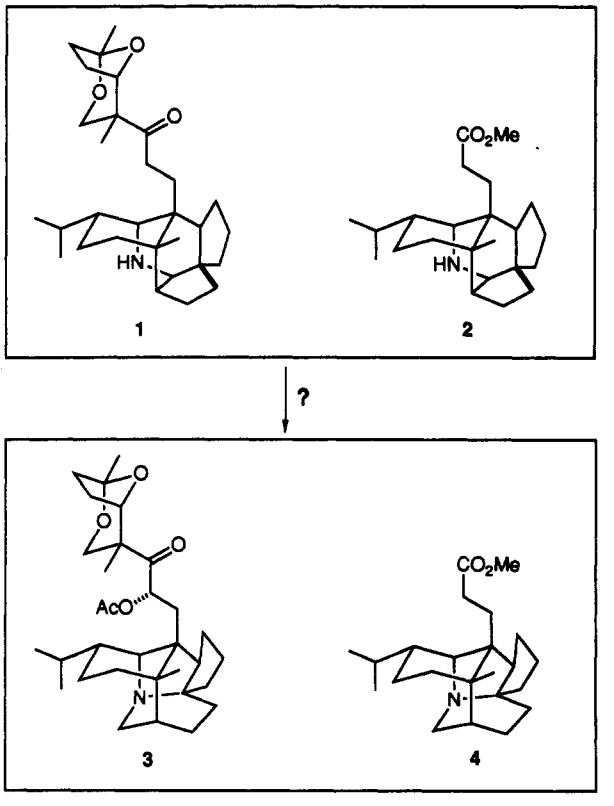
Biomimetic total syntheses of (±)-daphnilactone A (**6**) and (±)-methyl homodaphniphyllate (**4**) have been carried out. The syntheses began with the preparation of tricyclic lactone ether **18d**, which was reduced to diol **19d** with $LiAlH_4$. Oxidation of **19d** gave a sensitive dialdehyde (**20d**), which was treated sequentially with ammonia and warm acetic acid to obtain the hexacyclic amino ether **22d**. The tetracyclization process leading from **19d** to **22d** proceeded in 47% yield and resulted in the formation of five new σ-bonds and four new rings. After hydrogenation of the double bond, the saturated amino ether **7** was fragmented by treatment with diisobutylaluminum hydride in refluxing toluene. Unsaturated amino alcohol **23** was obtained in 71% yield, accompanied by a smaller amount of the simple elimination product **24**. Compound **23** was converted into (±)-daphnilactone A (**6**) by oxidation to the unsaturated amino acid, which was cyclized by treatment with aqueous formaldehyde at pH 7. For the preparation of **4**, compound **23** was oxidized and the resulting amino acid esterified to obtain **26**. Treatment of this compound with phenyl isocyanate gave a urea derivative (**27**) that underwent smooth cyclization to (±)-methyl homodaphniphyllate (**4**) in refluxing formic acid. From homogeranyl iodide, the limiting starting material, compound **6** was obtained in 11 steps and 8% overall yield and compound **4** was obtained in 13 steps and 11% overall yield.

Although the secodaphnane skeleton, as embodied in secodaphniphylline (**1**) and the C-22 *Daphniphyllum* alkaloid methyl homosecodaphniphyllate (**2**), is probably the initial skeleton biosynthesized,[3] the daphnane skeleton, as typified by daphniphylline (**3**) and methyl homodaphniphyllate (**4**), is by far more common. It has been proposed[4] that the daphnane skeleton might arise from the secodaphnane skeleton by way of the unknown fragmentation product **5**. Intramolecular addition of the N—H bond to the C=C bond would give the daphnane skeleton (e.g., **3**, **4**, etc.). The possible intervention of a biosynthetic intermediate such as **5** is further suggested by the occurrence of the minor *Daphniphyllum* alkaloid daphnilactone A (**6**), since this compound could arise from **5** by a Mannich-type process involving formaldehyde or its equivalent. The purpose of the present work was to find a way to simulate the process outlined schematically, that is, to convert a secodaphnane intermediate into **5** and show that this material provides alkaloids **4** and **6**.[5] The basic plan of the project is outlined in Scheme I. Thus, we thought we could use the tetracyclization reaction[6] to prepare an angularly functionalized secodaphnane **A**, which would undergo Eschenmoser–Grob fragmentation[7] to an imine **B**; reduction of the latter intermediate would provide **C**, the putative biosynthetic link between the secodaphnanes and daphnanes.



(1) For part 14, see: Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.*, preceding paper in this issue.

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(3) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.*, third paper in the series in this issue.

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(5) For preliminary communications, see: (a) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745. (b) Ruggeri, R. B.; McClure, K. F.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1530. (b) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714.

(6) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.*, second paper in the series in this issue.

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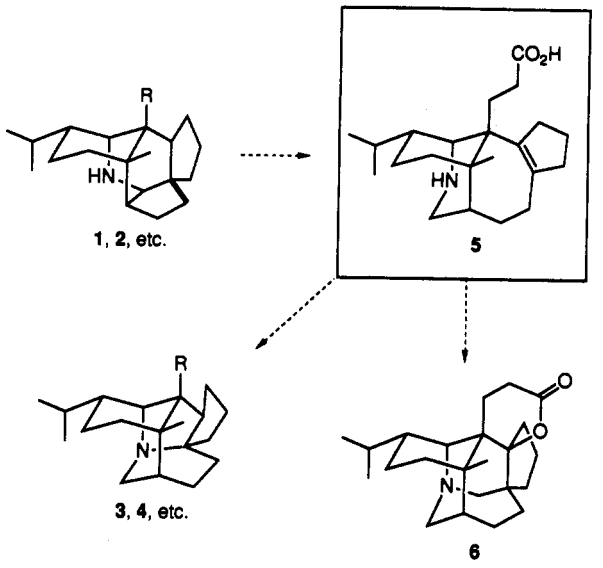
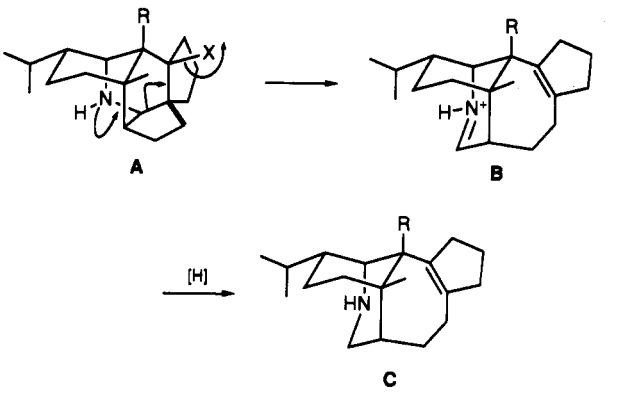


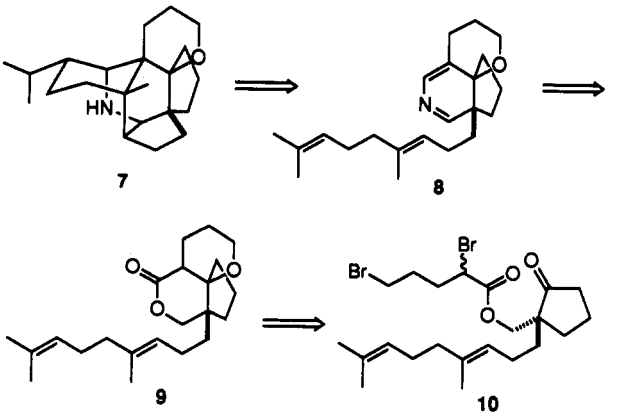
It occurred to us that compound 7 (Scheme II), in which the three-carbon side chain of methyl homosecodaphniphyllate is tied back into the pentacyclic skeleton by an ether link, might provide a suitable substrate for fragmentation. To prepare 7 by the tetracyclization reaction, we would need the tricyclic aza diene 8. With this goal in mind, we set about to investigate a new bisannulation process that would lead to a tricyclic lactone ether (9) by an intramolecular Reformatsky reaction followed by cyclic ether formation.

Although a few examples of intramolecular Reformatsky reactions were known,[8] the subsequent ring closure was not precedented. To examine the feasibility of the proposed bisannulation reaction, we prepared the simple substrates shown in Scheme III. Treatment of ethyl 2-oxocyclopentanecarboxylate (11) with triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid gave the intermediate diethyl ketal **12**. Triethylamine was added to neutralize the acid and the mixture was distilled, with elimination of ethanol, to provide a nearly equal mixture of isomeric enol ether isomers **13**. The methyl ester corresponding to **11** was also employed for this process, and the resulting product corresponding to **13** was obtained without detectable transesterification. The mixture of enol ethers was deprotonated with LDA or potassium hexamethyldisilazane in THF and alkylated with methyl iodide or methallyl chloride to obtain **14a** or **14b**. Unsaturated ester **14b** was also obtained in excellent yield by treatment of diethyl ketal **12** with excess potassium hexamethyldisilazane and methallyl chloride. Reduction of the ester function with $LiAlH_4$ provided alcohols **15a** and **15b**. Treatment of these compounds with dibromopentanoyl bromide (**16**)[9] furnished esters **17a** and **17b** as diastereomeric mixtures. Treatment of these substrates with activated zinc, prepared by treatment of $ZnCl_2$ with sodium naphthalenide in THF,[10] gave tricyclic lactone ethers **18a** and **18b**. Although the Reformatsky reaction was found to be quite rapid, the ensuing ether-forming step was slow in pure THF. For this reason, HMPA was added immediately after addition of the cyclization substrate to the activated zinc suspension. Both **18a** and **18b** are crystalline solids; the stereochemistry indicated was determined by single-crystal X-ray analysis of **18a**. The identical sequence of reactions, employing homoprenyl iodide[11] and homogeranyl iodide,[12] afforded the oily tricyclic lactone ethers **18c** and **18d**.

Scheme I



Scheme II



The most problematic element of the synthetic plan was the possiblity that the tertiary ether might not survive the acidic conditions of the tetracyclization protocol. We initially explored this reaction with the homoprenyl analogue **18c** (Scheme IV) Reduction of **18c** with $LiAlH_4$ provided diol **19c**, which was oxidized by the Swern procedure.[13] The intermediate dialdehyde **20c** is rather fragile and undergoes retro-Michael reaction to give a monocyclic diene dial upon brief exposure to silica gel. Thus, the crude dialdehyde was treated directly with gaseous ammonia, whereupon highly polar materials, presumably various isomeric aminals, were produced. Stirring this crude mixture over anhydrous potassium carbonate provided aza diene **21c**, which when heated in benzene slowly gave imine **22c** in low yield. However, **22c** was also gradually formed

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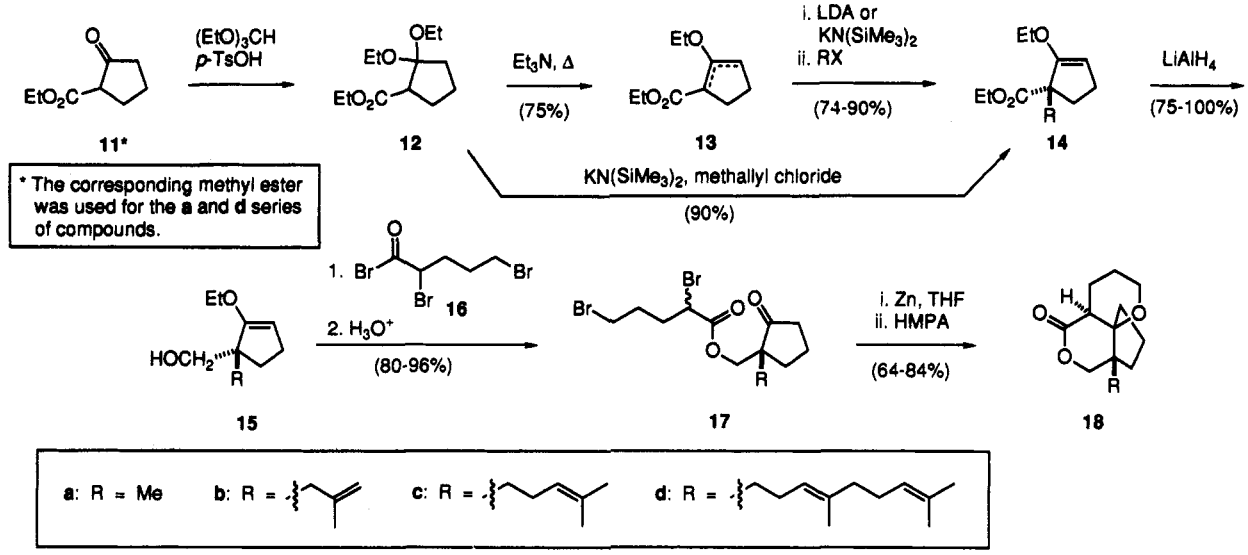
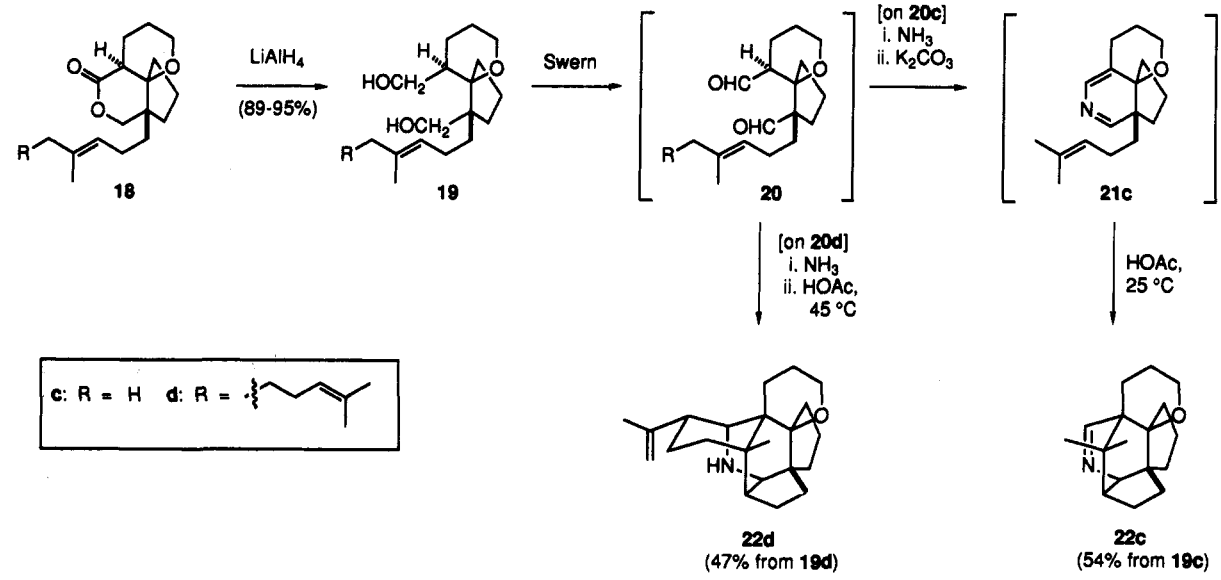
Scheme III



Scheme IV

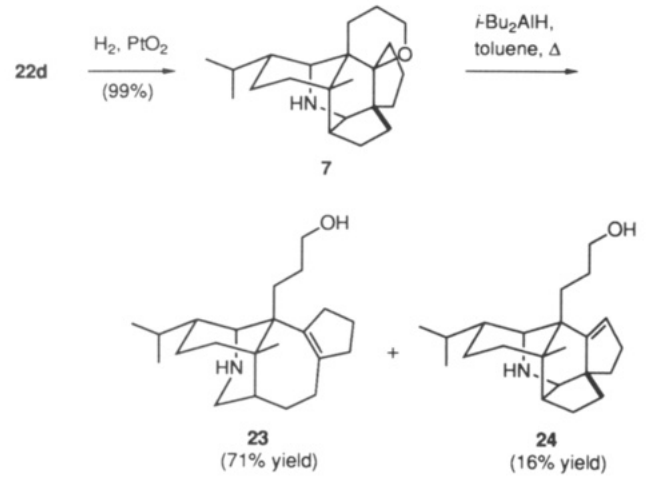


at room temperature when a chloroform solution of the initial adduct of **20c** and ammonia was dried over $MgSO_4$ and extended exposure in this manner eventually provided **22c** in acceptable yield. Finally, pentacyclic imine **22c** was rapidly produced upon addition of acetic acid to the crude adduct of **20c** and ammonia. The overall yield of **22c** was 54%, based on diol **19c**. Although this yield was not as high as we have observed in other applications of the tetracyclization reaction, it was nevertheless quite encouraging, given the added complication of the tertiary ether function in this system.

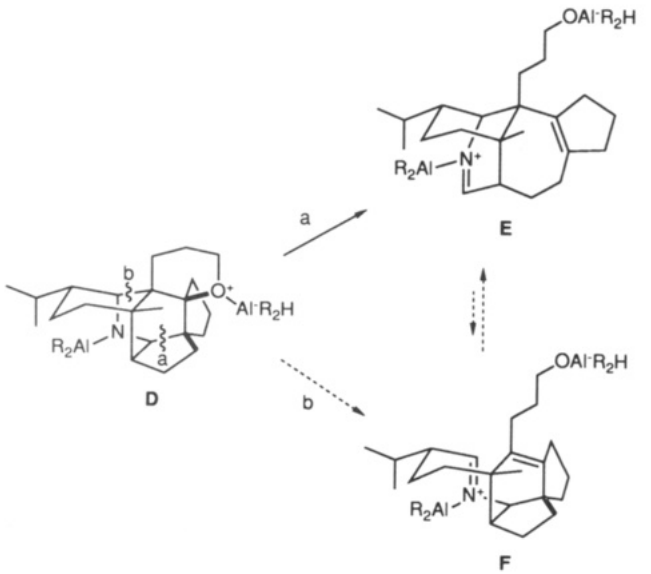
With the Diels–Alder step of the tetracyclization process authenticated, we moved to the actual system required for the synthesis of our target hexacyclic amino ether **7**. As shown in Scheme IV, diol **19d** was oxidized by the Swern protocol, ammonia was added to the CH_2Cl_2 solution, and an acetic acid solution of the crude product was warmed at 45 °C, to obtain **22d** in 47% yield. Given the overall result of the process, formation of five σ-bonds and four new rings, the modest yield was considered quite acceptable.

Hydrogenation of the double bond over Adam's catalyst proceeded in quantitative yield to provide the saturated hexacyclic amino ether **7**. To bring about the fragmentation suggested in Scheme I, we needed a Lewis acid to activate the alkoxy leaving group and a reducing agent to reduce the imine or immonium ion expected to result. We thought that a dialkylaluminum hydride might fulfil both functions and perhaps also activate the nucleofugal group by deprotonation of the secondary amine. To this end, **7** was treated with excess diisobutylaluminum hydride in refluxing toluene for 72 h to obtain the desired unsaturated amino alcohol **23**, accompanied by some of the simple elmination product **24**. Compounds **23** and **24** were not separable by silica gel chromatography. However, they differ considerably in their solubility in benzene and could be separated by extracting the solid mixture with hot benzene. In this manner, pure **24** was obtained as a high-melting, insoluble solid in 16% yield and **23** was obtained as a slightly impure glass in 71% yield.

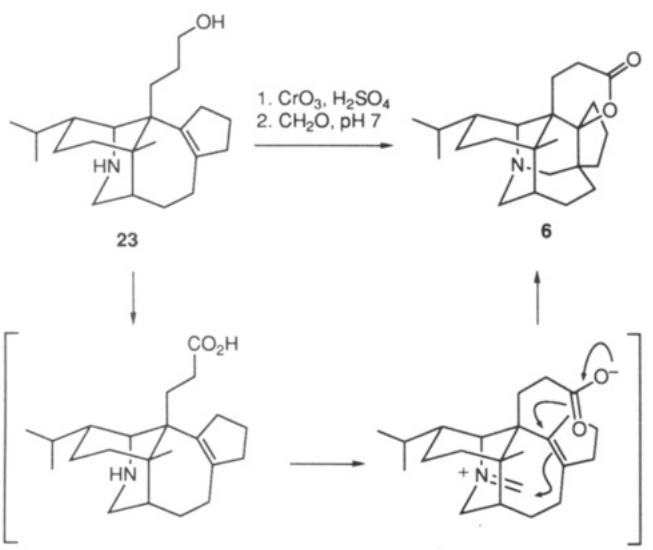
The structure of byproduct **24** was initially assigned on the basis of its ^1H and ^{13}C NMR spectra, which showed the presence of a trisubstituted double bond and also contained resonances characteristic of the secodaphnane methine groups. This assignment was confirmed by converting the material into (±)-methyl homosecodaphni-



Scheme V



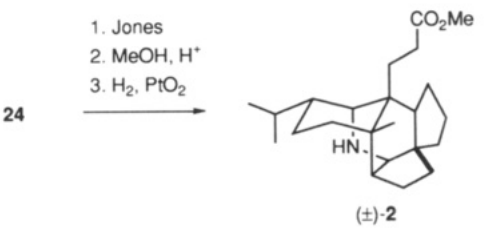
Scheme VI



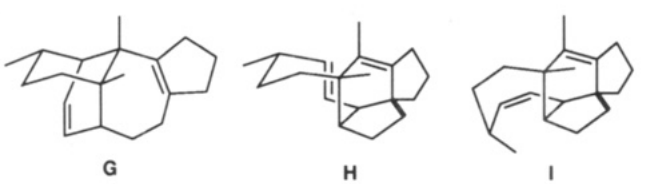
phyllate ((±)-2) by Jones oxidation, Fischer esterification, and hydrogenation over Adam's catalyst. The product of this sequence was identical by ^1H NMR spectroscopy and TLC mobility with an authentic sample provided by Professor S. Yamamura of Keio University.

The fragmentation reaction that produces **23** is interesting because the pseudosymmetry of the 4-alkoxy-

Figure 1. Skeleton of hexacyclic amino ether **7**, with hydrogens omitted for clarity. The dihedral angles 2–3–11–22 and 13–12–11–22 are 175° and 135°, respectively.



piperidine subunit could, a priori, permit two different bond-cleavages. Thus, the postulated fragmentation substrate **D** could suffer cleavage of bond "a" to give **E** or bond "b" to provide isomer **F** (Scheme V). An examination of molecular models actually suggests that the latter mode of fragmentation should be preferred on stereoelectronic grounds, since the dihedral angle between bond "b" and the C–O bond is 175° whereas that between bond "a" and the C–O bond is 135° (Figure 1).[14] However, it is also clear from models that the product of fragmentation mode "a" is of much lower energy than that from fragmentation mode "b". The possible products were modelled as their carbocyclic analogues **G**, **H**, and **I**. The calculated heats of formation of isomers **H** and **I** were greater than that of **G** by 12 and 29 kcal/mol, respectively. The high regioselectivity of the fragmentation reaction may be a manifestation of this excess strain energy in the transition state for mode "b" fragmentation. However, it is also worthy of note that immonium ions **E** and **F** might be in equilibrium by the Cope rearrangement and it is possible that, even if the fragmentation provided **F**, its high strain energy would probably result in complete conversion to **E**. Rapid Cope rearrangements of similar systems are well-precedented.[15]



For completion of the synthesis of daphnilactone A (Scheme VI), amino alcohol **23** was oxidized to the corre-

(14) The structure was optimized by the Allinger MM2 molecular mechanics program using PCMODEL 4.0, Serena Software, Bloomington, IN 47402-3076.
(15) Marshall, J. A.; Babler, J. H. *J. Org. Chem.* **1969**, *34*, 4186.
(16) Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.*, first paper in the series in this issue.

sponding amino acid, which was treated directly with aqueous formaldehyde at pH 7 to obtain (±)-daphnilactone A (**6**), identical by ^{1}H NMR spectroscopy and TLC mobility with an authentic sample provided by Professor Yamamura. The overall yield of the two-step conversion of **23** to **6** was only 50%, with the principal loss coming in the oxidation step. Since the infrared spectrum of the crude oxidation product showed enone absorptions, we think that the double bond undergoes competing allylic oxidation. The complete synthesis of daphnilactone A required 11 steps (homogeranyl iodide → **14d** → **15d** → **17d** → **18d** → **19d** → **20d** → **22d** → **7** → **23** → **6**) and proceeded in 8% overall yield.

In the first paper in this series, we reported a classical 15-step total synthesis of (±)-methyl homodaphniphyllate (**4**),[16] a synthesis that was flawed by our inability to control the stereochemistry at the isopropyl-bearing stereocenter. As we have seen, however, the tetracyclization process delivers the secodaphnane skeleton in a completely stereoselective manner. With **23** in hand, it was only necessary to cause transannular addition of the secondary amine to the double bond to complete a stereocontrolled synthesis of **4**. To this end, **23** was subjected to Jones oxidation and the resulting amino acid treated with sulfuric acid in refluxing methanol to obtain unsaturated amino ester **26** (Scheme VII). Although disappointed, we were not surprised when **26** was recovered unchanged from other acidic media (e.g., refluxing formic acid, *p*-toluenesulfonic acid in refluxing benzene). Under these acidic conditions the amine is presumably firmly protonated and therefore not nucleophilic even if the double bond also happens to be protonated. However, the *N*-phenylurea derivative **27**, formed by the reaction of **26** with phenyl isocyanate, cyclized smoothly in refluxing formic acid to provide (±)-methyl homodaphniphyllate (**4**) in 63% overall yield. In an alternative sequence of steps, unsaturated amino alcohol **23** was treated serially with phenyl isocyanate, refluxing formic acid, and methanolic potassium hydroxide to obtain (±)-homodaphniphyllol (**28**). Jones oxidation of this material and Fischer esterification of the resulting amino acid provided (±)-**4** in an overall yield of about 70%. These successful cyclizations therefore permitted us to solve the problem of a stereocontrolled synthesis of methyl homodaphniphyllate. The synthesis of (±)-**4** by this route required a total of 13 steps (homogeranyl iodide → **14d** → **15d** → **17d** → **18d** → **19d** → **20d** → **22d** → **7** → **23** → **26** → **27** → **4**) and proceeded in 11% overall yield.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled under N_2 from sodium/benzophenone immediately prior to use. Benzene, dichloromethane, diisopropylamine, and diisopropylamine, and diisopropylethylamine were distilled under N_2 from CaH_2 and used immediately or stored over 3- or 4-Å molecular sieves. Dimethyl sulfoxide (DMSO) was distilled from BaO and stored over 3-Å molecular sieves. The concentration of commercially available solutions of *n*-butyllithium in hexanes was checked by titration using diphenylacetic acid.[17] All reactions involving organometallic reagents or strong bases (e.g., LDA) were conducted under a N_2 atmosphere in dry flasks. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through a fritted-glass funnel, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 230–400-mesh silica gel according to the procedure described by Still.[18] Reactions and chromatography fractions were analyzed using Analtech 250-μm silica gel GF plates. Infrared spectra were recorded as films on NaCl plates unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were measured as $CDCl_3$ solutions at 250 MHz and 50 MHz, unless noted otherwise. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative to internal $CHCl_3$. *J* values are in hertz.

2,5-Dibromopentanoic Acid Bromide (16). A 3-necked 100-mL round-bottomed flask, equipped with an overhead mechanical stirrer, addition funnel, and reflux condenser, was charged with red phosphorus (2.70 g, 90.0 mmol) and δ-valerolactone (18.56 mL, 200 mmol). The reaction mixture was cooled with a room temperature water bath as bromine (24.60 mL, 480 mmol) was added dropwise with the addition funnel (addition time = 30 min, as the initial reaction was quite exothermic, the rate of addition began slowly and was gradually increased). After the addition was completed, the dark slurry was heated with an oil bath at 50 °C for 12 h. The black sludge was stirred at room temperature as a stream of N_2 was passed through the vessel to expel the copious amounts of HBr generated by the reaction. After the noxious brown vapors had been dissipated, the dark liquid was poured into a 100-mL round-bottomed flask and distilled at reduced pressure, employing a 15-cm Vigreux column. A troublesome white solid (postulated to be $POBr_3$) was observed to collect and crystallize in the distillation condenser prior to collection of the desired product. The distillation pathway must be wide enough to not be clogged by this material. The condenser and collection apparatus were changed just before the product began to distill to remove this solid impurity. As the distillation was resumed, the remaining solid was dissolved by the acid bromide and swept over in the initial distillate. The major product-fraction collected (bp = 70–80 °C at 0.150 Torr) yielded 52.70 g (82%) of the acid bromide as a pale yellow liquid. This sample was found to contain small percentages of the α,α-dibromo and α-debromo products. Fractional distillation of this material afforded the desired tribromide, as a colorless liquid, practically free from these impurities. IR: 1795 (s), 1445 (s), 1260 (s). ^{1}H NMR: δ 1.90–2.45 (m, 4), 3.45 (t, 2, *J* = 6.2), 4.62 (dd, 1, *J* = 7.9, 5.6). ^{13}C NMR: δ 29.34, 31.63, 33.08, 57.40, 165.26. Anal. Calcd for $C_5H_7Br_3O$: C, 18.60; H, 2.19; Br, 74.26. Found: C, 18.80; H, 2.35; Br, 73.97.

Alkylation of Ester 13. Methyl 2-Ethoxy-1-(4,8-dimethyl-3,7-nonadienyl)-2-cyclopentene-1-carboxylate (14d). A solution of diisopropylamine (2.24 mL, 16.0 mmol in 40 mL of THF) was cooled with an ice/water bath as *n*-BuLi (9.10 mL of a 1.59 M solution in hexanes, 14.5 mmol) was added by syringe. After 5 min, the reaction vessel was immersed in a dry ice/acetone bath and the methyl ester corresponding to **13** (2.64 g, 15.5 mmol) was added dropwise by syringe. After 1 h, homogeranyl iodide[12] (2.70 g, 9.70 mmol in 10 mL of THF) was added by a cannula to the orange enolate solution and the reaction vessel was immersed in an ice/water bath. After 3 h, the reaction was quenched with 50 mL of water and combined with 50 mL of hexanes, and the aqueous layer was separated and extracted with ether (2 × 50 mL). The combined organic phases were washed with 25 mL of brine, which was back-extracted with 25 mL of ether, and the combined organic extracts were dried, filtered, and concentrated to give 3.5 g of a yellow oil. This crude material was purified by column chromatography on silica (75 g), eluting with 2:98 ether–hexanes, to provide 2.64 g (85%) of the desired ester as a colorless oil. IR: 1740 (s), 1650 (s), 1450 (s). ^{1}H NMR: δ 1.28 (t, 3, *J* = 7.1), 1.59 (bs, 6), 1.62–1.71 (m, 1), 1.68 (s, 3), 1.83–2.11 (m, 8), 2.24–2.42 (m, 3), 3.69 (s, 3), 3.77 (dq, 1, *J* = 9.5, 7.1), 3.82 (dq, 1, *J* = 9.5, 7.1), 4.58 (bs, 1), 5.06–5.17 (m, 2). ^{13}C NMR: δ 14.48, 15.85, 17.68, 23.10, 25.69, 26.70 (2), 32.67, 34.80, 39.68, 51.93, 57.62, 65.08, 96.24, 124.08, 124.32, 131.27, 135.12, 158.62, 175.83. Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.69; H, 10.15.

Ethyl 2-Ethoxy-1-(4-methyl-3-pentenyl)-2-cyclopentene-1-carboxylate (14c). Homoprenyl iodide[11] (1.45 g, 6.90 mmol) was treated in the foregoing manner to afford 1.00 g (55%) of the ethyl ester as a pale yellow oil. IR: 1740 (s), 1655 (s), 1455 (s). ^{1}H NMR (250 MHz): δ 1.24 (t, 3, *J* = 7.1), 1.27 (t, 3, *J* = 7.0), 1.59 (s, 3), 1.67 (s, 3), 1.64–1.69 (m, 1), 1.80–2.02 (m, 4), 2.18–2.43 (m, 3), 3.77 (dq, 1, *J* = 9.7, 7.0), 3.80 (dq, 1, *J* = 9.7, 7.0), 4.14 (q, 2, *J* = 7.1), 4.56 (bs, 1), 5.10–5.16 (m, 1). ^{13}C NMR: δ 14.19, 14.46, 17.49, 23.25, 25.65, 26.68, 32.60, 34.75, 57.57, 60.38, 64.96,

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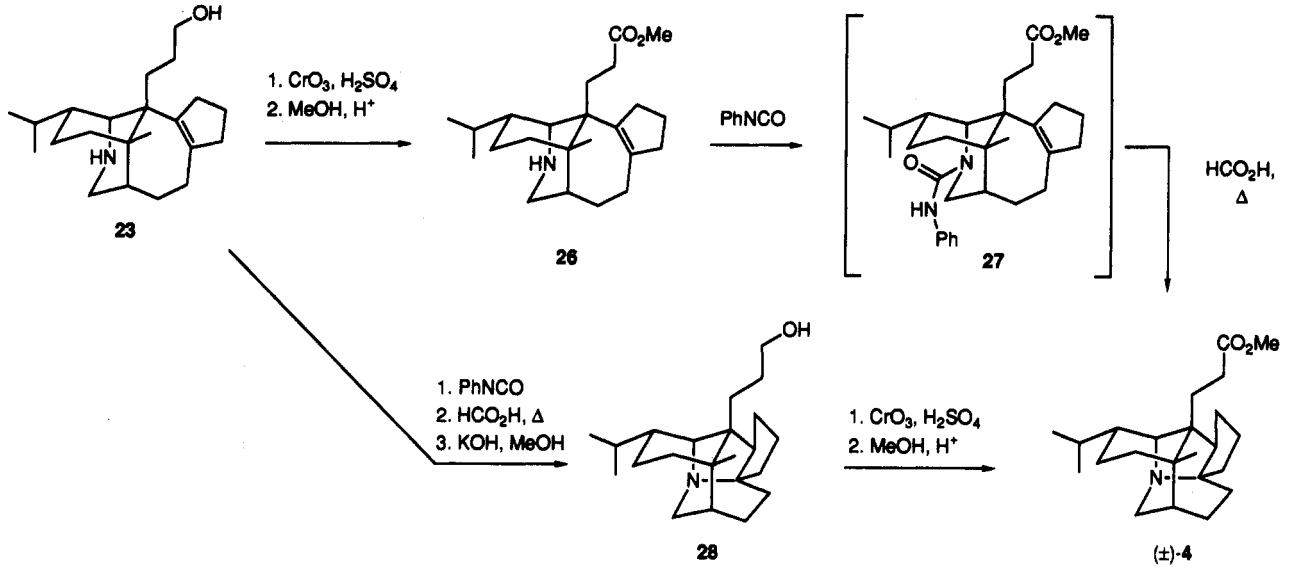
Scheme VII



96.02, 124.35, 131.38, 158.80, 175.23. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.30; H, 9.94.

Methyl 2-Ethoxy-1-methyl-2-cyclopentene-1-carboxylate (14a). The methyl ester corresponding to **13** (2.00 g, 11.7 mmol) was treated in the foregoing manner with a solution of LDA [prepared from diisopropylamine (1.99 mL, 14.2 mmol in 15 mL of THF) and *n*-BuLi (8.10 mL of a 1.59 M solution in hexanes, 12.9 mmol)] and methyl iodide (0.91 mL, 14.6 mmol). Workup and column chromatography on silica (40 g), eluting with 2:98 ether–hexanes, provided 1.60 g (74%) of the desired ester as a pale yellow oil. IR: 1740 (s), 1650 (s), 1450 (s). ^{1}H NMR: δ 1.26 (t, 3, J = 7.0), 1.32 (s, 3), 1.68–1.82 (m, 1), 2.20–2.40 (m, 3), 3.66 (s, 3), 3.76 (dq, 1, *J* = 9.7, 7.0), 3.80 (dq, 1, *J* = 9.7, 7.1), 4.52 (t, 1, *J* = 2.1). ^{13}C NMR: δ 13.92, 21.09, 25.96, 35.60, 51.37, 53.19, 64.60, 94.52, 160.00, 175.62. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.87; H, 8.83.

Ethyl 2-Ethoxy-1-(2-methyl-2-propenyl)-2-cyclopentene-1-carboxylate (14b). A solution of diethyl ketal **12** (6.25 g, 27.1 mmol in 40 mL of THF) was stirred in a 250-mL round-bottomed flask, cooled with an ice/water bath, as KHMDS (90.5 mL of a 0.75 M solution in toluene, 67.8 mmol) was added gradually by syringe. After 1 h, methallyl chloride (4.02 mL, 40.7 mmol) was added to the slurry by syringe. After 2 h, the reaction mixture was combined with 100 mL of a saturated aqueous NH_4Cl solution and warmed to room temperature, and 25 mL of water was added to dissolve solids. The aqueous layer was separated and extracted with ether (2 × 100 mL). The combined organic phases were washed with 100 mL of a saturated aqueous $NaHCO_3$ solution, which was back-extracted with ether (2 × 50 mL), and the combined organic phases were dried, filtered, and concentrated. The residue was purified by column chromatography on silica (100 g), eluting with 5:95 ether–hexanes, to provide 5.82 g (90%) of the ethyl ester as a colorless liquid. IR: 3080 (s), 1730 (s), 1650 (s), 900 (s), 780 (s). ^{1}H NMR: δ 1.24 (t, 3, *J* = 7.1), 1.28 (t, 3, *J* = 7.0), 1.69 (s, 3), 1.90–2.00 (m, 1), 2.20–2.40 (m, 4), 2.72 (d, 1, *J* = 14.2), 3.75 (dq, 1, *J* = 9.6, 7.0), 3.79 (dq, 1, *J* = 9.6, 7.0), 4.14 (dq, 1, *J* = 10.9, 7.1), 4.15 (dq, 1, *J* = 10.9, 7.1), 4.53 (t, 1, *J* = 2.0), 4.68 (bs, 1), 4.79 (bs, 1). ^{13}C NMR: δ 14.02, 14.32, 23.35, 26.51, 31.56, 41.92, 57.06, 60.39, 64.86, 96.03, 113.60, 142.72, 158.66, 174.79. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.71; H, 9.31.

Reduction of Ester 14. 2-Ethoxy-1-(4,8-dimethyl-3,7-nonadienyl)-2-cyclopentene-1-methanol (15d). A solution of the methyl ester corresponding to **14d** (2.27 g, 7.08 mmol in 25 mL of ether) was stirred in a 100-mL round-bottomed flask, cooled with an ice/water bath, as $LiAlH_4$ (0.40 g, 10.6 mmol) was added gradually through a powder funnel. Upon completion of the exothermic addition, the flask was fitted with a rubber septum and the reaction mixture stirred under N_2 as it was warmed in a room temperature water bath. After 1 h, the reaction mixture was diluted with 25 mL of THF and stirred vigorously as the following were added slowly by syringe in order: 0.40 mL of water, 0.40 mL of a 15% aqueous NaOH solution, and 1.20 mL of water. The resulting slurry was diluted with 50 mL of THF and stirred for 1 h to produce a white flocculent precipitate. After filtration, rinsing with ether, the filtrate was concentrated and the residue was purified by column chromatography on silica (30 g), eluting with 10:90:5 ether–hexanes–triethylamine, to provide 2.00 g (96%) of the alcohol as a colorless oil. IR: 3400 (s), 1650 (s), 1450 (s). ^{1}H NMR: δ 1.29 (t, 3, *J* = 7.0), 1.37–1.57 (m, 2), 1.60 (s, 6), 1.68 (s, 3), 1.73–1.80 (m, 2), 1.86–2.10 (m, 7), 2.19–2.25 (m, 2), 3.45 (dd, 1, *J* = 10.5, 5.6), 3.54 (dd, 1, *J* = 10.5, 6.8), 3.76 (dq, 1, *J* = 9.7, 7.0), 3.82 (dq, 1, *J* = 9.7, 7.0), 4.52 (t, 1, *J* = 2.3), 5.05–5.20 (m, 2). ^{13}C NMR: δ 14.62, 15.81, 17.65, 22.69, 25.66, 26.25, 26.70, 29.81, 33.92, 39.68, 51.80, 64.87, 69.04, 95.34, 124.30, 124.56, 131.19, 134.73, 160.65. Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.78; H, 11.05.

2-Ethoxy-1-(4-methyl-3-pentenyl)-2-cyclopentene-1-methanol (15c). Ethyl ester **14c** (1.00 g, 3.75 mmol) was treated in the foregoing manner and purified by column chromatography on silica (25 g), eluting with 20:80 ether–hexanes, to provide 0.754 g (82%) of the alcohol as a colorless oil. IR: 3410 (s), 1650 (s), 1455 (s). ^{1}H NMR: δ 1.29 (t, 3, *J* = 7.0), 1.40–1.60 (m, 2), 1.60 (s, 3), 1.68 (s, 3), 1.73–1.80 (m, 2), 1.87 (t, 2, *J* = 6.2), 1.90–2.20 (m, 1), 2.20–2.30 (m, 2), 3.45 (dd, 1, *J* = 10.6, 5.6), 3.54 (dd, 1, *J* = 10.6, 6.8), 3.76 (dq, 1, *J* = 9.6, 7.0), 3.82 (dq, 1, *J* = 9.6, 7.0), 4.52 (t, 1, *J* = 2.3), 5.13 (bt, 1, *J* = 7.2). ^{13}C NMR: δ 14.59, 17.45, 22.76, 25.63, 26.22, 29.76, 33.92, 51.76, 64.84, 69.98, 95.32, 124.73, 131.05, 160.57. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.69; H, 10.65.

2-Ethoxy-1-(2-methyl-2-propenyl)-2-cyclopentene-1-methanol (15b). Ethyl ester **14b** (2.33 g, 9.77 mmol) was treated in the foregoing manner and purified by column chromatography on silica (50 g), eluting with 10:90 ether–hexanes, to provide 1.43 g (75%) of the alcohol as a colorless oil. IR: 3420 (s), 3080 (s), 1650 (s). ^{1}H NMR: δ 1.31 (t, 3, *J* = 7.1), 1.73 (s, 3), 1.73 (dt, 1, *J* = 13.6, 2.3), 1.94 (dt, 1, *J* = 13.6, 2.3), 2.07 (bs, 1), 2.13 (d, 1, *J* = 13.4), 2.19 (td, 2, *J* = 6.9, 2.3), 2.33 (d, 1, *J* = 13.4), 3.45 (bd, 1, *J* = 10.4), 3.52 (bd, 1, *J* = 10.4), 3.74 (dq, 1, *J* = 9.6, 7.1), 3.82 (dq, 1, *J* = 9.6, 7.1), 4.50 (t, 1, *J* = 2.3), 4.72 (bs, 1), 4.82 (bs, 1). ^{13}C NMR: δ 14.54, 23.77, 26.06, 29.15, 41.31, 51.83, 64.76, 69.52, 95.50, 113.90, 143.37, 160.57. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.42; H, 10.19.

Preparation of Keto Ester 17. [1-(4,8-Dimethyl-3,7-nonadienyl)-2-oxocyclopentyl]methyl 2,5-Dibromopentanoate (17d). A solution of alcohol **15d** (2.00 g, 6.83 mmol in 25 mL of CH_2Cl_2) and pyridine (0.69 mL, 8.50 mmol) was cooled with an ice/water bath as acid halide **16** (1.31 mL, 8.50 mmol) was added dropwise by syringe. After 10 min, 10 mL of a 10% aqueous H_2SO_4 solution was added to the flask, and the mixture was stirred vigorously to form an emulsion. Hydrolysis of the enol ether was complete after 30 min (as indicated by TLC). The mixture was combined with 40 mL of water and extracted with ether (3 × 50 mL). The combined organic phases were washed with 50 mL of

a saturated aqueous $NaHCO_3$ solution, which was back-extracted with ether (2 × 25 mL). The combined organic extracts were dried, filtered, and concentrated to give a yellow oil. This material was purified by column chromatography on silica (50 g), eluting with 15:85 ether–hexanes, to provide 3.29 g (95%) of the keto ester as a very viscous golden oil. The product was obtained as a nearly equal mixture of diastereomers.

In practice, the alkylation, reduction, acylation, and hydrolysis steps were performed without chromatography of the labile enol ether intermediates to provide the final keto ester in approximately 85% overall yield. IR: 1745. ^1H NMR: δ 1.44–1.52 (m, 2), 1.59 (s, 6), 1.67 (s, 3), 1.87–2.34 (m, 16), 3.42 (t, 2, J = 6.2), 4.13–4.92 (m, 3), 5.01–5.10 (m, 2). ^{13}C NMR: δ 16.00, 17.67, 18.89, 22.57, 25.67, 26.55, 29.97, 30.00, 30.80, 30.97, 32.07, 33.08, 33.22, 33.27, 33.35, 38.39, 39.56, 44.50, 44.70, 51.60, 68.35, 68.44, 122.98, 123.01, 124.07, 131.37, 136.12, 136.15, 168.86, 168.98, 219.76, 219.98. Anal. Calcd for $C_{22}H_{34}Br_2O_3$: C, 52.19; H, 6.77. Found: C, 52.04; H, 6.70.

[1-(4-Methyl-3-pentenyl)-2-oxocylcopentyl]methyl 2,5-Dibromopentanoate (17c). Alcohol **15c** (0.897 g, 4.00 mmol) was treated in the foregoing manner, and the crude product was purified by column chromatography on silica (75 g), eluting with 10:90 ether–hexanes, to provide 1.67 g (95%) of the keto ester as a very viscous golden oil. The product was obtained as a nearly equal mixture of diastereomers. IR: 1750 (s), 1455 (s). ^1H NMR: δ 1.48 (td, 2, J = 8.4, 4.5), 1.59 (s, 3), 1.67 (s, 3), 1.80–2.30 (m, 12), 3.43 (t, 2, J = 6.3), 4.10–4.27 (m, 3), 5.03 (bt, 1, J = 7.0). ^{13}C NMR: δ 17.62, 18.84, 22.61, 25.57, 29.92, 29.94, 30.75, 30.92, 32.08, 33.02, 33.16, 33.21, 33.29, 38.31, 38.33, 44.47, 44.67, 51.52, 68.28, 68.36, 123.10, 123.14, 132.46, 168.82, 168.93, 219.72, 219.93. Anal. Calcd for $C_{17}H_{26}Br_2O_3$: C, 46.60; H, 5.98. Found: C, 46.78; H, 6.02.

[1-(2-Methyl-2-propenyl)-2-oxocyclopentyl]methyl 2,5-Dibromopentanoate (17b). Alcohol **15b** (1.20 g, 6.10 mmol) was treated in the foregoing manner, and the crude product was purified by column chromatography on silica (50 g), eluting with 15:85 ether–hexanes, to provide 2.01 g (80%) of the keto ester as a very viscous golden oil. The product was obtained as an approximately 2:1 mixture of diastereomers. IR: 1750 (s), 1650 (s). ^1H NMR: δ 1.71 (s, 3), 1.90–2.40 (m, 12), 3.43 (t, 2, J = 6.2), 4.10–4.30 (m, 3), 4.77 (bs, 1), 4.91 (bs, 1). ^{13}C NMR: δ 18.70, 24.13, 29.88, 30.41, 30.57, 32.07, 32.98, 33.08, 38.16, 41.04, 41.12, 44.44, 44.59, 51.50, 68.42, 68.58, 116.06, 140.52, 140.59, 168.76, 168.84, 219.68, 219.91. Anal. Calcd for $C_{15}H_{22}Br_2O_3$: C, 43.93; H, 5.41. Found: C, 43.88; H, 5.42.

(1-Methyl-2-oxocyclopentyl)methyl 2,5-Dibromopentanoate (17a). Crude alcohol **15a** (0.440 g, 2.82 mmol), obtained by reduction of ester **14a**, was treated in the foregoing manner, and the crude product was purified by column chromatography on silica (20 g), eluting with 25:75 ether–hexanes, to provide 1.00 g (96%) of the keto ester as a very viscous golden oil. The product was obtained as a nearly equal mixture of diastereomers. IR: 1750 (s), 1460 (s). ^1H NMR: δ 1.06 + 1.07 (s, 3), 1.80–2.45 (m, 10), 3.44 (t, 2, J = 6.3), 4.08 + 4.19 (d, 1, J = 10.8), 4.14 (s, 2), 4.26 + 4.27 (dd, 1, J = 7.8, 6.2). ^{13}C NMR: δ 18.32, 19.15, 29.63, 32.04, 32.67, 32.72, 32.83, 37.52, 44.36, 44.52, 47.92, 68.50, 168.36, 168.42, 219.32, 219.38. Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.95; H, 4.90. Found: C, 38.68; H, 4.66.

General Procedure for Reformatsky Reactions. The $ZnCl_2$ used in this procedure must be anhydrous and due to its hygroscopic nature appropriate measures are required. For a single or large experiment, $ZnCl_2$ was weighed into the reaction vessel (using a slight excess as some weight is lost) and the atmosphere evacuated with a vacuum pump. A loosely packed cotton plug or other protection in the vacuum line is recommended to guard the vacuum manifold and/or pump against fine particles and sublimation of the salt, especially during heating. The flask was gently heated over a flame, while slowly being rolled until all of the white solid had been melted (mp 293 °C) to form a colorless glass. Caution should be exercised during this process as rapid heating can cause violent water loss, increasing the material swept from the flask. Also, localized overheating discolors the salt, although reactions where slight amounts of this presumed decomposition was observed were not noticeably affected. The vacuum was maintained while the salt cooled to room temperature. An inert atmosphere was introduced and maintained as the $ZnCl_2$ was dissolved in THF added by syringe.

For numerous small-scale reactions it was more convenient to prepare a stock solution of $ZnCl_2$ and deliver the quantity necessary for each reaction by syringe. Standard solutions were prepared as described above and any insoluble material was allowed to settle overnight before the supernatant was decanted into a suitable container by a cannula under an inert atmosphere. The solution titer was determined by concentrating a known volume to a constant weight under vacuum. Values as high as 2 M in THF were obtained when using excess $ZnCl_2$. Such solutions, stored in a sealed vessel equipped with a 3-way glass stopcock under nitrogen, were reliably employed to produce activated zinc over periods longer than a year.

Sodium naphthalenide solutions were prepared in a flask just larger than the total volume. A slight excess of naphthalene was placed in the vessel, which was purged with N_2 before addition of THF by syringe to dissolve the solid. Sodium metal was weighed into a beaker containing hexanes to rinse residual oil, transferred to a small beaker containing THF, finely divided with a spatual/chisel, and then added rapidly (through the neck of the flask) to the naphthalene solution. The seputm was removed as briefly as possible while this operation was performed to minimize exposure to air. Under optimal conditions, the solution immediately began to turn dark-green from the radical-anion, and after 1 h the metal completely dissolved to form the thick black reducing mixture. The practical concentration limit for forming this reagent appeared to be about 1 M; at higher concentrations the solution became difficult to stir and transfer. If the final reaction volume was not an issue, a sodium naphthalenide concentration around 0.5 M seemed to work best for this procedure.

For the preparation of activated zinc, a solution of $ZnCl_2$ (>1 equiv in THF, stirred rapidly under N_2, was cooled with an ice/water bath as a freshly prepared sodium naphthalenide solution (2 equiv) was added dropwise by a cannula, immediately forming a very fine, black suspension of zinc metal (1 equiv). Reduction of the zinc salt is essentially instantaneous and quantitative, and the active metal formed is best used directly. The requisite 2:1 stoichiometry for Na:Zn metals in this reaction can be easily overlooked and bears emphasizing.

While the concentration for sodium naphthalenide was mentioned above, the $ZnCl_2$ solution should also be considered. Since the reaction is very rapid and probably diffusion controlled, the concentration of $ZnCl_2$ could affect particle size and thus the active surface of the zinc metal formed. Although this is speculation, mixing efficiency was noticeably important. Procedures where stirring was accidently interrupted during addition provided granular preparations and poor results. However, the concentration of $ZnCl_2$ was not observed to be critical for the success of any of the reactions reported herein. Generally, concentrations varying between 0.5 and 1.5 M were used, as was convenient for the reaction scale, with good results.

(4a*α*,7a*β*(*E*),10a*S)-7a-(4,8-Dimethyl-3,7-nonadienyl)-octahydro-5*H*,7*H*-cyclopenta[*c*]pyrano[2,3-*d*]pyran-5-one (18d).** A solution of naphthalene (3.44 g, 26.9 mmol in 20 mL of THF), in a 25-mL, round-bottomed flask, was stirred as sodium metal (0.46 g, 20.1 mmol divided into small pieces) was added through the neck of the flask. After 2 h, the resulting dark green solution of sodium naphthalenide was added dropwise by a cannula to a stirring solution of $ZnCl_2$ (9.60 mL of a 1.40 M solution in THF, 13.4 mmol) in a nitrogen-purged, 100-mL, round-bottomed flask, cooled with an ice/water bath. Dihalo ester **17d** (3.40 g, 6.70 mmol in 10 mL of THF) was added dropwise by a cannula (addition time = 10 min) to the suspension of activated zinc, followed by HMPA (4.67 mL, 26.9 mmol) by syringe. After 9 h at room temperature, the reaction mixture was combined with 50 mL of a 0.6 M aqueous HCl solution. After the excess zinc had reacted, the mixture was extracted with ether (3 × 50 mL), and the extracts were washed with 50 mL of a saturated aqueous $NaHCO_3$ solution, which was back-extracted with ether (2 × 25 mL). The combined organic extracts were dried, filtered, and concentrated to give a crude solid mixture. This material was dissolved in a minimum quantity of benzene and purified by column chromatography on silica (125 g), eluting with 20:80 ether–hexanes, to provide 2.06 g (89%) of the desired lactone–ether as a colorless oil and as a single diastereomer. IR: 1760. ^1H NMR: δ 1.33–1.52 (m, 4), 1.59 (s, 6), 1.68 (s, 3), 1.60–2.10 (m, 12), 2.28 (bs, 1), 2.33 (bs, 1), 2.46 (bs, 1), 3.55 (td, 1, J = 12.0,

2.0), 3.73 (dd, 1, J = 12.0, 3.5), 3.80 (d, 1, J = 11.9), 4.18 (d, 1, J = 11.9), 5.06–5.16 (m, 2). ^{13}C NMR: δ 15.84, 17.57, 20.27, 21.03, 22.77, 23.17, 25.57, 26.56, 31.78, 35.25, 37.81, 39.57, 40.36, 49.50, 62.93, 69.53, 83.49, 124.18, 124.27, 131.12, 134.72, 173.00. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.98; H, 9.69.

7a-(4-Methyl-3-pentenyl)octahydro-5*H*,7*H*-cyclopenta[*c*]pyrano[2,3-*d*]pyran-5-one (18c). Dibromo ester **17c** (0.714 g, 1.63 mmol) was treated in the foregoing manner and the crude product mixture purified by column chromatography on silica (60 g), eluting with 25:75 ether–hexanes, to provide 0.393 g (87%) of the desired lactone–ether as a colorless oil and as a single diastereomer. IR: 1755 (s), 1640 (s), 1460 (s). ^{1}H NMR: δ 1.30–1.52 (m, 4), 1.60 (s, 3), 1.67 (s, 3), 1.60–2.10 (m, 8), 2.28–2.34 (m, 2), 2.45 (bs, 1), 3.54 (bt, 1, J = 12.0), 3.73 (bd, 1, J = 12.0), 3.80 (d, 1, J = 11.8), 4.18 (d, 1, J = 11.8), 5.13 (bt, 1, J = 7.1). ^{13}C NMR: δ 17.56, 20.34, 21.10, 22.84, 23.29, 25.65, 31.92, 35.30, 37.87, 40.45, 49.54, 63.02, 69.62, 83.54, 124.48, 131.22, 173.08. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.13; H, 9.38.

7a-(2-Methyl-2-propenyl)-octahydro-5*H*,7*H*-cyclopenta[*c*]pyrano[2,3-*d*]pyran-5-one (18b). Dibromo ester **17b** (0.339 g, 0.827 mmol) was treated in the foregoing manner and the crude product mixture purified by column chromatography on silica (10 g), eluting with 20:80 ether–hexanes, to provide 0.132 g (64%) of the desired lactone–ether as a colorless solid, mp 86–88 °C (pentane). IR (benzene): 1755 (s), 1645 (s). ^{1}H NMR: δ 1.30–1.50 (m, 3), 1.78 (s, 3), 1.70–2.10 (m, 5), 2.04 (d, 1, J = 13.9), 2.30–2.40 (m, 2), 2.45 (d, 1, J = 13.9), 2.46 (bs, 1), 3.56 (td, 1, J = 12.0, 2.4), 3.74 (bd, 2, J = 11.7), 4.25 (d, 1, J = 11.7), 4.83 (bs, 1), 4.94 (dq, 1, J = 2.3, 1.4). ^{13}C NMR: δ 20.28, 20.99, 22.93, 24.87, 36.14, 37.97, 38.98, 40.31, 49.35, 62.98, 68.89, 83.57, 115.65, 142.57, 173.01. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.10; H, 9.12.

7a-Methyloctahydro-5*H*,7*H*-cyclopenta[*c*]pyrano[2,3-*d*]pyran-5-one (18a). Dibromo ester **17a** (1.25 g, 3.37 mmol) was treated in the foregoing manner and the crude product mixture purified by column chromatography on silica (55 g), eluting with 25:75 ether–hexanes, to provide 0.600 g (84%) of the desired lactone–ether as a colorless solid, mp 82–83 °C (pentane). IR ($CDCl_3$): 1750 (s), 1450 (m). ^{1}H NMR: δ 1.10 (s, 3), 1.33–1.40 (m, 1), 1.46–1.62 (m, 3), 1.70–2.00 (m, 4), 2.17–2.35 (m, 2), 2.43 (bs, 1), 3.55 (bt, 1, J = 12.0), 3.75 (bd, 1, J = 12.0), 3.89 (d, 1, J = 11.4), 3.95 (d, 1, J = 11.4). ^{13}C NMR: δ 20.30, 20.77, 21.08, 22.59, 37.57, 37.67, 40.59, 46.60, 63.20, 74.17, 82.69, 172.95. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.39.

Reduction of Lactones 18. [1α,1(*E*),5b(*S)]-1-(4,8-Dimethyl-3,7-nonadienyl)-6-oxaspiro[4.5]decane-1,10-dimethanol (19d).** A solution of lactone **18d** (2.06 g, 5.94 mmol in 30 mL of ether) was stirred, cooling with a room temperature water bath, as $LiAlH_4$ (0.68 g, 17.8 mmol) was added gradually with a spatula. After 6 h, the reaction mixture was stirred vigorously as the following were added slowly by syringe in order: 0.68 mL of water, 0.68 mL of a 15% aqueous NaOH solution, and 2.04 mL of water. The resulting white slurry was filtered, rinsing with ether, and the filtrate was concentrated to give a white solid. This material was purified by column chromatography on silica (50 g), eluting first with 25:75 ether–hexanes (to elute nonpolar impurities), then with 50:50 ether–hexanes until the product began to elute, and finally with pure ether to remove the last of the compound which elutes gradually in the final fractions, providing 1.87 g (90%) of the desired diol as a colorless solid, mp 87–91 °C. IR: 3480 (s), 3260 (s). ^{1}H NMR: δ 1.28–2.10 (m, 18), 1.60 (s, 6), 1.69 (s, 3), 2.60–2.70 (m, 1), 3.50–3.85 (m, 7), 4.31 (dd, 1, J = 11.0, 5.5), 5.10 (bt, 1, J = 6.5), 5.18 (bt, 1, J = 6.5). ^{13}C NMR: δ 15.99, 17.67, 18.09, 20.91, 23.83, 25.68, 26.18, 26.72, 28.78, 29.73, 34.59, 39.72, 41.91, 54.35, 60.61, 62.83, 65.26, 86.21, 124.38, 125.38, 131.21, 134.44. Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.03; H, 10.72.

1-(4-Methyl-3-pentenyl)-6-oxaspiro[4.5]decane-1,10-dimethanol (19c). Lactone **18c** (0.291 g, 1.05 mmol) was treated in the foregoing manner and the crude product was purified by column chromatography on silica (15 g), eluting with 75:25 ether–hexanes, to provide 0.262 g (89%) of the diol as a colorless solid, mp = 114–117 °C. IR ($CHCl_3$): 3500 (s), 3300 (s), 1450 (s). ^{1}H NMR: δ 1.25–2.10 (m, 14), 1.61 (s, 3), 1.67 (s, 3), 2.62–2.64 (m, 1), 3.24 (bs, 2), 3.54 (d, 1, J = 11.6), 3.63 (d, 1, J = 11.6), 3.63–3.85 (m, 3), 4.31 (dd, 1, J = 11.0, 5.6), 5.17 (bt, t, J = 6.9). ^{13}C NMR: δ 17.58, 18.05, 20.86, 23.83, 25.65, 26.11, 28.76, 29.67, 34.53, 41.80, 54.26, 60.56, 62.60, 65.03, 86.14, 125.61, 130.61. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.30; H, 10.69.

2-Aza Diene Reactions. 17,18-Didehydro-8,23-epoxy-12,16-cyclo-1,12-secodaphnane (22d). A solution of oxalyl chloride (0.35 mL, 3.96 mmol in 20 mL of CH_2Cl_2) was stirred in a 50-mL round-bottomed flask, cooled by a dry ice/acetone bath, as a solution of dimethyl sulfoxide (0.56 mL, 7.92 mmol in 0.44 mL of CH_2Cl_2) was very carefully added by syringe. After 5 min, a solution of diol **19d** (460.0 mg, 1.31 mmol, dissolved in 5 mL of CH_2Cl_2) was added to the cooled solution by a cannula. After 20 min, triethylamine (2.76 mL, 19.8 mmol) was added to the resulting white slurry by syringe, and after 5 min the clear colorless solution was warmed in an ice/water bath. After 1 h, the septum was removed and the chilled dialdehyde solution was stirred vigorously as a rapid stream of gaseous ammonia was passed into the reaction vessel, resulting in the formation of a copious white precipitate. After the solution has been saturated (approximately 15 s), the cooling bath was removed and the excess ammonia allowed to evaporate as the stirring mixture warmed to room temperature. After 1 h, the stirring bar was removed, rinsing with chloroform into the flask (adding several mL reduces "bumping" at the end of solvent removal). The solvent was evaporated and the white solid residue placed under vacuum for 3 h. The residue was combined with ammonium acetate (0.77 g, 10 mmol) and suspended in 20 mL of glacial acetic acid. The reaction vessel was equipped with a reflux condenser and purged with nitrogen, and the solution was stirred in an oil bath at 45 °C. After 15 h, the dark reaction mixture was cooled, diluted with 100 mL of water, and extracted with CH_2Cl_2 (4 × 25 mL). The extracts were washed with 50 mL of a 2 N aqueous NaOH solution, and the aqueous wash (still basic to litmus) was back-extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried, filtered, and concentrated to give 513 mg of a dark tar. This crude product was purified by column chromatography on basic alumina (15 g), eluting with 50:50 ether–hexanes, to obtain 268 mg of a slightly yellow oil. This material was purified further by column chromatography on silica (15 g), eluting with 10:90 ether–hexanes, to give 202.5 mg (47%) of the desired product, which after an extended period under vacuum formed a colorless solid, mp 82–84 °C. IR: 1645. ^{1}H NMR: δ 1.15–1.60 (m, 9), 1.22 (s, 3), 1.63–2.37 (m, 12), 1.72 (s, 3), 2.69 (d, 1, J = 4.4), 2.78 (d, 1, J = 1.2), 3.66–3.84 (m, 2), 4.72 (s, 1), 4.86 (s, 1). ^{13}C NMR: δ 20.41, 22.24, 22.44, 23.93, 24.07, 24.13, 27.31, 28.49, 32.35, 36.64, 36.82, 38.15, 40.21, 41.76, 48.67, 53.73, 56.60, 59.50, 64.35, 87.64, 110.63, 147.16. Anal. Calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.87; H, 10.02; N, 4.22.

(4aα,6aβ,7α,9a*S,12a*S**)-(±)-3,4,6a,7,8,9,11,12-Octahydro-13,13-dimethyl-2*H*-4a,7-methano-10*H*-dicyclopenta[*b*,*c*]-pyrano[2,3-*d*]pyridine (22c).** Diol **19c** (0.090 g, 0.32 mmol) was treated as in the foregoing procedure until the residue was dissolved in acetic acid. Heating was unnecessary; the crude mixture was stirred in 8 mL of acetic acid for 1 h at room temperature and extracted as above. The crude product was purified by column chromatography on silica (2 g), eluting with ether, to provide 0.045 g (54%) of the desired imine as a yellow oil. IR: 1630 (s), 1470 (s), 1450 (s). ^{1}H NMR: δ 0.77 (s, 3), 1.23 (s, 3), 1.20–1.82 (m, 11), 1.99–2.24 (m, 4), 3.74–3.81 (m, 2), 3.94 (d, 1, J = 3.9), 7.61 (s, 1). ^{13}C NMR: δ 21.37, 22.21, 24.58, 24.97, 26.20, 26.59, 30.94, 36.68, 38.05, 39.60, 45.35, 49.19, 56.46, 60.45, 73.58, 87.03, 176.40. Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.85; H, 9.56; N, 5.27.

8,23-Epoxy-12,16-cyclo-1,12-secodaphnane (7). Unsaturated amine **22d** (275.0 mg, 0.84 mmol) was placed in a 25-mL round-bottomed flask and dissolved in 10 mL of absolute ethanol, and PtO_2 (19.0 mg, 0.084 mmol) was added to the solution. The mixture was stirred vigorously under a hydrogen atmosphere for 1 h before the contents of the flask were filtered through a plug of Celite, rinsing with absolute ethanol. The filtrate was concentrated, and the residue was taken up in CH_2Cl_2, filtered through a cotton plug, and concentrated to give an oil. After an extended period under vacuum, this material solidified to provide 274.0 mg (98.5%) of the amine as a faintly yellow solid, mp 80–82 °C, suitable for combustion analysis. IR: 1460 (s). ^{1}H NMR: δ 0.85 (d, 3, J = 6.5), 0.88 (d, 3, J = 6.5), 0.90–1.00 (m, 1), 1.10–2.15 (m, 19), 1.19 (s, 3), 2.20–2.40 (m, 2), 2.71 (d, 1, J = 4.4), 2.78 (s, 1), 3.64–3.82 (m, 2). ^{13}C NMR: δ 20.95, 21.12, 21.18, 22.56, 24.01,

24.03, 24.34, 27.33, 28.63, 28.67, 33.23, 36.39, 36.71, 38.22, 40.96, 42.07, 48.83, 53.43, 56.05, 59.54, 64.58, 87.56. Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.24; H, 10.73; N, 4.10.

8,12-Didehydro-1,12-secodaphnan-23-ol (23) and 8,9-Didehydro-12,16-cyclo-1,12-secodaphnan-23-ol (24). Amino ether **7** (274.0 mg, 0.840 mmol) was placed in a 10-mL round-bottomed flask, the vessel was purged with nitrogen, and diisobutylaluminum hydride (5.00 mL of a 1.5 M solution in toluene, 7.50 mmol) was introduced with a syringe. After the amine had dissolved, the flask was fitted with a reflux condenser and the reaction mixture heated at reflux with a hot oil bath. After 72 h, the yellow mixture was cooled to room temperature and transfered with a pipet to a 100-mL round-bottomed flask, employing 50 mL of CH_2Cl_2. The solution was stirred, cooling with a room temperature water bath, as NaF (1.26 g, 30.0 mmol) was added, followed by water (0.40 mL, 22.5 mmol) dropwise by syringe. After 10 min, the slurry was diluted with 50 mL of THF and 5 mL of ethanol, and the mixture was stirred for several hours to provide a freely flowing white precipitate. The precipitate was filtered and rinsed thoroughly with 100 mL of a 95:5 ether–ethanol solution. The filtrate was concentrated and the residue dissolved in 25 mL of benzene. After 3 h at room temperature, a precipitate was collected by filtration and dried under vacuum to give 44.5 mg (16%) of the elimination product **24** as a colorless solid, mp 203–208 °C. The filtrate was concentrated to give 280 mg of an oil, which was purified by column chromatography on silica (10 g), eluting with 10:90:5 ether–hexanes–triethylamine, to provide 199.0 mg (71%) of the desired fragmentation product **23** as a yellow glass, contaminated with a minor amount of the elimination product **24**. As these compounds were inseparable by chromatography, this material was used directly in subsequent reactions.

Compound 23. IR: 3300 (s). ^1H NMR: δ 0.91 (d, 6), 1.03 (s, 3), 1.30–2.20 (m, 17), 2.25–2.40 (m, 6), 2.42 (d, 1, J = 4.2), 2.68 (d, 1, J = 15.1), 3.36 (dd, 1, J = 15.1, 7.4), 3.61 (td, 2, J = 6.9, 1.7). ^{13}C NMR: δ 20.99, 21.04, 21.90, 27.53, 28.23, 28.50, 29.39, 31.54, 31.60, 31.63, 36.17, 37.67, 40.06, 40.21, 41.49, 43.26, 47.16, 49.23, 55.44, 64.27, 137.45, 140.07. Anal. Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.22. Found: C, 79.93; H, 10.93; N, 3.99.

Compound 24. IR ($CDCl_3$): 1220 (s). ^1H NMR (500 MHz): δ 0.74 (s, 3), 0.85–0.90 (m, 1), 0.87 (d, 3, J = 6.6), 0.89 (d, 3, J = 6.7), 1.02–1.25 (m, 1), 1.35–1.40 (m, 2), 1.49–1.64 (m, 10), 1.68 (dd, 1, J = 10.9, 5.1), 1.75–1.89 (m, 3), 2.08 (t, 1, J = 5.0), 2.18 (ddd, 1, J = 15.3, 8.0, 3.5), 2.46 (ddd, 1, J = 15.3, 11.5, 5.1), 2.83 (bs, 1), 2.90 (d, 1, J = 4.4), 3.68 (t, 2, J = 6.1), 5.44 (bs, 1). ^{13}C NMR (125 MHz, partial: due to limited solubility): δ 20.52, 20.98, 21.05, 22.17, 23.38, 25.66, 27.98, 28.74, 31.03, 35.34, 35.60, 37.46, 37.52, 43.46, 48.42, 56.48, 60.21, 64.07, 119.69. HRMS (FAB): exact mass calcd for $C_{22}H_{36}NO$ (MH^+) 330.2797, found 330.2796.

(±)-Daphnilactone A (6). Amino alcohol **23** (20.0 mg, 0.60 mmol) was placed in a 10-mL round-bottomed flask and dissolved in 5 mL of acetone. The reaction vessel was immersed in an ice/water bath, and 1 drop of concd H_2SO_4 was added. Celite (100 mg) was added, followed by 2 drops of Jones reagent. After 30 min, the slurry was diluted with 5 mL of acetone and 10 drops of 2-propanol was added to consume excess oxidant. After 30 min, the mixture was filtered through a plug of Celite, eluting with acetone, and the filtrate was concentrated. The residue was diluted with 20 mL of a pH 7 phosphate buffer solution to attain neutrality and formaldehyde (0.075 mL of a 37% aqueous solution, 1.0 mmol) was added with a syringe. After 1 h, the reaction mixture was made basic by adding 5 mL of a 4 M aqueous K_2CO_3 solution and extracted with CH_2Cl_2 (4 × 25 mL). The organic extracts were dried, filtered, and concentrated to give 13.0 mg of crude product. This material was purified by column chromatography on silica (2.5 g), eluting with 50:50 ether–hexanes, to provide 11.1 mg (50%) of (±)-daphnilactone A as a colorless solid, mp 134–137 °C. This material was identical by ^1H NMR spectrometry to a natural sample, mp 194.5–195.5 °C, kindly provided by S. Yamamura. IR: 1735 (lit. 1737). ^1H NMR (400 MHz): δ 0.90 (d, 3, J = 6.7), 0.93 (d, 3, J = 6.5), 1.04 (s, 3), 1.20–2.20 (m, 19), 2.55 (d, 1, J = 15.0), 2.60–2.77 (m, 3), 2.64 (d, 1, J = 14.3), 2.87 (d, 1, J = 14.3), 3.77 (dd, 1, J = 15.0, 6.2). ^{13}C NMR (50.8 MHz): δ 18.65, 20.89, 21.14, 24.10, 26.80, 27.89, 28.91, 29.60, 30.24, 31.09, 37.03, 37.36, 37.75, 39.13, 40.16, 40.22, 46.14, 50.54, 57.04, 61.08, 65.56, 98.79, 172.71. Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.23; H, 10.04; N, 3.83.

Methyl 8,12-Didehydro-1,12-secodaphnan-23-oate (26). Amino alcohol **23** (42.0 mg, 0.127 mmol) was placed in a 10-mL round-bottomed flask and dissolved in 5 mL of acetone. The reaction vessel was immersed in an ice/water bath, and 1 drop of concd H_2SO_4 was added. Celite (150 mg) was added, followed by 3 drops of Jones reagent. After 20 min, the slurry was diluted with 5 mL of acetone and 10 drops of 2-propanol was added to consume excess oxidant. After 40 min, the mixture was filtered through a plug of Celite, eluting with acetone, and the filtrate was concentrated. The residue was transferred to a 25-mL round-bottomed flask with methanol and concentrated. This material was dissolved in 15 mL of absolute methanol, the flask was equipped with a reflux condenser, and the solution was heated at reflux with a hot oil bath. After 1 h, the reaction mixture was cooled to room temperature, combined with 50 mL of a 2 M aqueous K_2CO_3 solution, and extracted with CH_2Cl_2 (4 × 25 mL). The extracts were washed with 25 mL of brine, which was back-extracted with 25 mL of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give 36.5 mg of crude product. This material was purified by column chromatography on silica (5 g), eluting with 50:50 ether–hexanes, to provide 27.5 mg (60%) of the desired amino ester as a yellow solid, mp 74–76 °C. IR: 1745 (s). ^1H NMR: δ 0.91 (d, 6, J = 6.5), 0.98 (s, 3), 1.35–2.15 (m, 14), 2.19–2.60 (m, 9), 2.68 (d, 1, J = 15.0), 3.37 (dd, 1, J = 15.0, 7.2), 3.68 (s, 3). ^{13}C NMR: δ 20.90, 20.98, 21.95, 27.49, 28.10, 28.52, 29.31, 29.76, 31.64, 33.18, 36.19, 37.68, 40.07, 40.19, 41.48, 43.27, 47.14, 49.35, 51.62, 55.41, 136.82, 140.96, 174.85. Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.85; H, 10.37; N, 3.77.

(±)-Daphnan-23-ol (28). Amino alcohol **23** (106.0 mg, 0.320 mmol) was placed in a 25-mL round-bottomed flask, dissolved in 10 mL of CH_2Cl_2, and phenyl isocyanate (0.104 mL, 0.94 mmol) was added with a syringe. After 1 h, the mixture was concentrated, and the residue was dissolved in 10 mL of 97% formic acid. The flask was equipped with a reflux condenser and the solution was heated at reflux with a hot oil bath. After 2 h, the reflux condenser was removed and a stream of N_2 was passed over the reaction mixture as it was stirred in the hot oil bath. After evaporation of the solvent, the yellow residue was dissolved in 10 mL of a 2 M methanolic KOH solution. The flask was equipped with a reflux condenser and the solution was heated at reflux with a hot oil bath. After 3 h, the reaction mixture was cooled and concentrated. The residue was dissolved in 10 mL of water and extracted with ether (4 × 10 mL). The extracts were dried, filtered, and concentrated to give 170 mg of crude product. This material was purified by column chromatography on silica (10 g), eluting first with 50:50 ether–hexanes and then with 50:50:5 ether–hexanes–triethylamine to elute the product, providing 101.0 mg (94%) of the desired amino alcohol as a colorless solid, mp 168–171 °C. IR: 3250 (s). ^1H NMR: 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 (bd, 1, J = 14.2), 3.54–3.59 (m, 2). ^{13}C NMR: 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. HRMS (FAB): exact mass calcd for $C_{22}H_{38}NO$ (MH^+) 332.2954, found 332.2953.

(±)-Methyl Homodaphniphyllate (4). Method A. A solution of amino ester **26** (23.0 mg, 0.064 mmol in 5 mL of CH_2Cl_2) was stirred in a 10-mL round-bottomed flask as phenyl isocyanate (0.010 mL, 0.096 mmol) was added with a syringe. After 15 min, the mixture was concentrated, and the residue was dissolved in 5 mL of 97% formic acid. The flask was equipped with a reflux condenser and the solution was heated at reflux with a hot oil bath. After 2 h, the reflux condenser was removed and a stream of N_2 was passed over the reaction mixture as it was stirred in the hot oil bath. After evaporation of the solvent, the yellow residue was dissolved in 5 mL of a 1 M aqueous NaOH solution, and the solution was extracted with ether (4 × 5 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica (10 g), eluting with 10:90:5 ether–hexanes–triethylamine, to provide 14.5 mg (63%) of (±)-methyl homodaphniphyllate as a colorless solid, mp 88–90 °C, identical by ^1H NMR spectroscopy and TLC mobility to a natural sample kindly provided by S. Yamamura.

IR: 1740 (s). ^{1}H NMR (500 MHz): δ 0.88 (s, 3), 0.90 (d, 3, J = 6.6), 1.00 (d, 3, J = 6.4), 1.21-1.44 (m, 8), 1.52-1.92 (m, 10), 2.00-2.07 (m, 1), 2.14 (dd, 1, J = 10.5, 7.3), 2.44 (ddd, 1, J = 16.4, 10.9, 4.4), 2.51 (ddd, 1, J = 16.4, 11.4, 6.4), 2.73 (d, 1, J = 4.9), 2.74 (d, 1, J = 14.2), 3.25 (dt, 1, J = 14.2, 3.0), 3.67 (s, 3). ^{13}C NMR (125 MHz): δ 20.98, 21.33, 22.67, 25.37, 25.79, 26.06, 27.02, 28.54, 28.70, 31.01, 32.56, 36.60, 36.99, 37.90, 41.58, 41.69, 47.17, 47.98, 51.33, 51.49, 62.89, 72.17, 174.50. Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.93, H, 10.35; N, 3.90.

Method B. A solution of amino alcohol **28** (42.0 mg, 0.127 mmol in 10 mL of acetone) was stirred in a 25-mL round-bottomed flask, cooled by an ice/water bath, as 1 drop of concd H_2SO_4 was added. Celite (250 mg) was added, followed by 5 drops of Jones reagent. After 30 min, the slurry was diluted with 10 mL of acetone, and 20 drops 2-propanol were added to consume excess oxidant. After 15 min, the mixture was filtered through a plug of Celite (2.5 g), eluting with acetone, and the filtrate was concentrated. The residue was transferred to a 25-mL round-bottomed flask with methanol and concentrated. This material was dissolved in 15 mL of absolute methanol, the flask was equipped with a reflux condenser, and the solution was heated at reflux with a hot oil bath. After 1 h, the cooled reaction mixture was combined with 10 mL of a 2 M aqueous K_2CO_3 solution, and the mixture was concentrated. The condensate was diluted with 15 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with 10 mL of brine, which was back-extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried, filtered, and concentrated. The crude product was purified by column chromatography on silica (10 g), eluting with 10:90:5 ether-hexanes-triethylamine, to provide 63.5 mg (73%) of methyl homodaphniphyllate as a colorless solid, mp 88-90 °C, identical by ^{1}H NMR and TLC mobility with the material prepared by method A.

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Registry No. (±)-**4**, 104115-43-7; (±)-**6**, 111795-09-6; (±)-**7**, 138285-48-0; (±)-**11**, 53229-93-9; **13** (1-ene isomer), 74036-88-7; (±)-**13** (2-ene isomer), 138260-30-7; (±)-**14a**, 138260-33-0; (±)-**14b**, 111794-96-8; (±)-**14c**, 138260-32-9; (±)-**14d**, 138260-31-8; (±)-**15a**, 138260-36-3; (±)-**15b**, 111795-08-5; (±)-**15c**, 138260-35-2; (±)-**15d**, 138260-34-1; (±)-**16**, 111794-99-1; (±)-**17a** (isomer 1), 138260-41-0; (±)-**17a** (isomer 2), 138260-42-1; (±)-**17b** (isomer 1), 111795-01-8; (±)-**17b** (isomer 2), 111795-10-9; (±)-**17c** (isomer 1), 138260-39-6; (±)-**17c** (isomer 2), 138260-40-9; (±)-**17d** (isomer 1), 138260-38-5; (±)-**17d** (isomer 2), 138260-37-4; (±)-**18a**, 138260-44-3; (±)-**18b**, 138332-64-6; (±)-**18c**, 138260-43-2; (±)-**18d**, 118893-20-2; (±)-**19c**, 138260-45-4; (±)-**19d**, 118893-21-3; (±)-**22c**, 138260-46-5; (±)-**22d**, 118893-22-4; (±)-**23**, 118893-23-5; (±)-**24**, 118893-24-6; (±)-**26**, 138260-47-6; (±)-**28**, 104154-53-2; (±)-S5, 138260-48-7; (±)-S6, 138260-49-8; (±)-S7, 138260-50-1; (±)-S9, 138260-51-2; (±)-S10, 138260-52-3; (±)-S11, 138260-53-4; (±)-S12, 138260-54-5; (±)-S13, 138260-55-6; S14, 138260-56-7; (±)-S15, 138260-57-8; (±)-S16, 138260-58-9; S17, 138260-59-0; S18, 138260-60-3; S19, 138260-61-4; (±)-S20, 111794-97-9; (±)-S21, 111794-98-0; (±)-S22 (isomer 1), 111794-93-5; (±)-S22 (isomer 2), 111794-95-7; S24, 111794-94-6; (±)-S25, 138260-62-5; (±)-S26, 138260-63-6; (±)-S27 (isomer 1), 138260-64-7; (±)-S27 (isomer 2), 138260-65-8; S28, 138260-66-9; $ClCH_2C(CH_3)=CH_2$, 563-47-3; MeI, 74-88-4; $PhCH_2NH_2$, 100-46-9; $MeNH_2$, 74-89-5; δ-valerolactone, 542-28-9; homogeranyl iodide, 22339-13-5; homoprenyl iodide, 43161-11-1.

Supplementary Material Available: Discussion and experimental details on support studies dealing with the preparation of tricyclic lactam ethers analogous to lactone ethers **18**, details on the X-ray structural determination of compound **18a**, ^{1}H NMR spectra of synthetic and natural daphnilactone A and methyl homodaphniphyllate, and the ^{1}H NMR spectrum of compounds **24** and **28** (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

β-(*N*,*N*-Dialkylamino)ethyl Arylthiosulfonates: New Simulants for *O*-Ethyl *S*-[2-(Diisopropylamino)ethyl] Methylphosphonothioate

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β-(*N*,*N*-Dialkylamino)ethyl arylthiosulfonates **2**, new simulants for the hydrolysis and oxidation chemistry of VX (**1**), are prepared in good yield by reaction of a potassium arylthiosulfonate with a 2-chloroethylamine. Alkaline hydrolysis of **2** results in cleavage of the S-S bond to give sulfinic acids and disulfides. Like VX, oxidation of **2** by *N*-sulfonyloxaziridine **12** occurs exclusively on nitrogen to give the corresponding amine oxide which subsequently undergoes a Cope elimination reaction affording the vinyl sulfide **14**.

The development of simple, but effect methods for the detoxification (decontamination) of toxic organophosphorus compounds is a goal of considerable practical importance because these compounds appear in the environment as pesticides and as chemical warfare agents.[1] The decontamination of VX (*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate) (**1**), a chemical warfare nerve agent, generally involves conditions that are themselves corrosive and/or harmful to the environment, i.e., hydrolysis with caustic alkaline solutions and/or oxidation with hypochlorite.[2,3] Simple hydrolysis results in multiple products, some of which are as toxic as VX itself. A recent study of the oxidative chemistry of VX, by Yang and co-workers, revealed that it can be detoxified by oxidation followed by hydrolysis.[4] An impediment to the

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