at this point is crystalline). Also furnished was 2.31 g (75.5% based on recovered starting material) of **29** as a viscous oil: $[\alpha]^{25}_D$ 115.6° (*c* 0.1, $CHCl_3$); IR (film) 3220 (HC≡C), 2220 (CN), 1712 (C=O), 1640 (C=C), 1450 (CH_3), 1360-1380 [C-$(CH_3)_2$], 1070-1120 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$) δ 5.4 (m, 1 H, vinyl H), 3.35-3.65 (dd, 4 H, O-CH_2-CH_2-O), 2.6-2.75 (t, 2 H, CH_2), 2.25-2.41 (m, 3 H), 1.85-2.15 (m, 6 H), 1.6-1.73 (br s, 3 H, vinyl CH_3), 1.4 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.0 (s, 3 H, CH_3), 0.9 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 205.5, 147.6, 122.8, 119.0, 98.2, 70.4, 54.3, 51.4, 46.3, 33.9, 32.5, 30.9, 30.6, 29.8, 23.0, 22.4, 20.2, 17.4, 12.0; ^{13}C NMR (C_6D_6) δ 204.6, 147.4, 122.9, 119.1, 98.4, 70.4, 54.2, 51.6, 46.2, 34.7, 33.7, 32.3, 31.3, 30.7, 29.7, 29.6, 23.0, 22.3, 20.1, 17.4; 11.8; mass spectrum calculated for $C_{21}H_{31}O_3N$-CH_3 = 330.2070, found = 330.2071.

Keto Ketal 30. Into an oven-dried 250-mL three-neck round-bottomed flask (stirring bar, Ar-vacuum inlet) was placed 11.7 g of neutral alumina (activity greater than 1 according to Boeckman). The alumina was then heated to 180 °C for 12 h under vacuum (to remove any remaining water). An argon atmosphere was introduced and potassium chunks (1.9 g, 0.05 g-atom) were carefully added with rapid stirring. Once a fine black snd resulted, the reaction temperature was lowered to room temperature and tetrahydrofuran (125 mL) introduced. Next, the **29** (1.3 g, 3.77 mmol) was dissolved in tetrahydrofuran (5 mL) and added in one portion, via syringe, to the reaction mixture. After 1 h the reaction mixture ws allowed to settle and then rapidly decanted into a coarse sintered glass funnel connected to a filtration flask under vacuum (the filtration flask contained 200 mL of a rapidly stirring ice-cold 20% NH_4Cl solution). Ether was added to the residue in the reaction vessel, the mixture was stirred and allowed to settle. This solution was also decanted rapidly through the sintered glass funnel into the filtration flask. This process was repeated twice. (Note: to quench the K-Al_2O_3 add hexane and slowly add ethanol until the yellow color persists; then add water.) The solution in the filtration flask was then placed in a separatory funnel, and ether and water were added until two distinct phases became apparent. The organic phase was collected and the aqueous phase was twice extracted with ether. The combined organic phases were washed with brine and dried (Na_2SO_4) and the solvent was removed via rotary evaporation. The resulting oil was subjected to medium-pressure liquid chromatography using 10% EtOAc-hexane as the solvent (the desired product has an R_f = 0.5 with 20% EtOAc-hexane). The pure (+)-keto ketal **30** was obtained in 51.7% yield (620 mg) as a viscous oil: $[\alpha]^{25}_D$ +48.8° (*c* 0.05, $CHCl_3$); IR (film) 3030 (H-C=C), 1708 (C=O), 1638 (C=C), 1450 (CH_3), 1370-1390 [C-$(CH_3)_2$], 1090-1110 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$) δ 5.3-5.4 (m, 1 H, vinyl H) 3.5 (s, 4 H, O-CH_2-CH_2-O), 2.35-2.55 (m, 3 H), 1.5-2.3 (m, 1 OH), 1.35 (s, 3 H, CH_3), 1.2-1.45 (t, 2 H), 1.0 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.3, 149.k, 123.6, 99.2, 70.4, 53.7, 49.5, 46.5, 38.0, 34.1, 33.9, 31.8, 29.9, 22.7, 21.7, 21.4, 14.8, 12.5; mass spectrum calculated for $C_{20}H_{32}O_3$ = 320.2353, found = 320.2330.

(+)-Dione 31. Into a 50-mL one-neck round-bottomed flask was placed the **30** (0.595 g, 1.86 mmol) and 90% aqueous acetic acid (20 mL). The reaction was stirred for 2 h, poured into a separatory funnel containing 30 mL of water, and extracted 3 times with ether. The combined ethereal layers were washed with saturated $NaHCO_3$ until neutralized and then with brine. The organic layer was dried (Na_2SO_4) and removed via rotary evaporation to furnish 400 mg (91.9%) of pure (+)-dione **31** as an oil: $[\alpha]^{25}_D$ +29.11 (*c* = 0.0615, $CHCl_3$); IR (film) 3040 (HC=C), 1695-1720 (C=O), 1660 (C=C), 1440 cm^{-1} (CH_3); ^1H NMR ($CDCl_3$) δ 5.3-5.4 (m, 1 H, vinyl H), 2.4-2.8 (m, 6 H), 2.2 (s, 3 H, CH_3-C=O), 1.7-2.2 (m, 6 H), 1.65 (br s, 3 H, vinyl methyl), 1.0 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.5, 208.7, 149.5, 123.5, 53.7, 48.7, 46.4, 41.4, 38.0, 33.8, 31.6, 29.8, 21.7, 14.7, 12.5; mass spectrum calculated for $C_{15}H_{22}O_2$ = 234.1621, found = 234.1620.

(+)-BCD Tricycle 32. Into an oven-dried 25-mL round-bottomed flask (magnetic stirring bar, N_2 atmosphere) was placed (+)-dione **31** (0.37 g, 1.58 mmol), benzene (10 mL), and a previously made 0.1 M $NaOCH_3$-CH_3OH solution (0.5 mL). The reaction mixture was allowed to stir for 15 h, after which time thin-layer chromatography (40% EtOAc-hexane) revealed a UV-active product (R_f = 0.41), a second product (R_f = 0.3), and the absence of starting material (R_f = 0.36). All volatiles were removed by rotary evaporation and the residue taken up in ether. The ethereal solution was washed with water and then brine, dried (Na_2SO_4), and finally removed under reduced pressure. The mixture ws subjected to medium-pressure liquid chromatography (10% EtOAc-hexane), which yielded the ketol (0.1 g, 27%) as a solid and the desired (+)-BCD tricycle **32** (0.21 g, 62%) as an oil. Ketol: mp 171-173 °C; IR (Nujol mull) 3390 (OH), 3020 (H-C=C), 1700 (C=O), 1630 (C=C), 1120 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 5.2-5.4 (m, 1 H, vinyl H), 2.3-2.5 (m, 4 H), 1.3-2.0 (m, 13 H), 0.8 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.3, 151.7, 123.7, 75.8, 56.3, 50.0, 47.9, 42.1, 42.0, 37.2, 31.5, 30.9, 26.3, 15.2, 13.5, mass spectrum calculated for $C_{15}H_{22}O_2$ = 234.1621, found = 234.1642. BCD tricycle **32**: $[\alpha]^{35}_D$ +11.58° (*c* 0.01, $CHCl_3$); IR (film) 3040 (H-C=C), 1675 (C=O), 1620 (C=C), 1450 (CH_2), 970 (C=C), 800 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 5.83-5.88 (m, 1 H, enone H), 5.27-5.35 (m, 1 H, vinyl H), 1.7-2.75 (m, 9 H), 1.65 (br s, 3 H, vinyl CH_3), 1.4-1.6 (m, 3 H), 0.92 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 199.5, 166.7, 150.2, 125.4, 122.8, 55.6, 46.4, 37.3, 37.0, 34.0, 31.4, 31.0, 27.7, 14.4, 12.4; mass spectrum calculated for $C_{15}H_{20}O$ = 216.1515, found = 216.1510.

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Registry No. 6, 464-45-9; **7**, 464-48-2; **8**, 64474-54-0; **10**, 64474-56-2; **11**, 64474-57-3; **15**, 64421-34-7; **16**, 64421-35-8; **18**, 64421-37-0; **19**, 64478-24-6; **22** (enone), 51297-42-8; **22** (ketal), 87803-76-7; **25**, 87803-77-8; **27a**, 87803-78-9; **27b**, 87803-79-0; **28**, 87803-80-3; **29**, 87803-81-4; **30**, 87803-82-5; **31**, 87803-83-6; **32**, 87803-84-7; ethylene glycol, 107-21-1; dimethyl malonate, 108-59-8; 2,2-dimethyl-1,3-propanediol, 126-30-7; methyl vinyl ketone, 78-94-4.

Studies on the Synthesis of Vitamin B-12. 3

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Abstract: An enantiospecific approach to the synthesis of four precursors to vitamin B-12 from dextrorotatory and levorotatory camphor is described.

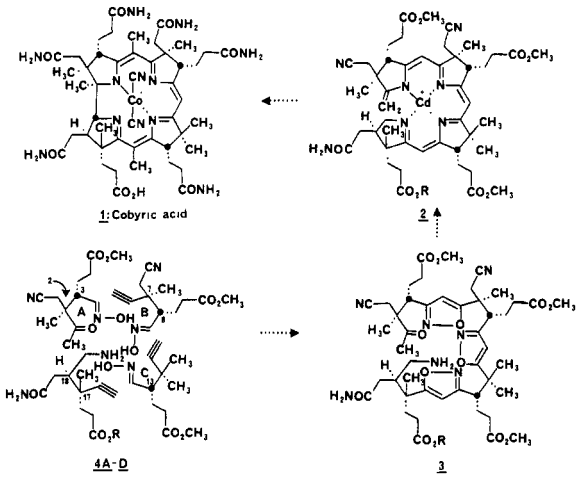
Previous accounts from this laboratory[1] have dealth with the design and development of a different strategy for the synthesis of cobyric acid (**1**) (Scheme I) and related corrinoid natural products. These studies established the feasibility of incorporating all of the essential features of this substance into a triisoxazole scaffold (e.g., **3**) that can serve as a latent synthon for the crucial secocorrin intermediate **2**. The triisoxazole **3** could, in turn, be assembled from four precursors (**4A-D**) via nitrile oxide cycloaddition technology. During the course of these previous studies the fundamental issue of stereochemistry, especially absolute stereochemistry, was largely ignored. In this paper and those that will follow[2] we address this fundamental problem.

(1) cf.: Stevens, R. V.; Lapalme, R.; Fitzpatrick, J. M.; Germeraad, P. B.; Harrison, B. L. *J. Am. Chem. Soc.* **1976**, *98*, 6313. Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *Ibid.* **1976**, *98*, 6317. Stevens, R. V. *Tetrahedron* **1976**, *32*, 1599. Stevens, R. V. "Vitamin B-12. Proceedings of the Third European Symposium on Vitamin B-12 and Intrinsic Factors", Zagalak, B.; Friedrich, W., Ed.; W. de Gryter: Berlin, 1979, and references cited therein.

(2) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Takeda, T.; Waldner, A.; Zutter, U.; Daniewski, A. R., unpublished results.

0002-7863/83/1505-7719$01.50/0

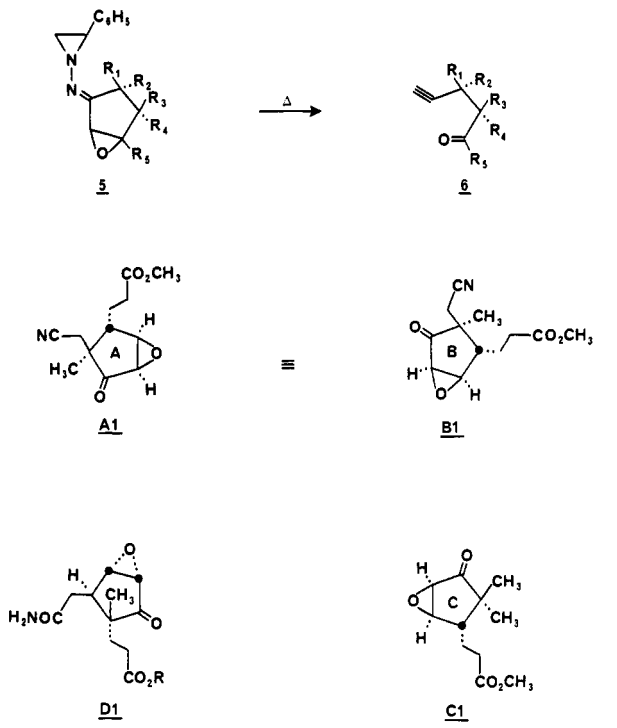
Scheme I



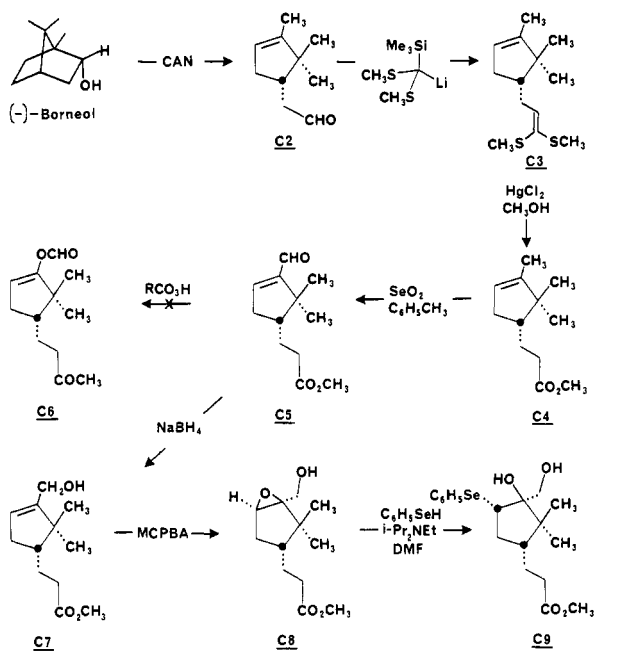
For the most part, the asymmetric centers incorporated by nature into each of the four five-membered rings are too remote from one another to permit effective stereochemical control via asymmetric induction *between* the rings. However, from the pioneering synthetic investigations of Schenmoser and Woodward[3,6h] we know now that the relative stereochemistry *within* the A and B rings at C-3 and C-8 can be partially controlled thermodynamically; however, no simple method for control of the labile center C-13 of the C ring is known. Further inspection of the periphery reveals that the substitution pattern *and* chirality of C-3, C-8, and C-13 are identical, and an analogous relationship exists between C-2 and C-7. These structural and stereochemical similarities suggested a common synthetic strategy and, perhaps more importantly, a common chiral origin. The substitution pattern at C-17 and C-18 of the D ring does not differ dramatically from those found at C-2 and C-3, suggesting once again a synthetic strategy in common with the A–C rings. However, these two centers are of precisely the opposite absolute configuration. Accordingly, they must be derived from an enantiomeric chiral origin. Therefore, we required a chiral source wherein both enantiomers would be readily available.

Of the various methods that were considered for the synthesis of these acyclic precursors, one seemed uniquely qualified, mainly, the Eschenmoser–Tanabe fragmentation[4,5] of appropriately substituted cyclopentenone oxides (cf. **5** to **6**) (Scheme II). In fact we had utilized this methodology to advantage in our earlier investigations.[1] The problem, therefore, quickly reduced itself to the synthesis of these substances in chirally pure form.

Scheme II



Scheme III



In the epochal Eschenmoser–Woodward synthesis of vitamin B-12[3] naturally occurring camphor was utilized on two occasions as a chiral starting material.[6h] This readily available substance has found wide employment as a source of chirality in a number of other synthetic investigations as well.[6] Since this substance is available in both the dextrorotatory and levorotatory forms it occurred to us that these substances might also be employed to advantage in the present study. As will be seen in the sequel this has been achieved with partially gratifying results.

Synthesis of the C Ring. With but one chiral center, this synthesis appeared to be the most straightforward. Oxidative fragmentation of (-)-borneol with ceric ammonium nitrate (CAN) was known to produce α-campholenaldehyde, C2[7] (Scheme III).

(3) For an account of this monumental achievement, see: Stevens, R. V. "Vitamin B-12"; Dolphin, D., Ed.; Wiley: New York, 1982; Vol. 1, Chapter 6.

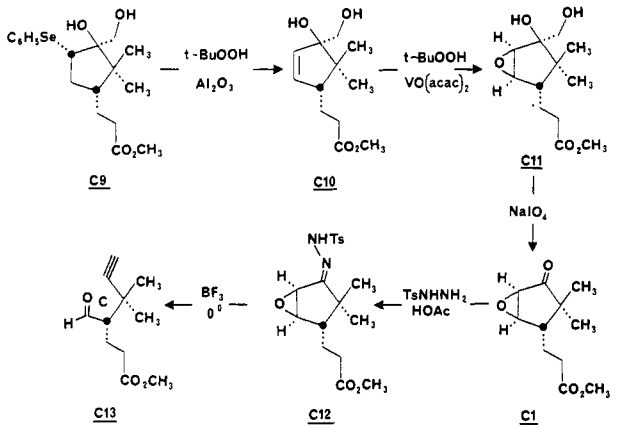
(4) Felix, D.; Müller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276. Eschenmoser, A.; Felix, D.; Ohloff, G. *Ibid.* **1967**, *50*, 708. Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *Ibid.* **1971**, *54*, 2896.

(5) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739. Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Ibid.* **1967**, 3943.

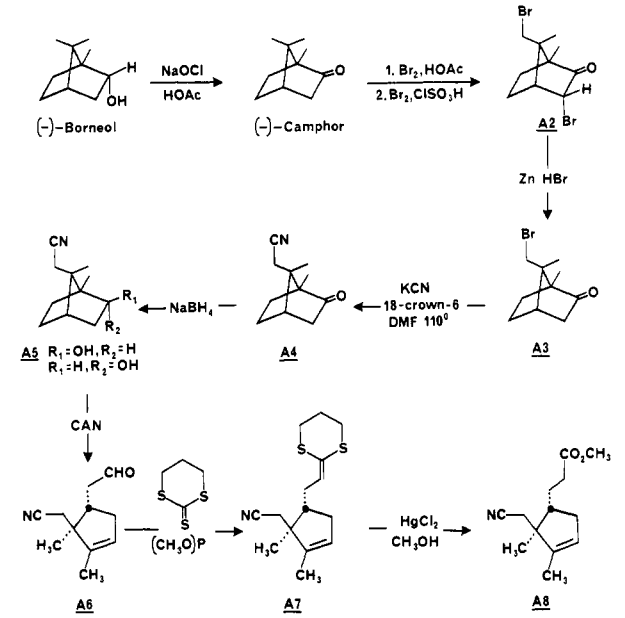
(6) (a) Corey, E. J.; Chow, S. W.; Scherrer, R. A. *J. Am. Chem. Soc.* **1957**, *79*, 5773. (b) Corey, E. J.; Semmelhack, M. F. *Ibid.* **1967**, *89*, 2775. (c) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *Ibid.* **1970**, *92*, 6314. (d) Corey, E. J.; Yamamoto, H. *Ibid.* **1970**, *92*, 226. (e) Kamet, S. Y.; Chakravarti, K. K.; Bhattacharyya, S. C. *Tetrahedron* **1967**, *23*, 4487. (f) Colonge, J.; Descorte, G.; Bahurel, Y.; Menet, A. *Bull. Soc. Chim. Fr.* **1966**, 374. (g) Lewis, R. G.; Gustafson, D. G.; Erman, W. F. *Tetrahedron Lett.* **1967**, 401. (h) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519; **1973**, *25*, 283; **1973**, *33*, 145. (i) Stevens, R. V.; Gaeta, F. C. A. *J. Am. Chem. Soc.* **1977**, *99*, 6105. (j) Eck, C. R.; Hodgson, G. L.; MacSweeney, D. F.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1938. (k) Allen, M. S.; Lamb, N.; Money, T. *J. Chem. Soc., Chem. Commun.* **1979**, 112. (l) Darby, N.; Lamb, N.; Money, T. *Can. J. Chem.* **1979**, *57*, 742. Liu, H.-J.; Chan, W. H. *Ibid.* **1979**, *57*, 708. Cachia, P.; Darby, N.; Mak, T. C. W.; Money, T.; Trotter, J. *Ibid.* **1980**, *58*, 1172. (m) Kitagawa, I.; Shibuya, H.; Fujioka, H.; Yamamoto, Y.; Kajiwara, A.; Kitamura, K.; Miyano, A.; Hakoshima. T.; Tomita, K. *Tetrahedron Lett.* **1980**, 1963. (m) Seebach, D.; Kalinowski, H. O. *Nachr. Chem. Tech.* **1976**, *24*, 415. (o) Szabo, W. A.; Lee, H. T. *Aldrichimica Acta* **1980**, *13*, 13.

(7) Trahanovsky, W. S.; Fox, N. S. *J. Am. Chem. Soc.* **1974**, *96*, 7968, and references cited therein.

Scheme IV



Scheme V

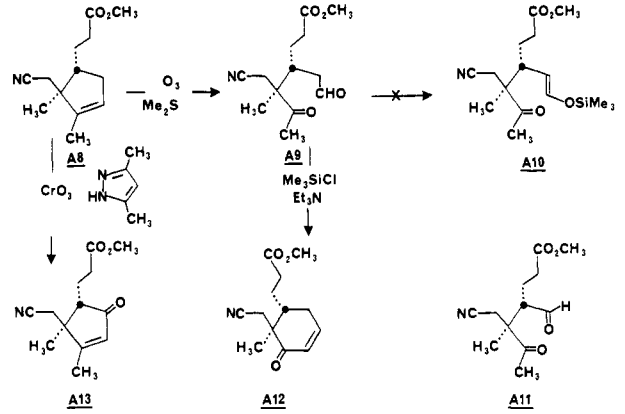


Alternatively, this substance can be prepared from (−)-α-pinene oxide by rearrangement with zinc bromide in refluxing benzene.[8] Homologation of the aldehyde side chain to the requisite propionate side chain C4 was achieved via ketene thioacetal C3.[9] Allylic oxidation of C4 with selenium dioxide to afford aldehyde C5 was studied extensively and found to proceed best in refluxing toluene. We had planned originally to complete the synthesis of C1 by peracid oxidation of C5 to enol formate C6 and subsequent obvious transformations; however, all attempts to effect this Baeyer-Villiger reaction resulted in the formation of the corresponding carboxylic acid. Accordingly, a new plan was devised. Reduction of C5 with sodium borohydride followed by peracid oxidation afforded a single epoxide (C8) in virtually quantitative yield. Although we could not be certain of the stereochemistry of C8 at this stage, this result was important from a practical point of view because we could proceed with further manipulations without concern for handling mixtures of diastereomers. Epoxide C8 was opened regio- and stereospecifically with selenophenol to afford selenide C9.

The final steps in the synthesis of the C ring are shown in Scheme IV. The selenide C9 was converted to epoxy ketone C1 in 70% overall yield without purification of the intermediates C10 and C11.[10] The overall yield for the entire nine-step synthesis of **C1** from readily available C2 was a satisfactory 17.5%. The stereochemistry of each of the intermediates in this sequence could be deduced from the stereochemistry of epoxide C1; however, a discussion of how this was accomplished will be postponed until later in the sequel. The important point here is that even though the stereochemistry of these additional centers of asymmetry is ultimately unimportant to the overall objectives (**4A–D**) we were able to avoid handling potentially troublesome mixtures of diastereomers along the way. Fragmentation of C1 to the C-ring precursor C13 proved to be much more difficult than we had anticipated. Numerous standard conditions[4,5] gave very complicated mixtures containing little if any acetylene C13. After numerous experiments a set of conditions was finally uncovered that did work albeit in modest overall yield.

Synthesis of the A Ring. (−)-Camphor is available commercially but for our purposes at a prohibitive cost. During the course of this work a new, simple, and inexpensive procedure was developed for the large-scale oxidation of readily available (−)-borneol as well as other secondary alcohols to the corresponding ketone[11] (Scheme V). With a firm supply of (−)-camphor in hand, we proceeded to functionalize the C-9 methyl group via a remarkable sequence of reactions introduced nearly a century ago[12] and subsequently shown[13] to proceed with complete retention of chirality (cf. A2 and A3). The displacement of bromide from A3 with cyanide to afford nitrile A4 required forcing conditions as was anticipated for this neopentyl-type of halide. Reduction of the ketone gave a mixture of epimeric alcohols (A5) that was submitted directly to oxidative fragmentation with CAN[7] to afford A6. Homologation[14] of the aldehyde side chain provided A8 in which the two chiral centers required for the A and B rings have been established unambiguously. The overall yield from borneol to A8 was a satisfactory 16%.

Scheme VI



As shown in Scheme VI, oxidative cleavage of A8 afforded A9. We had envisaged conversion of the latter intermediate to the corresponding enol ether A10 followed by a second oxidative cleavage to provide ring-A precursor A11. However, this approach was abandoned when it was discovered that A9 underwent an unexpectedly mild intramolecular aldol condensation to afford A12 in high yield. All other attempts to employ A9 further met with an equal lack of success. Accordingly, we returned to an alternate ultimately successful deployment of A8 that involved as its initial step allylic oxidation to afford cyclopentenone A13.

Attempts to convert A13 directly to epoxide A16 with alkaline hydrogen peroxide were complicated by competing hydrolysis reactions of the ester and nitrile. This was overcome by the indirect

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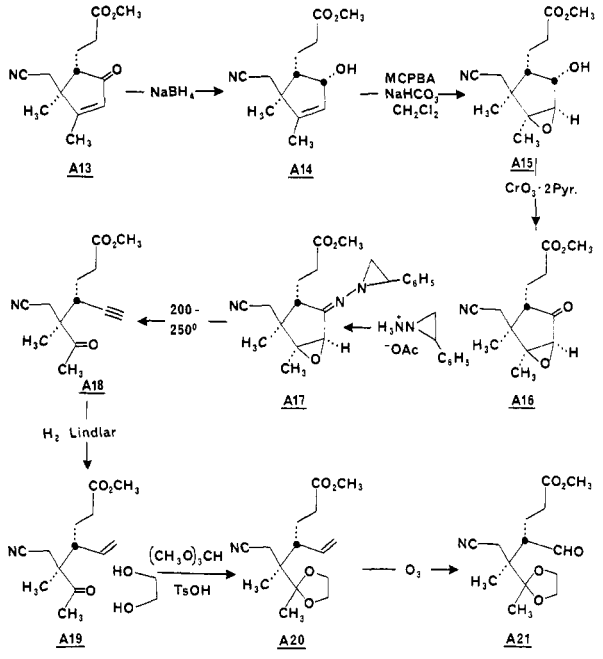
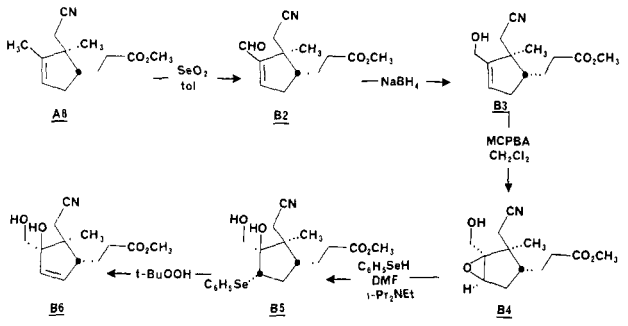
(9) Seebach, D.; Kolb, M.; Grobel, B. *Chem. Ber.* **1973**, *106*, 2277.
(10) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136; **1974**, *96*, 5254.
(11) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030. Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, 4647.
(12) Kipping, F. S.; Pope, W. J. *J. Chem. Soc.* **1893**, *63*, 549, 577, 593.
(13) Meyer, W. L.; Lobo, A. P.; McCarty, R. N. *J. Org. Chem.* **1967**, *32*, 1754. Finch, A. M. T., Jr.; Vaughan, W. R. *J. Am. Chem. Soc.* **1961**, *91*, 416. Joshi, G. C.; Warnhoff, E. W. *J. Org. Chem.* **1972**, *37*, 2383. Corey, E. J.; Ohno, M.; Chow, S. W.; Scherrer, R. A. *J. Am. Chem. Soc.* **1959**, *81*, 6304. Eck, C. R.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 251. Eck, C. R.; Hodgson, G. L.; McSweeney, D. F.; Mills, R. W.; Money, T. *Ibid.* **1974**, 1938.
(14) Corey, E. J.; Markel, G. *Tetrahedron Lett.* **1967**, 3201.

Scheme VII



Scheme VIII

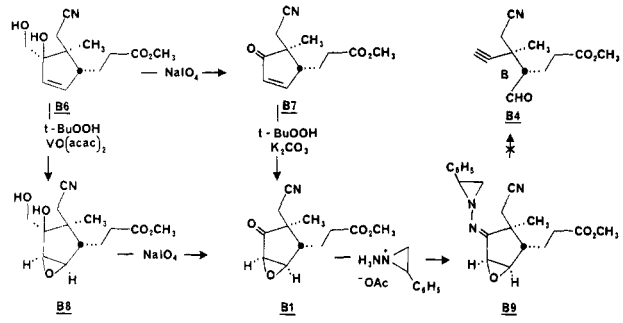


route outlined in Scheme VII involving reduction to allylic alcohol A14 followed by epoxidation to A15 and finally oxidation to A16 without extensive purification of the intermediates. In contrast to the difficulties encountered in the fragmentation of C1, A16 proceeded to alkynone A18 without incident as did the remaining three steps to the ring-A precursor A21.

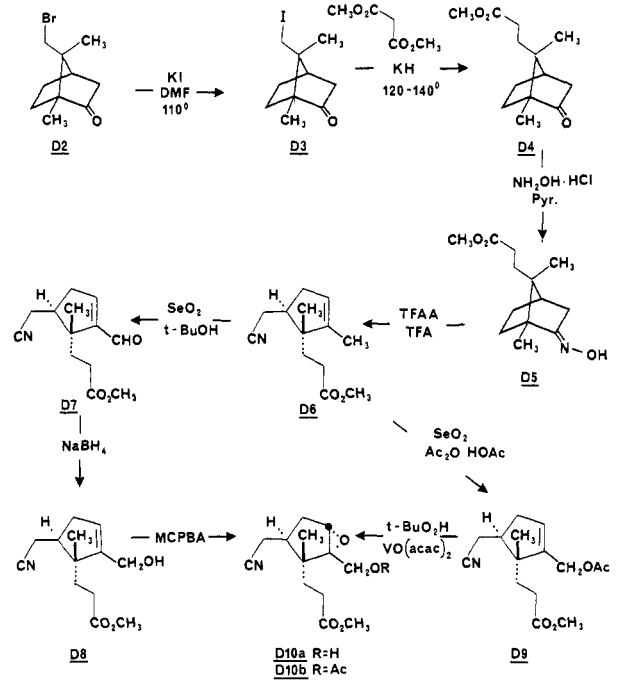
Attempted Synthesis of the B Ring. Cyanoester A8 also service as the point of departure for the projected synthesis of this ring (Scheme VIII). Allylic oxidation with selenium dioxide proceeded regiospecifically to afford aldehyde B_2, which was reduced to the allylic alcohol B3 and oxidized with *m*-chloroperbenzoic acid to give a single crystalline epoxide (B4) in 40% overall yield. The epoxide was opened regiospecifically with selenophenol to provide selenide B5 and then eliminated oxidatively to afford enediol B6.

Enediol B6 was converted to the desired target (B1) via two routes as outlined in Scheme IX. In the first route the diol was cleaved with periodate to afford enone B7, which oxidized with slightly basic *tert*-butyl hydroperoxide to afford a single epoxy ketone (B1). Since the conditions of the latter reaction could have placed the stereochemistry of the propionate side chain in jeopardy, an independent route to B1 was also developed. Thus, vanadium-assisted[10] epoxidation of enediol B6 afforded a single epoxide (B8) in which the stereochemical integrity of the propionate side chain is no longer in jeopardy. Periodate-induced oxidative cleavage of diol B8 led to the same epoxide (B1) as obtained by the previous route, confirming the fact that at least under mildly basic conditions eneone B7 is resistant to epimerization. The overall yield of B1 from B6 was 26%. Unfortunately, all attempts to fragment B1 via B9 (or similar intermediates) failed. In each case reaction was observed, but the resulting complex mixtures were devoid of aldehyde or acetylenic protons as ascertained by ^{1}H NMR spectroscopy.

Scheme IX



Scheme X

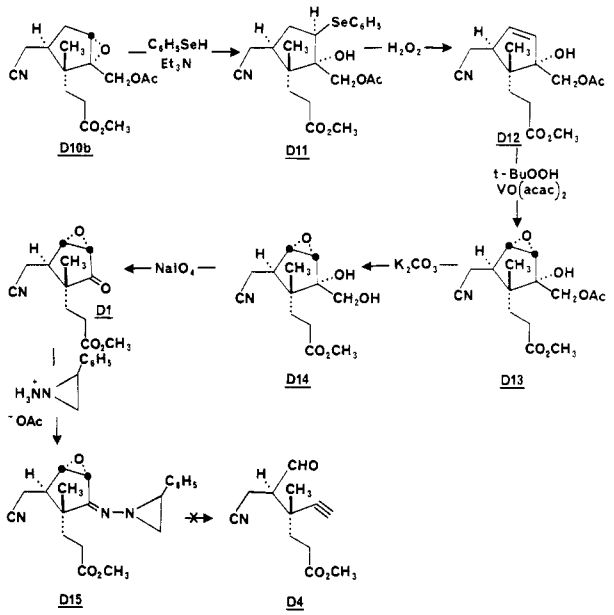


Attempted Synthesis of the D Ring. As noted above, the two chiral centers incorporated into the D ring are of the opposite absolute configuration to the analogous centers found in the "northern" part of the vitamin. Accordingly, readily available dextrorotatory 9-bromocamphor[12,13] (D1) was selected as our point of departure. The Finkelstein reaction of D2 to yield D3 (Scheme X) required forcing conditions as to be expected for an S_N2 displacement on a neopentyl-like halide of this type. With this in mind we were somewhat apprehensive about the possibility of using this halide in a malonic ester synthesis. These fears proved unfounded. Under appropriate conditions not only does D3 alkylate malonic eseter but also the resultant intermediate concomitantly decarbomethoxylates to afford the desired D4 directly in good yield. It has been established previously that the oxime of camphor does not undergo appreciable rearrangement under acidic conditions but rather suffers fragmentation.[15] Oxime D5 behaved analogously to provide D6. At this stage the experiences gained in connection with functionalization of the A–C rings proved invaluable. Thus, allylic oxidation to aldehyde D7 followed by sodium borohydride reduction afforded allylic alcohol D8, which underwent stereospecific oxidation with *m*-chloroperbenzoic acid to provide epoxide D10a. The corresponding acetate D10b could be prepared more conveniently by allylic oxidation in acetic anhydride followed by stereospecific epoxidation with the Sharpless reagent.[10]

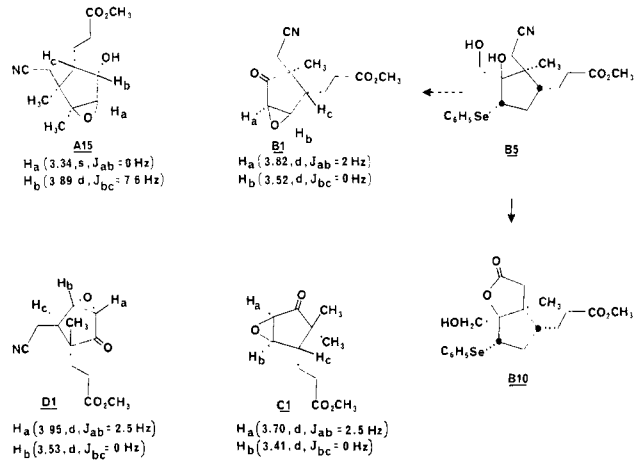
The final conversion of D10b to the desired cyclopentene oxide D1 (Scheme XI) followed lines strictly analogous to those outlined above and, except for the question of stereochemistry, requires

(15) cf.: Gream, G. E.; Wege, D.; Mular, M. *Aust. J. Chem.* **1974**, *27*, 567, and references cited therein.

Scheme XI



Scheme XII



no further comment. As in the case of the B ring all attempts to effect fragmentation of D1 to D4 via hydrazone derivative D15 or analogues thereof were unsuccessful.

Stereochemical Assignments. Each of the above routes establishes unambiguously the relative and absolute stereochemistry of those centers that were destined to be incorporated into the periphery of the vitamin. As noted above, from the practical point of view, we were also interested in being able to control the stereochemistry at those additional centers of asymmetry in each of our intermediates in order to avoid handling complex mixtures of diastereomers. The stereochemical assignments are based on a combination of ^{1}H NMR data, certain chemical observations, and knowledge about the stereochemical course of certain key reactions.

The first intermediate which allowed us to assign stereochemistry to each of the A-ring precursors shown above in Scheme VII was cyclopentene oxide A15. The ^{1}H NMR spectrum of A15 at 200 MHz for each of the centers in question is summarized in Scheme XII: H_a is assigned to a singlet at 3.34 ppm. Since H_a is a singlet, the coupling constant $J_{ab} = 0$ Hz. H_b is assigned to a doublet at 3.89 ppm and since we know that $J_{ab} = 0$ Hz, the observed coupling must represent $J_{bc} = 7.6$ Hz. These assignments were confirmed by a decoupling experiment. Although we have no knowledge of the precise dihedral angles involved, it is clear that a zero coupling constant in a five-membered ring can only be assigned to two vicinal protons that are trans to one another, certainly not cis. From this knowledge we can assign stereochemistry to all of the remaining intermediates associated with the synthesis of the A ring.

The stereochemical assignments for each intermediate associated with the B ring (cf. Schemes VIII and IX) follow a similar line of spectroscopic reasoning coupled with chemical observations. Note in Scheme IX that the penultimate intermediate B1 was prepared from diol B6 by two different routes. The first route, B6 to B7 to B1, proceeds in much better overall yield but we were concerned that the alkaline conditions required for epoxidation of B7 could have jeopardized the stereochemical integrity of the propionate side chain. In order to rule out this possibility, the epoxide B1 was also prepared from B6 via intermediate B8. At no time in the latter sequence is the stereochemistry of the propionate side chain jeopardized so that we could be confident that the more efficacious route did not alter the stereochemistry of this crucial center. Scheme VIII outlines the origin of the chiral center bearing the vicinal diol moiety. The stereochemistry of this center was ordained in the epoxidation step B3 to B4. A priori we have no way of predicting the stereochemistry of this step. However, we soon discovered that attempts to purify diol B5 by liquid chromatography on either neutral alumina or even Florisil lead cleanly to γ-lactone B10 (see Scheme XII). The facile formation of this bicyclic γ-lactone can only be explained in terms of the stereochemistry depicted: the corresponding epimeric diol would lead to a highly strained trans-bicyclic γ-lactone. Furthermore, since it is known[10] that vanadium-assisted epoxidation of allylic alcohols is biased to occur on the same face as the allylic hydroxyl group, we could assign the stereochemistry shown with considerable confidence. The ^{1}H NMR of B1 is consistent with these chemical arguments; note once again that $J_{bc} = 0$ Hz. The additional chiral centers generated in the production of the C-ring and D-ring precursors were likewise deduced from analogous chemical and spectroscopic arguments.

Experimental Section

Ester C4. To a solution of (trimethylsilyl)formaldehyde dimethyl thioacetal (30.7 g, 0.17 mol) in THF (350 mL) under Ar at −78 °C was slowly added *n*-BuLi solution (75.0 mL of 2.27 M) in hexane (0.17 mol). When the addition was complete, the reaction was allowed to warm to 0 °C over 5 h and was then recooled to −78 °C. Aldehyde C2[7] (23.6 g, 0.15 mol, $[\alpha]^{25}_D$ −9.7°) in THF (25 mL) was then added, and the reaction mixture was allowed to warm to room temp over 12 h. The mixture was then poured into brine (1.5 L) and extracted with 20–40 petroleum ether (4 × 500 mL). The extracts were combined, washed twice with water, dried (K_2CO_3), and concentrated by rotary evaporation. The residue was filtered through silica gel (eluting with cyclohexane) and then was dissolved in methanol (1 L). Mercuric chloride (94 g, 0.35 mol) was then quickly added with rapid stirring; after 3 min, Na_2CO_3 (31.3 g) was added slowly and stirring was continued for 30 min. The solution was then filtered and concentrated by rotary evaporation to give a brown residue. Water was added and the mixture was extracted several times with petroleum ether. The extracts were then combined, washed sequentially with aqueous Na_2CO_3 solution and brine, dried (K_2CO_3), and concentrated by rotary evaporation. Distillation of the residue through a 20-cm Vigreaux column gave 21.0 (69%) of ester C4: bp 55–58 °C/0.3 torr; $[\alpha]^{25}_D$ (neat) −9.87°; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.22 (1 H, br s, HC=C), 3.67 (3 H, s, OCH_3), 1.5–2.4 (7 H, m, $-CH_2-$), 0.99 (3 H, s, CH_3), 0.78 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.3 (C=O), 148.6 (C=C), 121.5 (C=C), 51.4, 50.0, 46.9, 35.2, 33.5, 25.7, 25.5, 19.6, 12.6; IR (neat film) 3030 (w), 2950 (s), 2930 (m), 2860 (w), 2830 (w), 1744 cm^{-1} (s); mass spectrum *m/e* 196.1463, calculated for $C_{12}H_{20}O_2$ = 196.1463.

Aldehyde C5 and Alcohol C7. To a solution of ester C4 (20.7 g, 0.11 mol) in toluene (1.3 L) at reflux was added SeO_2 (25.8 g, 0.23 mol) in portions over 5 h. When the addition was complete, the dark red brown reaction mixture was cooled, filtered through Celite (to remove Se black), and concentrated by rotary evaporation. The residue was dissolved in CH_2Cl_2 (500 mL) and *m*-chloroperbenzoic acid (Aldrich, 85%) was added until no more color change was observed. The solution was then washed twice with aqueous Na_2CO_3 solution and once with brine and dried (K_2CO_3). Removal of solvent by rotary evaporation gave the crude aldehyde C5 (18.4 g, 79%), which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 9.75 (s, CHO), 6.8 (m, HC=C), 3.75 (s, OCH_3), 1.3 (s, CH_3), 1.00 (s, CH_3).

The crude aldehyde (18.4 g, 0.88 mol) in a minimum amount of CH_3OH was slowly added to $NaBH_4$ (5.0 g, 0.13 mol) in CH_3OH (250 mL) at 0 °C. The mixture was stirred for 30 min after the addition was

complete, after which it was poured into water (700 mL). The mixture was extracted into CH_2Cl_2 (4 × 200 mL) and the extracts were combined, washed sequentially with saturated aq $NaHCO_3$ solution and brine, dried (K_2CO_3), and concentrated by rotary evaporation. Medium-pressure liquid chromatography (silica gel, 5:1 cyclohexane–ethyl acetate) of the residue gave the allylic alcohol C7 (10.8 g, 46% overall from C4). An analytical sample was obtained by short path distillation (110 °C/0.02 torr): $[\alpha]^{25}_D$ ($CHCl_3$) −19.9°; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.56 (1 H, br s, HC=C), 4.17 (2 H, br s, CH_2OH), 3.68 (3 H, s, OCH_3), 1.2–2.6 (7 H, m, $-CH_2-$), 1.06 (3 H, s, CH_3), 0.87 (3 H, s, CH_3); ^{13}C NMR ($CHCl_3$) δ 174.3 (CO_2CH_3), 152.5 (C=C), 122.3 (C=C), 59.4, 51.4, 50.7, 46.3, 35.3, 33.4, 25.8, 25.2, 24.9, 20.6; IR (neat film) 3100–3600 (s), 2950 (s), 2920 (s), 2860 (m), 2830 (w), 1735 cm^{-1} (s); mass spectrum *m/e* 212, 194.1302, calculated for $C_{12}H_{20}O_3$ = 212, calculated for $C_{12}H_{18}O_3$ = 194.1307.

Epoxide C8. To a solution of alcohol C7 (9.71 g, 0.046 mol) in CH_2Cl_2 (250 mL) at 0 °C was added *m*-chloroperbenzoic acid (Aldrich, 85%, 12.1 g, 0.059 mol) in portions over 30 min. Stirring was continued for 60 min as the solution warmed to 25 °C, and then the solution was washed 3 times with an aqueous K_2CO_3 solution and once with brine, dried (K_2CO_3), and concentrated by rotary evaporation to give a semicrystalline solid (10.4 g, 100%) that could be recrystallized from hexane–chloroform or chromatographed (silica gel, 5:1 cyclohexane–ethyl acetate) to give pure compound: mp 53–55 °C; $[\alpha]^{25}_D$ ($CHCl_3$) −0.44°; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.81–3.96 (2 H, m, CH_2OH), 3.67 (3 H, s, OCH_3), 3.51 (1 H, br s, epoxide H), 1.2–2.5 (7 H, m, $-CH_2-$), 1.06 (3 H, s, CH_3), 0.82 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.9 (C=O), 71.8, 59.8, 57.5, 51.6, 43.3, 40.6, 33.2, 31.5, 24.4, 21.7, 18.0; IR (neat) 3200–3700 (s), 2950 (s), 2870 (m), 1740 cm^{-1} (s); mass spectrum *m/e* 228 (small), calculated for $C_{12}H_{20}O_4$ = 228, *m/e* 210.1257, calculated for $C_{12}H_{18}O_3$ = 210.1256.

Diol C9. To a solution of epoxide C8 (2.0 g, 8.8 mmol) in dimethylformamide (30 mL) under N_2 was added selenophenol (7.8 g, 50 mmol) and diisopropylethylamine (4.4 g, 34 mmol). The reaction mixture was heated at 100 °C for 1 h, then cooled to 25 °C, and poured into diluted HCl (300 mL). The mixture was extracted 4 times with ether; the extracts were combined, washed sequentially with a saturated aqueous Na_2CO_3 solution and brine, dried (K_2CO_3), and concentrated by rotary evaporation. Elution chromatography of the oily residue on neutral alumina gave a first fraction (1:1 ethyl acetate–hexane) of nonpolar impurities, followed by a second fraction (1:1 ethyl acetate–methanol) of selenide C9, which crystallized upon removal of the solvent: mp 61–64 °C; yield, 2.7 g (79%); $[\alpha]^{25}_D$ ($CHCl_3$) +5.00°; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.5–7.6 (2 H, m, aromatic H), 7.2–7.3 (3 H, m, aromatic H), 4.03 (1 H, dd, *J* = 5, 12 Hz, CH_2OH), 3.66 (3 H, s, OCH_3), 3.50–3.65 (2 H, m, CH_2OH + CHSe), 3.05 (1 H, s, OH), 1.2–2.8 (8 H, m, $-CH_2-$ + OH), 0.99 (3 H, s, CH_3), 0.80 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 133.0 (aromatic), 130.7 (aromatic), 129.4 (aromatic), 127.5 (aromatic), 85.6, 64.8, 51.6, 50.3, 46.7, 46.2, 39.2, 33.3, 24.7, 21.2, 17.4; IR (neat) 3200–3600 (s), 2940 (s), 2860 (m), 1760 cm^{-1} (s); mass spectrum *m/e* 386.0995, calculated for $C_{18}H_{26}O_4Se$ = 386.0994.

Epoxy Ketone C1. To a mixture of diol C9 (2.06 g, 5.3 mmol) and basic alumina (0.63 g, HF-254 basic for TLC) in CH_2Cl_2 (25 mL) was added 70% *t*-BuOOH (redistilled, 4.0 mL). The mixture was stirred for 5.5 h and then was poured into water. The organic layer was separated, dried (K_2CO_3), and concentrated by rotary evaporation at 25 °C to give crude enediol C10, which was used directly. To the crude enediol was added benzene (40 mL) and *t*-BuOOH (4.0 mL). The solution was cooled in an ice bath and $VO(AcAc)_2$[10] (0.40 g, 1.5 mmol) was added to give a red-purple solution. The mixture was stirred at 0 °C for 30 min and then at 25 °C for 2 hr, during which the solution turned green and then a precipitate formed, leaving a yellow-brown solution. The mixture was filtered and concentrated by rotary evaporation to give a dark brown oil (epoxy diol, 16), which was dissolved in CH_3OH (35 mL) and a pH 8 buffer solution (25 mL). To this solution was added $NaIO_4$ (3.0 g, 14.0 mmol) with rapid stirring. The mixture was stirred at 25 °C for 40 min and then was poured into a saturated aqueous Na_2CO_3 solution (150 mL). The mixture was extracted 4 times with ether, the extracts were combined, washed with brine, and dried (K_2CO_3), and the solvent was removed by rotary evaporation. Chromatography (silica gel, cyclohexane to ethyl acetate polarity gradient) gave nearly pure epoxy ketone C1 (793 mg, 70% overall). Short path distillation (80–90 °C/0.02 torr) of this gave an analytical sample: $[\alpha]^{25}_D$ ($CHCl_3$) −5.73°; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.71 (3 H, s, OCH_3), 3.70 (1 H, d, *J* = 2.5 Hz, epoxide H), 3.41 (1 H, d, *J* = 2.5 Hz, epoxide H), 1.4–2.6 (5 H, m, $-CH_2-$), 1.16 (3 H, s, CH_3), 0.99 (3 H, s, CH_3); ^{13}C NMR (C_6D_6) δ 211.9 (ketone C=O), 172.5 (ester C=O), 59.0, 55.5, 51.2, 45.4, 45.0, 32.0, 29.2, 23.4, 22.7; IR (neat) 2970 (m), 2950 (m), 2970 (w), 1740 cm^{-1} (s); mass spectrum *m/e* 212 (small), calculated for $C_{11}H_{16}O_4$ = 212, *m/e* 197.0816, calculated for $C_{10}H_{13}O_4$ = 197.0814.

Acetylenic Aldehyde C13. To 400 mg (1.88 mmol) of epoxy ketone C1 in 7.5 mL of CH_3CO_2H and 7.5 mL of CH_2Cl_2 at 0 °C was added 386 mg (2.07 mmol) of (*p*-toluenesulfonyl)hydrazine and the mixture was stirred for 2 h and then for 10 min at room temperature. The mixture was poured into H_2O and the organic layer separated, dried, and evaporated to provide the crude hydrazone C12. The hydrazone was dissolved in 30 mL of CH_2Cl_2 and 10 drops of $BF_4{\cdot}OEt_2$ added at room temperature. Gas evolution was vigorous. The mixture was poured into H_2O, washed with saturated Na_2CO_3 and then brine, and dried (Na_2SO_4). Chromatography on silica gel (petroleum ether–ether, 2:1) gave 145 mg (39%) of C13. An analytical sample was prepared by distillation (110 °C at 0.2 mm): $[\alpha]_D$ +0.647°, $[\alpha]_{435}$ +3.632°; IR (film) 3280; 2730, 2100, 1738, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 [s, 6 H, $C(CH_3)_2$], 1.90–2.20 (m, 3 H, $-CH_2CH-$), 2.20–2.50 (m, 2 H, $-CH_2CO$), 2.27 (s, 1 H, HC≡), 3.67 (s, 3 H, CH_O), 9.78 (d, *J* = 3.5 Hz, 1 H, CHO); mass spectrum calculated 181.0854, found 181.0861.

Oxidation of (−)-Borneol to (−)-Camphor. (−)-Borneol (502 g, 3.26 mol, $[\alpha]^{25}_D$ ($CHCl_3$) −35.3°) was dissolved in glacial acetic acid (1.5 L) in a 5-L, three-neck flask fitted with a mechanical stirring apparatus and thermometer. Aqueous sodium hypochlorite solution (2 L of 2.0 M solution, 3.6 mol) was added dropwise over 2.5 h. The mixture was cooled in an ice bath as necessary to keep the internal temperature in the range 15–25 °C. The mixture was stirred for 1 h after completion of the addition, at which time a positive potassium iodide–starch test was obtained. Saturated aqueous sodium bisulfite solution (200 mL) was added until the color of the mixture changed from yellow to white and the potassium iodide–starch test was negative. The mixture was then poured over an ice–brine mixture (10 L), and the resulting white solid was collected on a Büchner funnel and was washed with saturated aqueous Na_2CO_3 solution until foaming was no longer evident. The solid product was pressed as dry as possible and was dissolved in petroleum ether (2 L, bp 20–60 °C), and the aqueous and organic layers were separated. The aqueous layer was extracted twice with petroleum ether and discarded. The organic layers were combined and dried over anhydrous $CaCl_2$. The mixture was concentrated by rotary evaporation until most of the petroleum ether was removed and a white slurry remained. The remainder of the petroleum ether was then removed by high-vacuum rotary evaporation with the condenser cooled to −78 °C to prevent sublimation of camphor, leaving 475 g (95.8%) of (−)-camphor as a free flowing white powder: mp 175.5–176.5 °C; $[\alpha]^{25}_D$ ($CHCl_3$) −42.1°; the ^1H NMR and IR spectra and VPC retention time of this product were identical with those of an authentic sample.

(−)-9-Cyanocamphor (A4). A mixture of (−)-9-bromocamphor [30 g, 0.13 mol; mp 91–93 °C; $[\alpha]^{25}_D$ −112.5 ± 1.1° ($CHCl_3$)], KCN (30 g, 0.46 mol), and 18-crown-6 ether (2.1 g) in *N,N*-dimethylformamide (150 mL, dried by storage over calcium hydride and molecular sieves) was heated at 110 °C under N_2 for 96 h. The mixture was then cooled to 25 °C, poured into water (500 mL), and extracted 3 times with ether (3 × 250 mL). The combined ether extract was washed twice with water, dried ($MgSO_4$), and concentrated by rotary evaporation. The resulting white semisolid was recrystallized from 1:1 cyclohexane–ether to give 17.5 g (76%) of (−)-9-cyanocamphor as colorless needles. Occasionally the reaction produces a brown oil at this point that will not crystallize. The reason for this variation has not been determined. When this occurs, the product may be obtained by filtration through Fluorisil (eluting with 1:1 cyclohexane–ether) followed by recrystallization. Yields range from 18% to 47% when this occurs. In cases of only slight discoloration, the mixture may be cleaned up by stirring over Florisil followed by filtration. This is usually done along with the $MgSO_4$ drying step: mp 167.5–168 °C; $[\alpha]^{25}_D$ −61.9 ± 0.4° in $CHCl_3$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 3 H, bridgehead CH_3), 1.075 (s, 3 H, CH_3), 1.42–2.01 (m, 5 H), 2.21–2.52 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 215.8 (C=O), 117.5 (CN), 57.7, 48.6, 42.6, 41.3, 29.3, 26.4, 22.2, 17.2, 9.3; IR (CCl_4) 2980 (m), 2920 (w), 2880 (w), 2240 (CN, w), 1740 cm^{-1} (C=O, s); mass spectrum *m/e* 177.1150, calculated for $C_{10}H_{15}NO$ = 117.1153.

Preparation of 9-Cyanoborneols (A5). To a solution of (−)-9-cyanocamphor (28.5 g, 0.161 mol) in tetrahydrofuran (225 mL) containing 2.5 mL of 5% aqueous NaOH solution was added solid $NaBH_4$ (6.5 g, 0.171 mol) in a single portion. The mixture was then heated at reflux with magnetic stirring for 15 h, after which it was cooled to 25 °C and poured into water (500 mL). The mixture was extracted once with ether; the ether layer was washed once with water and set aside. The aqueous layers were then combined and extracted 3 times with CH_2Cl_2. The methylene chloride extracts were combined and the combined extract was washed with water. The methylene chloride and ether extracts were then combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give a solid white residue. Recrystallization from ether afforded a mixture of *exo*- and *endo*-9-cyanoborneols (24.5 g, 85%) that was normally used in the next step without further purification.

The isomers were separated by preparative medium-pressure liquid chromatography on silica gel, eluting with 3:1 cyclohexane–ethyl acetate. The individual isomers were recrystallized from ether and were homogeneous by TLC (silica gel, 3:1 cyclohexane–ethyl acetate). The major isomer ("isomer A", exo-OH) had the following characteristics: R_f = 0.32; mp = 167.5–168.5 °C; $[\alpha]^{25}_D$ +8.0°; mass spectrum *m/e* 179.1310, calculated for $C_{11}H_{17}NO$ = 179.1310; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (m, 1 H, C*H*OH), 1.28 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.05–2.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 119.2 (C≡N), 79.2 (*C*HOH), 49.5, 48.8, 43.4, 39.7, 33.3, 26.6, 23.2, 17.3, 11.4; IR ($CHCl_3$) 3590 (m), 3450 (m), 2940 (s), 2870 (m), 2230 cm^{-1} (m). The minor isomer ("isomer B", endo-PH) had the following characteristics: R_f = 0.22; mp 174.0–175.0 °C; $[\alpha]^{25}_D$ −4.3°; mass spectrum *m/e* 179.1310, calculated for $C_{11}H_{17}NO$ = 179.1310; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.05 (m, 1 H, C*H*OH), 1.11 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 1.0–2.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 118.8 (C≡N), 76.3 (CHOH), 50.1, 49.7, 43.3, 38.1, 27.6, 25.6, 22.8, 16.0, 13.2; IR ($CHCl_3$) 3600 (m), 3460 (m), 2940 (s), 2875 (m), 2240 (w).

Preparation of (−)-2-[2-(Cyanomethyl)-2,3-dimethylcyclopent-3-en-1-yl]acetaldehyde (A6). A solution of 9-cyanoborneols (isomer mixture, 8.45 g, 47.2 mmol) in 1:1 acetonitrile–water (200 mL) was cooled in an ice–water bath. Ceric ammonium nitrate (52 g, 95 mmol) was dissolved in water (100 mL) and this solution was also cooled in an ice–water bath. The cold ceric ammonium nitrate solution was then poured into the 9-cyanoborneol solution all at once, resulting in a deep red color. The solution was stirred for 15 min at 0 °C (during which the color faded to pale yellow) and was then poured into water (375 mL) and extracted with ether (3 × 125 mL). The ether extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation to give a yellow oil. The above procedure was performed a total of 5 times, using a total of 39.67 g of 9-cyanoborneols (222 mmol) and 242 g (442 mmol) of ceric ammonium nitrate. The oils were then combined and dissolved in ether. When the solution was cooled to −30 °C, pale yellow crystals of isomerically pure campholenaldehyde formed. The mother liquor was drawn off and concentrated and a second crop was grown from 1:1 ether–cyclohexane for a total yield of 30.4 g (77%). This material was used directly in the next step of the synthesis. The analytical sample was obtained as white plates by rapid chromatography on Florisil (ether–cyclohexane, 1:1) followed by recrystallization from ether–cyclohexane: mp = 55–56 °C; $[\alpha]^{25}_D$ −14.2°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.79 (1 H, t, *J* = 1.5 Hz, CHO), 5.42 (1H, m, CH=C), 1.8–2.8 (7 H, m), 1.69 (3 H, t, *J* = 1.6 Hz, CH=CC*H*$_3$), 0.98 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 201.3 (CHO), 143.3 [C=*C*(CH$_3$)], 124.9 [*C*=C(CH$_3$)], 118.1 (C≡N), 49.0, 45.1, 40.1, 35.9, 27.2, 18.5, 12.4; IR ($CHCl_3$) 3010 (w), 2960 (m), 2930 (m), 2910 (m), 2840 (m), 2720 (w), 2240 (w), 1730 (s); mass spectrum *m/e* 177.1150, calculated for $C_{11}H_{15}NO$ = 177.1153. Distillation of the mother liquor from the above crystallization gave 4.9 g of a yellow liquid, bp 115–131 °C/0.05 torr. Preparative VPC of this liquid on a 6 ft × 0.375 in. 10% Carbowax column at 180 °C and 300 mL/min He flow led to traces of the campholenaldehyde described above (retention time 18 min) and the exocyclic double bond isomer (retention time 21 min): $[\alpha]^{25}_D$ +24 ± 10°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.77 (1 H, m, CHO), 5.04 (1 H, t, *J* = 2.2 Hz, C=C*H*H), 4.94 (1 H, t, *J* = 2.2 Hz, C=CH*H*), 1.3–2.8 (m, 9 H), 1.04 (3 H, s, CH_3); IR ($CHCl_3$) 3000 (w), 2950 (m), 2920 (m), 2840 (m), 2720 (w), 2230 (w), 1730 (s); mass spectrum *m/e* 177.1151, calculated for $C_{11}H_{15}NO$ = 177.1153.

Preparation of (−)-Methyl 3-[2-(Cyanomethyl)-2,3-dimethylcyclopent-3-en-1-yl]propionate (A8). A mixture of 1,3-dithiacyclohexane-2-thione (22.0 g, 147 mmol) and trimethyl phosphite (300 mL) was stirred under N_2 at 50 °C for 3 h. The mixture was then cooled to 25 °C and a solution of A6 (21.2 g, 120 mmol) in trimethyl phosphite (100 mL) was added in a single portion. The mixture was stirred under N_2 for 12 h, after which the trimethyl phosphite was removed by distillation at water aspirator pressure (bath temperature = 50 °C) to leave a yellow residue. Methanol (500 mL) was then added to the residual and a mixture of $HgCl_2$ (66 g, 240 mmol) in CH_3OH (150 mL) was added in a single portion, resulting in a white gelatinous precipitate. After 3 min, solid sodium bicarbonate (100 g) was added to the mixture in small portions over 5 min. The mixture was then poured into ether (1 L) and was filtered. The resulting ethereal solution was concentrated by rotary evaporation to give an oily residue. Ether and water were added to the residue and the aqueous layer was extracted twice with ether. The ether layers were combined, washed twice with water, dried ($MgSO_4$), and concentrated by rotary evaporation to leave a foul-smelling yellow oil. Distillation gave a forerun of bp 45–50 °C/0.1 torr and then the desired product, bp 129–133 °C/0.1 torr (15.3 g, 58%). When 57 g of aldehyde was used, the yield was 78% at this stage (no. HNW-II-205). This material was pure enough for most purposes. The analytical sample was obtained by medium-pressure liquid chromatography (2:1 cyclohexane–ethyl acetate) as a colorless liquid (9.80 g, 46%) that was homogeneous by TLC (ethyl acetate, cyclohexane) and VPC (Carbowax): $[\alpha]^{25}_D$ −37.9°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.41 (1 H, m, CH=C), 3.69 (3 H, s, OCH_3), 1.5–2.6 (9 H, m), 1.69 (3 H, br s, HC=CC*H*$_3$), 0.95 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5 (C=O), 143.7, 124.7, 118.0 (CN), 51.3, 49.1, 46.5, 35.0, 32.6, 26.6, 25.0, 18.0, 12.3; IR (neat film) 3040 (w), 2950 (m), 2840 (w), 2240 (w), 1760 (s); mass spectrum *m/e* 221.1411, calculated for $C_{13}H_{19}NO_2$ = 221.1416.

Keto Aldehyde A9. A solution of cyclopentene A8 (4.00 g, 18.0 mmol; $[\alpha]^{25}_D$ −37.9°) in methanol (100 mL) was cooled to −30 °C and a stream of ozone was passed through for 30 min, after which the solution was flushed with oxygen. Solid potassium iodide (16.6 g, 100 mmol) was then added and the mixture was stirred vigorously as it warmed to 25 °C over a period of 12 h. The mixture was then concentrated to dryness by rotary evaporation; the residue was dissolved in a mixture of methylene chloride and aqueous sodium thiosulfate solution and was extracted 4 times into methylene chloride. The extract was dried ($MgSO_4$) and concentrated by rotary evaporation to give an orange oil. Trituration with ether led to formation of white crystals: mp 99.5–100.5 °C (1.75 g, 39%); $[\alpha]^{25}_D$ ($CHCl_3$) +14.8°; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.82 (1 H, s, CHO), 3.67 (3 H, s, CO_2CH_3), 2.28 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.5–2.8 (9 H, m); ^{13}C NMR ($CDCl_3$) δ 209.3 (CH_3C=O), 200.0 (CHO), 172.8 (CO_2CH_3), 118.2 (CN), 53.1, 51.7, 44.3, 35.5, 31.6, 26.4, 25.2, 21.7, 20.4; IR ($CHCl_3$) 3010 (m), 2940 (m), 2820 (m), 2720 (w), 2240 (w), 1730 (s), 1705 cm^{-1} (s); mass spectrum *m/e* 253; exact mass = 235.1179 (M^+ − 18), calculated for $C_{13}H_{17}NO_3$ ($M^+ - H_2O$) = 235.1208.

Cyclohexenone A12. To a solution of (+)-keto aldehyde (2.15 g, 8.5 mmol) in DMF (200 mL) were added chlorotrimethylsilane (1.5 mL, 11.5 mmol) and triethylamine (1.6 mL, 11.5 mmol). The resulting mixture was stirred under nitrogen at 60 °C for 16 h, after which is was concentrated by high-vacuum rotary evaporation to give an oily residue that was purified by medium-pressure liquid chromatography (2:1 cyclohexane–ethyl acetate eluant) to give the pure enone (1.41 g, 71%): $[\alpha]^{25}_D$ ($CHCl_3$) −75.4°; ^{1}H NMR ($CDCo_3$, 200 MHz) δ 6.98 (1 H, m, β-vinyl H), 6.03 (1 H, d, *J* = 10 Hz, α-vinyl H), 3.71 (3 H, s, CO_2CH_3), 1.08 (3 H, s, CH_3), 1.6–2.2 (9 H, m); ^{13}C NMR ($CDCl_3$) δ 199.7 (C=O), 173.1 (*C*O$_2$CH$_3$), 148.4 (*C*=C), 127.4 (C=*C*), 117.4 (CN), 51.8, 48.0, 39.4, 31.6, 28.3, 24.5, 22.7, 16.9; IR ($CDCl_3$) 3005 (m), 2950 (m), 2880 (m), 2240 (w), 1730 (s), 1675 cm^{-1} (s); UV (EtOH) λ_{max} = 224 nm (ϵ_{max} 7000); exact mass spectrum *m/e* 235.1210, calculated for $C_{13}H_{17}NO_3$ = 235.1208.

Enone A13. To a well-stirred suspension of CrO_3 (16.0 g, 160 mmol) in CH_2Cl_2 (300 mL) under N_2 at −25 °C was added 3,5-dimethypyrazole (16.0 g, 163 mmol) in a single portion. The mixture was stirred at −25 °C for 30 min, after which A3 (4.70 g, 21.3 mmol; $[\alpha]^{25}_D$ −37.9°) was added in a single portion. The resulting mixture was stirred at −25 °C for 1 h, after which stirring was continued for 12 h as the mixture warmed to +25 °C. Aqueous sodium hydroxide solution 300 mL of 5.0 M) was then added and the mixture was stirred for 1 h at 25 °C, after which it was filtered through a cotton plug to break the thick emulsion into a separatory funnel. The lower organic layer was drawn off, washed with 10% aqueous hydrochloric acid, and set aside. The addition of $CaCl_2$ to the CH_2Cl_2HCl mixture will break up an emulsion, if present, leaving the aqueous layer beneath the methylene chloride layer. The aqueous layers (NaOH and HCl) were separately extracted with ethyl acetate; the extracts were combined and washed with 10% aqueous hydrochloric acid and then water. The organic extracts (ethyl acetate and methylene chloride) were combined, dried ($CaCl_2$), and concentrated by rotary evaporation to give a green oil. This crude product was filtered through Florisil, eluting with ethyl acetate, to give (after evaporation of solvent) a colorless oil that crystallized on trituration with ether (2.85 g, 57% yield): mp 86.5–87 °C; $[\alpha]^{25}_D$ 157.4° ($CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.96 (s, 1 H, C=CH), 3.70 (s, 3 H, CO_2CH_3), 2.60–2.80 (m, 2 H, $-CH_2-$), 2.60 (2 H, d, *J* = 6 Hz, CH_2CN), 2.20–2.40 (1 H, t, *J* = 7 Hz, O=C–CH), 2.11 (3 H, s, C=CCH_3), 1.6–2.0 (2 H, m, $-CH_2-$), 1.20 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 206.6 (C=O), 177.5 (*C*O$_2$CH$_3$), 173.6 (*C*=C), 130.6 (C=*C*), 117.0 (CN), 53.6, 51.6, 47.7, 32.0, 26.7, 21.5, 21.3, 14.3; UV (EtOH) λ_{max} 222 nm (ϵ_{max} 15 000); IR ($CHCl_3$) 1730 (s, CO_2CH_3), 1700 (s, C=O), 1630 (m, C=C), 2240 cm^{-1} (w, CN); mass spectrum *m/e* 235.1215, calculated for $C_{13}H_{17}NO_3$ = 235.1208.

Intermediates A14, A15, and A16. To a solution of A13 (2.05 g, 8.72 mmol, $[\alpha]^{25}_D$ −57.4°) in CH_3OH (125 mL) at −30 °C under N_2 was added $NaBH_4$ (1.0 g, 26 mmol) in a single portion. The mixture was allowed to warm slowly, with stirring, to +25 °C over a period of 3.5 h, after which it was concentrated by rotary evaporation. To the resulting oil were added CH_2Cl_2 and water; the mixture was extracted 4 times with methylene chloride. The extracts were combined and dried (Na_2CO_3), and the solvent was removed by rotary evaporation to give the crude alcohol A14 (2.2 g) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.55 (1 H, s, C=CH), 4.30–4.55 (1 H, m, C*H*OH), 3.75 (3 H, s,

CO_2CH_3), 1.80 (3 H, s, C=CCH_3), 1.00 (3 H, s, CH_3), 1.4–2.8 (8 H, m); IR 3200–3600 (s, OH), 2870, 2910, 2940 (m, CH), 2240 (w, CN), 1730 cm^{-1} (s, C=O).

To a mixture of *m*-chloroperbenzoic acid (2.50 g of 85%, 12 mmol), CH_2Cl_2 (100 mL), and saturated aqueous $NaHCO_3$ solution (100 mL) at 25 °C was added in a single portion the crude alcohol A14 from above in CH_2Cl_2 (10 mL). The mixture was stirred vigorously at 25 °C for 4.5 h, after which it was poured into saturated aqueous $NaCO_3$ solution. The mixture was extracted 4 times with CH_2Cl_2; the extracts were combined and dried (Na_2CO_3). A few crystals of $NaHCO_3$ were added (to retard lactonization) and solvent was removed by rotary evaporation to give the crude epoxide A15 (approximately 2 g) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 (1 H, d, J_{bc} = 7.6 Hz, C*H*OH), 3.69 (3 H, s, CO_2CH_3), 3.34 (1 H, s, H_a), 1.45 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), 1.0–2.8 (8 H, m); IR 3200–3600 (m, OH), 2880, 2950 (m, CH), 2240 (w, CN), 1735 cm^{-1} (s, C=O).

Pyridine (13 mL, 160 mmol) was added to a stirred suspension of CrO_3 (8.0 g, 80 mmol) in CH_2Cl_2 (200 mL) under N_2. The resulting solution was stirred for 30 min, and then the crude epoxide A15 from above in CH_2Cl_2 (10 mL) was added in a single portion. The mixture was stirred for 1 h at 25 °C, after which it was decanted and washed twice with 10% aqueous NaOH solution and twice with 10% aqueous HCl. The extract was dried (Na_2CO_3), filtered through a short (10 cm × 1 cm) column of Florisil (eluting first with CH_2Cl_2 and then ethyl acetate), and the solvents were removed by rotary evaporation to give a pale yellow oil. Trituration with ether gave snow white crystals of pure epoxy ketone (800 mg, 37% overall): mp 132.5–133.5 °C; $[\alpha]^{25}_D$ ($CHCl_3$) −79°; ^1H NMR (200 MHz, $CDCl_3$) 3.67 (3 H, s, CO_2CH_3), 3.24 (1 H, s, epoxide H), 2.68 (2 H, d, J = 3 Hz, CH_2CN), 2.60 (1 H, t, J = 7 Hz, O=C–C*H*–CH_2–), 2.38 (2 H, t, J = 8 Hz, $CH_2CH_2CO_2CH_3$), 1.62 (3 H, s, CH_3), 1.60 (2 H, m, –CH_2–), 1.11 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 209.2 (C=O), 173.4 (CO_2R), 117.3 (CN), 68.3, 61.3, 51.7, 51.7, 48.8, 42.6, 32.0, 23.3, 18.9, 17.9, 13.4; IR ($CHCl_3$) 2940, 2970, 3005 (m, CH), 2240 (w, CN), 1730 cm^{-1} (very s, C=O + O=COR); mass spectrum m/e 251.1164, calculated for $C_{13}H_{17}NO_4$ = 251.1158.

Alkyne A18. A solution of epoxy ketone A16 (971 mg, 3.87 mmol, $[\alpha]^{25}_D$ −79.0°) in deuteriochloroform (5 mL) was added to a solution of freshly prepared phenylaziridine acetic acid salt (800 mg, 4.12 mmol) in $CDCl_3$ (10 mL) and the mixture was stirred at 25 °C for 1.5 h. The progress of the reaction was conveniently monitored by ^1H NMR spectroscopy, after which it was dried ($MgSO_4$) and filtered into a 50-mL round-bottomed flask containing glass helixes (ca. 5 mL). The solution was concentrated by rotary evaporation and the resulting oil (A17) was distilled bulb to bulb (kugelrohr) at 1.0 torr in an oven preheated to 200–250 °C. The distillate (1.25 g) was purified by medium-pressure liquid chromatography (eluting with 3:1 cyclohexane–ethane acetate) to give 450 mg (50%) of alkyne A18. The analytical sample was obtained from this as a colorless oil by preparative VPC (10 ft × $^3/_8$ in. 10% Carbowax column at 225 °C and 250 mL/min; R_t = 10 min): $[\alpha]^{25}_D$ ($CHCl_3$) −19.1°; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.68 (3 H, s, CO_2CH_3), 2.4–3.1 (6 H, m), 2.28 (3 H, s, O=CCH_3), 1.53 (3 H, s, CH_3), 1.3–1.7 (2 H, m); ^{13}C NMR (C_6D_6) δ 206.6 (C=O), 172.6 (CO_2CH_3), 117.7 (CN), 81.3 (*C*≡C), 74.0 (C≡*C*), 52.3, 51.1, 38.2, 31.2, 25.1, 24.9, 21.5, 21.3; IR ($CHCl_3$) 3300 (s, H–C≡C), 2950 (C–H), 2240 (w, CN), 1730 (s, C=O, ester), 1710 cm^{-1} (s, C=O, ketone); exact mass spectrum m/e 220, calculated for $C_{13}H_{17}NO_3$ M^+ = 235, $M^+ - CH_3$ = 220.

Alkene A19. To a 25-mL three-neck round-bottomed flask were added Lindlar's catalyst (150 mg) and benzene (20 mL); the flask was then fitted with two rubber septa and a balloon. Hydrogen gas was introduced via syringe needle until the balloon was fully expanded. The gas was then released (to purge air) via a second syringe needle. The balloon was then expanded and filled again by introduction of hydrogen as before. Quinoline (100 mg) and the acetylene A18 (435 mg, 1.85 mmol; $[\alpha]^{25}_D$ −19.1°) were introduced via syringe and the mixture was stirred vigorously for 48 h. (Hydrogen was introduced periodically to keep the balloon fully expanded). The reaction mixture was then filtered, washed with 20% HCl, dried (Na_2CO_3), and concentrated by rotary evaporation to give essentially pure keto olefin (350 mg, 80% yield). The analytical sample was obtained from this by column chromatography on silica gel (cyclohexane to ethyl acetate solvent polarity gradient): $[\alpha]^{25}_D$ ($CHCl_3$) +32.4°; ^1H NMR (200 MHz, $CDCl_3$) δ 5.1–5.6 (3 H, m, vinyl H), 3.66 (3 H, s, CO_2CH_3), 2.24 (3 H, s, acetyl H), 1.4–2.8 (7 H, m, –CH_2–), 1.38 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 209.2 (ketone C=O), 173.3 (ester C=O), 134.6 (*C*=C), 121.2 (C=*C*), 118.2 CN), 52.6, 51.6, 49.7, 31.4, 25.8, 24.1, 22.1, 21.1; IR ($CHCl_3$) 2940 (C–H), 2240 (CN), 1730 (ester C=O), 1700 cm^{-1} (ketone C=O); mass spectrum m/e 237; exact mass = 206.1190, calculated for $C_{12}H_{16}NO_2$ ($M^+ - OCH_3$) = 206.1181.

Ketal A20. To a solution of A19 (174 mg, 0.73 mmol; $[\alpha]^{25}_D$ +32.4°) in ethylene glycol (3.5 mL) were added trimethyl orthoformate (0.5 mL) and *p*-toluenesulfonic acid (one crystal). The mixture was stirred under nitrogen at 25 °C for 2 days and then at 50 °C for 2 additional days, after which solid sodium methoxide (150 mg) was added and the volatiles were removed by short path distillation (80 °C/0.1 torr) to leave a brown residue. The residue was dissolved in CH_3OH (4.0 mL). Sodium methoxide (150 mg) was added and the mixture was stirred at 25 °C for 18 h, after which it was poured into saturated aqueous sodium bicarbonate solution and extracted 5 times with CH_2Cl_2. The combined extract was dried (Na_2CO_3) and concentrated by rotary evaporation to give the crude ketal as a pale yellow liquid (135 mg, 66%). An analytical sample was obtained by preparative GC (10 ft × $^1/_4$ in. 10% SE-30 column at 210 °C and 200 mL/ min helium flow; retention time 6 min): optical rotations $[\alpha]^{25}_D$ ($CHCl_3$) +3.7°, $[\alpha]^{25}_{578}$ +4.2°, $[\alpha]^{25}_{546}$ +5.0°, $[\alpha]^{25}_{435}$ +11.5°, and $[\alpha]^{25}_{365}$ +22.6°; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.0–5.8 (3 H, m, vinyl H), 3.96–4.02 (4 H, m, OCH_2CH_2O), 3.66 (3 H, s, OCH_3), 1.4–2.6 (7 H, m), 1.31 (3 H, s, CH_3), 1.18 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.0 (C=O), 137.3 (*C*=C), 119.5 (CN), 118.8 (C=*C*), 112.8 (OCO), 65.0, 63.6, 51.5, 49.9, 46.3, 32.4, 24.2, 21.1, 20.8, 19.6; IR ($CHCl_3$) 2980 (m, C–H), 2940 (m, C–H), 2880 (m, C–H), 2240 (w, CN), 1730 (s, C=O), 1720 cm^{-1} (shoulder, C=O); mass spectrum m/e 266 (M^+ − 15); exact mass = 266.1388, calculated for $C_{14}H_{20}NO_4$ ($M^+ - CH_3$) = 266.1392.

Aldehyde A21. A solution of ketal A20 (20 mg, 0.07 mmol) in CH_3OH (4.0 mL) was cooled to −30 °C and a streamn of ozone was passed through for 10 min. The solution was flushed by passing oxygen through for 10 min, then soid potassium iodide (100 mg) was added, and the solution was stirred for 1 h as it warmed to 25 °C. Volatiles were removed by rotary evaporation and the residue was dissolved in a mixture of methylene chloride and an aqueous solution of sodium thiosulfate and sodium carbonate. The mixture was extracted 4 times with methylene chloride and dried (Na_2CO_3), and the solvents were removed by rotary evaporation to give the pure aldehyde (15 mg, 75% yield), which was homogeneous by VPC and TLC: $[\alpha]^{25}_D$ ($CHCl_3$) +14°; $[\alpha]^{25}_{578}$ = +16°; $[\alpha]^{25}_{435}$ = +39°; ^1H NMR (200 MHz, $CDCl_3$) δ 9.50 (1 H, d, J = 4.6 Hz, collapses to a singlet upon double irratiation of the region around 2.6 ppm, CHO), 3.7–4.0 (4 H, m, OCH_2CH_2O), 3.68 (3 H, s, CO_2CH_3), 1.6–2.8 (7 H, m), 1.35 (3 H, s, CH_3), 1.30 (3 H, s, CH_3); IR ($CHCl_3$) 3010 (m), 2980 (m), 2950 (m), 2880 (m), 2840 (w), 2240 (w), 1700–1730 cm^{-1} (s); exact mass spectrum m/e = 268.1174 (M^+ − 15), calculated for $C_{13}H_{18}NO_5$ ($M^+ - CH_3$) = 268.1184; ^{13}C NMR ($CDCl_3$) δ 199.0 (CHO), 173.2 (CO_2CH_3), 117.9 (CN), 112.1 (OCO).

Aldehyde B2. To a solution of ester A8 (1.60 g, 7.24 mmol) in toluene (25 mL) at reflux under N_2 was added SeO_2 (1.60 g, 14.4 mmol) in small portions over 60 min. When the addition was complete, the mixture was heated at reflux for 1 h more, after which it was cooled to 25 °C and filtered. The resulting deep red solution was cooled to 0 °C and *m*-chloroperbenzoic acid (80–90%) was added with stirring until the color no longer faded (1.7 g). The solution was stirred an additional 5 min at 0 °C and was then poured into aqueous K_2CO_3 soution. The mixture was extracted twice with toluene, and the organic layers were combined and washed with potassium carbonate solution, dried ($MgSO_4$), and concentrated by rotary evaporation to give a yellow liquid (1.11 g, 65%). Medium-pressure liquid chromatography (silica gel, 1:1 ethyl acetate–cyclohexane) gave the pure aldehyde (980 mg, 58%) as a colorless liquid: $[\alpha]^{25}_D$ ($CHCl_3$) −30.1°; UV (EtOH) λ_{max} 233 nm (ϵ 9150); ^1H NMR (200 MHz, $CDCl_3$) δ 8.86 (1 H, s, CHO), 6.90 (1 H, m, CH=C), 3.71 (3 H, s, OCH_3), 3.11 (1 H, d, J = 17 Hz, C*H*HCN), 2.60 (1 H, d, J = 17 Hz, CH*H*CN), 1.50–2.90 (7 H, m), 1.10 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 189.3 (CHO), 173.4 (CO_2CH_3), 15.3, 15.0,1 118.1 (CN), 51.8, 47.8, 46.9, 36.8, 32.7, 26.4, 24.3, 18.8; IR ($CHCl_3$) 3010 (m), 2965 (m), 2945 (m), 2880 (w), 2820 (m), 2730 (w), 2240 (w), 1730 (s), 1670 (s), 1610 cm^{-1} (m); mass spectrum m/e 235.1203, calculated for $C_{13}H_{17}NO_3$ = 235.1208.

Alcohol B3. To a solution of $NaBH_4$ (75 mg, 1.97 mmol) in CH_3OH (10 mL, distilled from Mg before use) under N_2 at −20 °C was added aldehyde B2 (419 mg, 1.78 mmol) in CH_3OH (4 mL) over 5 min. When the addition was complete, the solution was stirred at −20 °C for 10 min and was then poured into brine. The mixture was extracted once with ether and twice with CH_2Cl_2; the organic extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give chromatographically pure alcohol (366 mg, 87%) as a colorless liquid: $[\alpha]^{25}_D$ −53.9° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.75 (1 H, m, CH=C), 4.25 (2 H, br s, CH_2OH), 3.70 (3 H, s, OCH_3), 1.20–2.70 (9 H, m), 1.05 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.8 (CO_2CH_3), 147.6 (*C*=C), 127.8 (C=*C*), 118.6 (CN), 59.6 (CH_2OH), 51.7, 48.8, 47.4, 35.2, 32.8, 27.6, 24.8, 19.2; IR ($CHCl_3$) 3590 (m), 3480 (m), 3000 (m), 2940 (m), 2860 (m), 2840 (w), 2240 (w), 1720 cm^{-1} (s); mass spectrum m/e 237.1359, calculated for $C_{13}H_{19}NO_3$ = 237.1365.

Epoxide B4. To a solution of alcohol B3 (1.163 g, 4.91 mmol) in CH_2Cl_2 (20 mL) at −20 °C was added solid *m*-chloroperoxybenzoic acid (1.375 g, 85%, 6.80 mmol) over 5 min. The solution was stirred for 2

h as it was warmed slowly to 0 °C; it was then poured into saturated aqueous K_2CO_3 solution. The mixture was extracted 3 times with methylene chloride; the extracts were then combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give a colorless liquid (1.128 g, 91%). Crystallization from 1:1 cyclohexane–ether afforded 964 mg (78%) of a white crystalline material that was normally used in the next step of the synthesis. The analytical sample was obtained by a second crystallization; it had mp 74–75 °C; $[\alpha]^{25}_D$ ($CHCl_3$) −20.0°; ^1H NMR (200 MHz, $CDCl_3$) δ 4.19 (1 H, d, J = 13 Hz, CH_2OH), 3.78 (1 H, d, J = 13 Hz, CH_2OH), 3.68 (3 H, s, OCH_3), 3.50 (1 H, s), 2.60 (1 H, s, CH_2CN), 2.54 (1 H, s, CH_2CN), 1.2–2.3 (7 H, m), 1.07 (3 H, s, CH_3); ^{13}C NMR (C_6H_6) δ 173.3 (CO_2Me), 118.6 (CN), 70.7, 59.6, 59.5, 51.3, 43.0, 42.1, 32.7, 31.6, 24.7, 24.5, 16.1; IR ($CHCl_3$) 3300–3700 (br), 3000 (m), 2940 (m), 2860 (w), 2240 (w), 1725 cm^{-1} (s); mass spectrum m/e 253 (small), m/e 222.1125, calculated for $C_{12}H_{16}NO_3$ (M − OCH_3) = 222.1130.

Intermediates B5, B6, and B7. To a solution of epoxide B4 (420 mg, 1.66 mmol) in *N,N*-dimethylformamide (10 mL) under N_2 was added selenophenol (3 mL) and diisopropylethylamine (10 drops) with stirring. The mixture was warmed to 70 °C and was stirred at that temperature for 1 h, after which it was poured into water (ca. 50 mL). The aqueous solution was washed twice with petroleum ether and the petroleum ether layers were discarded. Sodium chloride was then added to the aqueous layer and it was extracted 3 times with ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give 824 mg of crude selenide B5 as a yellow oil. Preparative layer chromatography of a sample of crude selenide (Merck precoated plates of silica gel 60F-254, 0.25-mm layer, catalog no. 5765, elution with 1:1 cyclohexane–ethyl acetate) gave the pure selenide in 51% yield (R_f = 0.5): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55 (m, 2 H, aromatic), 7.30 (m, 3 H, aromatic H), 3.66 (s, 3 H, OCH_3), 3.3–4.2 (m, 3 H, CH_2OH + CHSe), 1.3–2.8 (m, 9 H, CH_2), 1.02 (s, 3 H, CH_3); IR ($CHCl_3$) 3520 (br m, OH), 2950 (m), 2240 (w, C≡N), 1725 (C=O); ^{13}C NMR ($CDCl_3$) δ 173.5 (C=O), 133.3 (aromatic), 129.9 (aromatic), 129.5 (aromatic), 127.9 (aromatic), 119.1 (C≡N), 85.0, 64.4, 51.7, 50.0, 47.6, 45.7, 38.6, 32.7, 24.8, 23.5, 15.0; mass spectrum m/e 411.0939, calculated for $C_{19}H_{25}NO_4Se$ = 411.0949.

The crude selenide (824 mg) was dissolved in CH_2Cl_2 (20 mL) and t-BuO_2H was added over ca. 30 s (5.0 mL of 70% solution). The resulting mixture was stirred at 25 °C for 1 h and was then poured into water and extracted 3 times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation to give 783 mg of crude B6 as a brown gum. A sample of B6 was obtained in 86% yield from reaction of pure selenide B5 with t-BuO_2H as described above. After PLC as described above (R_f = 0.2), the sample had a ^1H NMR spectrum as follows (200 MHz, $CDCl_3$): δ 5.92 (1 H, dd, J = 6, 1.7 Hz, vinyl H), 5.85 (1 H, dd, J = 6, ~1 Hz, vinyl H), 3.80 (1 H, d, J = 11 Hz, CH_2OH), 3.60 (1 H, d, J = 11 Hz, CH_2OH), 3.70 (3 H, s, OCH_3), 1.3–2.9 (9 H, m), 1.07 (3 H, s, CH_3). IR ($CHCl_3$) 3300–3600 (br), 3000 (m), 2940 (m), 2860 (w), 2240 (w), 1725 cm^{-1} (s).

To the crude diol B6 (783 mg) in THF (20 mL) was added $NaIO_4$ (4.5 g) in water (30 mL). The resulting mixture was stirred at 25 °C for 90 min, after which it was poured into water (150 mL) and extracted 3 times with CH_2Cl_2. The combined extract was dried ($MgSO_4$) and concentrated to give a yellow oil (226 mg). Preparative medium-pressure liquid chromatography (70:30 cyclohexane–ethyl acetate) gave 96 mg (26% overall) of chromatographically pure enone B7 as a colorless liquid: $[\alpha]^{25}_D$ ($CHCl_3$) −95.3°; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.66 (1 H, dd, J = 1.7, 5.9 Hz, CH=CH–C=O), 6.25 (1 H, dd, J = 1.9, 5.9 Hz, CH=CHj=C=O), 3.73 (3 H, s, OCH_3), 2.90 (1 H, m, O=C–C=C–CH), 2.30–2.65 (4 H, m, CH_2CN + C$H_2CO_2CH_3$), 2.10 (1 H, m, CH_2), 1.75 (1 H, m, CH_2), 1.17 (3 H, s, CH_3); IR (neat film) 3010 (w), 2940 (m), 2865 (w), 2240 (w), 1730 (s), 1705 cm^{-1} (s); ^{13}C NMR ($CDCl_3$) δ 209.4 (ketone C=O), 173.0 (ester C=O), 164.5 (C=C), 131.2 (C=C), 117.2 (CN), 51.9, 49.5, 47.6, 32.0, 26.0, 24.5, 19.2; UV (EtOH) λ_{max} 222 nm (ε 8800); mass spectrum m/e 221.1056, calculated for $C_{12}H_{15}NO_3$ = 221.1052.

Epoxide B1: Procedure A. A solution of K_2CO_3 (25 mg) in water (1 mL) was diluted with CH_3OH (25 mL) and t-BuO_2H (3 mL of 70% aqueous solution). The cyclopentenone **B7** (700 mg, 3.17 mmol) in CH_3OH (3 mL) was then added in a single portion at 25 °C. The mixture was stirred for 1 h, after whieh it was poured into water (250 mL) and extracted (4 × 50 mL) with CH_2Cl_2. The combined extract was washed with water, dried ($MgSO_4$), and concentrated by rotary evaporation at 25 °C to leave 850 mg of crude B1, which was contaminated with traces of t-BuOH and/or t-BuO_2H. Crystallization from 1:1 methanol–ether gave 377 mg (50%) of a single epoxy ketone: mp 54.5–55.0 °C; $[\alpha]^{25}_D$ ($CHCl_3$) +11.2°; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.82 (1 H, d, J = 2.0 Hz, α-epoxide H), 3.73 (3 H, s, CO_2CH_3), 3.52 (1 H, d, J = 2.0 Hz, β-epoxide H), 1.4–2.8 (7 H, m, $-CH_2-$), 1.19 (3 H, s, CH_3); IR ($CHCl_3$) 3010 (m), 2945 (m), 2240 (w), 1750 (s), 1730 cm^{-1} (s); ^{13}C NMR ($CDCl_3$) 208.0 (C=O), 172.7 (CO_2CH_3), 116.8 (CN), 59.2, 55.4, 52.0, 45.8, 43.1, 31.9, 29.9, 23.3, 18.1; mass spectrum m/e 222.0766, calculated for $C_{11}H_{12}NO_4$ (M − 15) = 222.1766. Examination of the mother liquors by ^1H NMR spectroscopy and VPC showed a mixture of remaining epoxy ketone and three minor components that could not be characterized.

Epoxide B1: Procedure B. To the crude diol B6 (derived from 380 mg = 1.50 mmol of epoxide B4 as described above) in benzene (10 mL) was added t-BuO_2H (3 mL of 70% aqueous solution). The mixture was cooled in an ice bath, and $VO(AcAc)_2$ (340 mg, 1.3 mmol) was added in a single portion; the solution quickly turned deep red. The mixture was stirred for 2 h as it warmed to 25 °C, leading to a brown solution and a brown precipitate. The mixture was filtered and concentrated by rotary evaporation to leave a brown gum that was dissolved in CH_3OH (10 mL) and pH 8 buffer (10 mL). Sodium metaperiodate (1.5 g) was added and the mixture was stirred at 25 °C for 1 h, after which it was poured into aqueous sodium bicarbonate solution and extracted with CH_2Cl_2. The extract was concentrated by rotary evaporation and distilled (150 °C, 0.1 torr) to give 54 mg of a yellow oil. Preparative layer chromatography (silica gel, 1:1 ethyl acetate–cyclohexane) led to 20 mg (5% overall) of nearly pure epoxy ketone. For characterization, this material was chromatographed again, leading to 5.0 mg of pure epoxy ketone, which was identical with that prepared by the above procedure.

Keto Ester D4. To 228 g (5.56 mmol) of KH (previously freed of the oil) in a 5-L round-bottomed flask was added 3 lb of absolute ether under Ar. With efficient mechanical stirring 750 g (5.68 mmol) of freshly distilled dimethylmalonate in 1 lb of absolute ether was *slowly* added by using a pump (takes about 2 h). The suspension was reflxed for another 2 h, then about 2 L of ether was distilled off and 1 L of dry DMF added, and then the temperature was raised to remove the rest of the ether. Another 3 L of DMF was added and 165 g (0.593 mol) of 9-iodo-9-methylcamphor (D3) introduced. The temperature was set to 120 °C and stirring continued for 40 h, then 50 g (0.3 mol) of dry KI was added, and the temperature was *carefully* raised to 140 °C to effect complete decarbomethoxylation. After a total of 64 h the suspension was cooled in ice and 70 mL of water added. By use of a high-vacuum rotavap (VRE), most of the DMF and dimethyl malonate were distilled off at room temperature. The brownish residue was taken up in 3 L of water and with vigorous stirring carefully (*foaming*!) acidified to pH 3 by using concentrated HCl. The suspension obtained was continuously extracted with petroleum ether (20–40) for 2 days. The extract was once washed with brine and dried with Na_2SO_4 and evaporated (VRE) to yield a dark brown oil that was taken up in a small amount of petroleum ether (30–60) and filtered through a column containing 250 g of basic alumina. After evaporation of the solvent 115.4 g of a light yellow oil was obtained. Distillation under high vacuum delivered 101.0 g (76%) of almost colorless ester: bp 90–92 °C/0.003 mm; IR (film on KBr) 2958, 2880, 1738, 1445, 1432, 1300, 1192, 1172, 1041, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, ester CH_3), 2.41–2.17 (m, 4 H), 1.92–1.71 (m, 4 H), 1.55–1.32 (m, 3 H) 0.94 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3); ^{13}C NMR MeSO-d_6) δ 217.30 (s, C-2), 173.66 (s, C-11), 57.89 (s, C-1), 51.28 (q, C-13); 48.52 (s, C-7), 42.18 (t, C-3), 39.36 (d, C-4), 29.26 (t), 28.23 (t), 26.65 (t), 26.08 (t, C-5, C-6, C-9, C-10), 16.13 (q, C-8), 9.25 (q, C-13); specific rotations ($CHCl_3$, c 1) $[\alpha]^{25}_D$ +69.2°, $[\alpha]^{25}_{578}$ +72.3°, $[\alpha]^{25}_{546}$ +85.8°, $[\alpha]^{25}_{436}$ +184.7°.

Oxime D5. A total of 100 g (0.45 mmol) of keto ester D4 and 200 g (2.88 mol) of NH_2OH·HCl (recrystallized from EtOH) in 700 mL of dry pyridine was stirred at room temperature for 24 h. Most of the pyridine was evaporated at 45 °C (VRE). The residue was diluted with 750 mL of water and acidified to pH 1 with concentrated HCl (ca. 125 mL) and extracted with ether 4 times. The extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness (VRE). Residual solvent was pulled off at the high-vacuum pump whereupon crystallization started. After recrystallization from ether 72.0 g of colorless prisms, mp 90.3–90.6 (corrected), were obtained: yield 67%; IR (KBr pellet) 3438 (OH), 2950, 2938, 1720 (C=O), 1679 (C=N), 1436, 1401, 1389, 1381, 1330, 1312, 1298, 1196, 1177, 995, 921 (N–O), 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (br, 1 H, OH), 4.73 (s, 3 H, OCH_3), 2.60–1.14 (complex, 11 H, scaffold), 1.09 (s, 3 H, CH_3), 0.81 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.42 (s, C-11), 169.39 (s, C-2), 52.82 (s, C-1), 51.64 (q, C-12), 50.61 (s, C-7), 40.76 (d, C-4), 32.78 (t, C-3), 32.57 (t), 29.75 (t), 27.14 (t), 26.93 (t, C-5, C-6, C-9, C-10), 16.16 (q, C-8), 11.10 (q, C-13); specific rotations ($CHCl_3$, c 1) $[\alpha]^{24.2}_D$ −18.5°, $[\alpha]^{24.2}_{578}$ −20.0°, $[\alpha]^{24.2}_{546}$ −22.1°, $[\alpha]^{24.2}_{436}$ −39.3°.

Cyano Ester D6. In a *250-mL* flask 36.0 g (0.163 mol) of oxime D5 was disperged in 36 mL of dry CH_2Cl_2 and under ice cooling and with stirring 36 mL (0.255 mol) of freshly distilled trifluoroacetic anhydride syringed in *slowly*. After 4 h 36 mL (0.150 mol) of freshly distilled trifluoroacetic acid was added at room temperature and stirring contin-

ued for at least 24 h. All volatiles were evaporated (VRE) in vacuo at 45 °C, the residual oil was taken up in ether (150 mL) and extracted with brine (3 × 25 mL) and saturated K_2HCO_3 (5 × 25 mL), the aqueous layer was once extracted with ether, and the combined extracts were dried (Na_2SO_4) and partially decolorized by shaking with Florisil (15 g). Evaporation of the ether (VRE) yielded a yellowish crude oil that was distilled under reduced pressure at an oil bath temperature no higher than 135 °C to give 25.2 g (76%) of a colorless liquid: bp 88–90 °C/0.002 torr; IR film on KBr) 3034 (C=C–H), 2950, 2930, 2865, 2842, 2239 (C≡N), 1730 (C=O), 1648 (br, C=C), 1433, 1374, 1292, 1200, 1164; ^{1}H NMR ($CDCl_3$) δ 5.35–5.34 (m, 1 H, vinyl H), 3.68 (s, 3 H, ester CH_3), 2.44–2.08 (m, 7 H, CH and CH_2), 1.79–1.71 (m, 2 H, CH_2), 1.60–1.57 (m, 3 H, allylic CH_3), 0.89 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.95 (s, C-11), 145.20 (s, C-1), 123.24 (d, C-6), 119.50 (s, C-2), 51.59 (q, C-12), 50.17 (s, C-7), 40.97 (d, C-4), 35.86 (t, C-5), 32.16 (t, C-9), 29.61 (t, C-10), 19.14 (q, C-8), 18.46 (t, C-3), 12.63 (q, C-13); specific rotations ($CHCl_3$, *c* 1) $[\alpha]^{24}_{589}$ +36.2°, $[\alpha]^{24}_{578}$ +37.6°, $[\alpha]^{24}_{546}$ +42.7°, $[\alpha]^{24}_{436}$ +74.1°.

Aldehyde D7. To 1.0 g (4.52 mmol) of cyano ester D6 in 15 mL of *t*-BuOH at reflux were added four 150-mg portions of SeO_2 (5.41 mmol) over a period of 4 h. Reaction was monitored on GC (OV-101, 200 °C). The selenium precipitated was centrifuged off, the solvent was evaporated in vacuo, and 20 mL of benzene was added and centrifuged again. The benzene layer was extracted with H_2O_2 (30% 3 × 5 mL) and evaporated after drying (Na_2SO_4) to yield a dark oil, which was kugelrohr-distilled (0.003 mm, 135–145 °C); yield 580 mg of a yellow oil (55%); IR (film on KBr) 2955, 2242 (C≡N), 1735 (ester C=O), 1676 (aldehyde C=O), 1437, 1380, 1320, 1302, 1204, 1172, 986 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, CHO), 6.83–6.82 (m, 1 H, HC=C), 3.66 (s, 3 H, $COOCH_3$), 2.95–2.83 (m, 1 H, C*H*CH_2CN), 2.54–2.06 (complex, 6 H, 3CH_2), 1.98–1.79 (m, 2 H, CH–CH_2CN), 1.10 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 189.40 (d, C-13), 173.66 (s, C-11), 152.10 (d, C-6), 151.19 (s, C-1), 118.90 (s, C-2), 51.64 (q, C-12), 48.91 (s, C-7), 42.00 (d, C-4), 36.72 (t, C-5), 31.63 (t, C-9), 29.90 (t, C-10), 19.41 (q, C-8), 17.59 (t, C-3); UV (EtOH) λ_{max} 234 mm (ε 9764); mass spectrum *m/e* 235.1216, calculated for $C_{13}H_{17}NO_3$ = 235.1208.

Allylic Alcohol D8. To a solution of 2.0 g (8.51 mmol) of aldehyde D7 in 35 mL of dry CH_3OH was added at −30 °C 450 mg (11.89 mmol) of $NaBH_4$ under Ar. GC monitoring (OV-101, 200 °C) revealed completion of reaction within 45 min, whereupon the mixture was poured on 50 mL of brine in a sepoaratory funnel. Any precipitate formed was dissolved in additional water. Extraction was effected with ether (2 × 25 mL) and CH_2Cl_2 (3 × 30 mL). Any water separating upon combining of the organic layers was removed and the latter dried (Na_2SO_4) and evaporated to give 2.10 g of yellowish oil, which was kugelrohr-distilled to yield 1.85 (92%) of an almost colorless material: bp 155 °C/0.003 mm; IR (film on KBr) 3470 (br), 2952, 2929, 2864, 2249, 1735, 1439, 1381, 1300 (br), 1204, 1173, 1024, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.69 (m, 1 H, CH=C), 4.15–4.12 (m, 2 H, CH_2OH), 3.68 (s, 3 H, $COOCH_3$), 2.75–1.78 (m, 9 H, 4 CH_2, CH), 1.63 (s, 1 H, OH, exchangeable with D_2O), 1.00 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.30 (s, C-11), 149.01 (s, C-1), 124.63 (d, C-6), 119.48 (s, C-2), 59.16 (t, C-13), 51.79 (q, C-12), 49.70 (s, C-7), 41.76 (d, C-4), 35.87 (t, C-5), 32.72 (t, C-9), 29.75 (t, C-10), 19.80 (q, C-8), 18.32 (t, C-3); mass spectrum *m/e* 219.1270, calculated for $M^+ - H_2O$, i.e., $C_{13}H_{17}NO_2$ = 219.1259; specific rotations ($CHCl_3$, *c* 1) $[\alpha]^{24}_{589}$ +42.3°, $[\alpha]^{24}_{578}$ +44.9°, $[\alpha]^{24}_{546}$ 51.0°, $[\alpha]^{24}_{436}$ +87.6°.

Epoxide D10a. To 1.2 g (5.06 mmol) of alcohol D8 in 15 mL of CH_2Cl_2 at −20 °C 1.2 g (6.1 mmol) of 85% MCPBA was added in portions over 5 min. Stirring was continued for 3 h and the solution allowed to warm to room temperature. *m*-Chlorobenzoic acid was centrifuged off and the oranic layer thoroughly extracted with saturated K_2CO_3. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated (VRE) to yield an almost colorless oil, which was submitted to liquid chromatography using the solvent sequence 100% cyclohexane → 5% ethyl acetate–95% cyclohexane, providing 600 mg (47%) of colorless *oil*: IR (film on KBr) 3480 (br), 2950, 2880, 2246, 1735, 1440, 1390, 1311, 1200 (epoxide), 1175, 1023, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.05 (d, *J* = 12.5, 1 H, C*H*–OH), 3.77 (d, *J* = 12.5, 1 H, C*H*OH), 3.69 (s, 3 H, $COOCH_3$), 3.43 (s, 1 H, epoxide H), 3.58–2.44 (complex, 9 H, 4 CH_2, CH), 1.82 (br), 1 H, OH, exchangeable with D_2O), 0.91 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.30 (s, C-11), 118.84 (s, C-2), 70.65 (s, C-1), 58.65 (t, C-13), 57.46 (d, C-6), 51.76 (q, C-12), 43.21 (s, C-7), 36.1 (d, C-4), 31.42 (t, C-5); 30.14 (t, C-9), 29.17 (t, C-10), 17.83 (q, C-8), 16.71 (s, C-3); mass spectrum *m/e* 235.1200, calculated for $M^+ - H_2O$, i.e., $C_{13}H_{17}NO_3$ = 235.1208; specific rotations ($CHCl_3$, *C* 1) $[\alpha]^{24}_{589}$ +9.7°, $[\alpha]^{24}_{578}$ +10.0°, $[\alpha]^{24}_{546}$ +11.1°, $[\alpha]^{24}_{436}$ +20.0°. The epoxide obtained in this manner consisted of both isomers, as can easily be seen from the ^{13}C NMR data.

Epoxide D10b. To 26.70 g (120.65 mmol) of cyano ester D6 in 270 mL of acetic anhydride and 200 mL of glacial acetic acid 16.0 g (144 mmol) of SeO_2 was added by means of a Soxhlet. At an oil bath temperature of 140–143 °C the reaction was carried out for 20 h (montiroing by GC). All volatiles were evaporated in vacuo and residual acetic acid and anhydride azeotroped out with undried toluene (3 × 100 mL). The black and oily residue was taken up in 100 mL of CH_2Cl_2 and cooled in ice whereupon 35.5 g (306 mmol) of MCPBa (85%) was added portionwise over a period of 1 h. The *m*-chlorobenzoic acid precipitated was filtered off and the filtrate extracted with saturated $KHCO_3$ (4 × 40 mL) and once with saturated K_2CO_3 (40 mL). The black aqueous layer was discarded after one back-extraction with 100 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and then passed through a Florisil column (5-cm diameter, 6-cm layer height) in order to decolorize. All solvent was evaporated (VRE) and 150 mL of anhydrous ether added to the remaining dark yellow oil. Upon seeding crystallization set in rapidly and was completed by cooling to −20 °C for 2 days. A total of 15.2 g (48%) of light yellow crystals was obtained. The mother liquor still contained a considerable amount of the product, especially the other isomer. However, it could be only obtained by purification using liquid chromatography. recrystallization from ether gave colorless material that melted at 84–86 °C (cor): IR (KBr pellet) 2960, 2241 (C≡N), 1735, 1725 (C=O), 1458, 1433, 1375, 1265, 1248 (epoxide), 1200, 1180, 1161, 1034, 888 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.64 (d, 1 H, *J* = 12 Hz, C*H*–OH_2), 4.10 (d, 1 H, *J* = 12 Hz, C*H*–OH_2), 3.68 (s, 3 H, OCH_3), 3.35 (s, 1 H, epoxy H); 2.65–1.5 (complex, 9 H, CH and GH_2), 2.09 (s, 3 H, $OCCH_3$), 0.94 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.06 (s) (C-11), 170.42 (s, C-14), 118.72 (s, C-2), 67.47 (s, C-1), 61.68 (t, C-13), 57.46 (d, C-6), 51.64 (q, C-12), 43.76 (s, C-7), 35.57 (d, C-4), 31.36 (t, C-9), 30.57 (t, C-S), 29.20 (t, C-10), 20.65 (q, C-15), 18.32 (q, C-8), 16.62 (t, C-3); mass spectrum *m/e* 264.1231, calculated for $M^+ - OCH_3$, i.e., $C_{14}H_{18}NO_4$ = 264.1236; specific rotations ($CHCl_3$, *c* 1) $[\alpha]^{23}_{589}$ +21.5°, $[\alpha]^{23}_{578}$ +22.1°, $[\alpha]^{23}_{546}$ +25.4°, $[\alpha]^{23}_{436}$ +45.1°.

Selenide D11. To 1.0 g (3.79 mmol) of epoxyacetate D10b in 15 mL of DMF were added under Ar 5.0 mL of selenophenol and 150 μL of diisopropylethylamine. This mixture was heated to 70 °C (oil bath temperature) for 7 h after which TLC (SiO_2, ethyl acetate–cyclohexane, 1:1 R_f of product = 0.36) indicated completion of reaction. By use of a freeze-dryer all the volatiles were distilled off (water bath ~60 °C) to yield a yellow semicrystalline mass to which 30 mL of anhydrous ether was added. The precipitate formed was filtered off and washed with ether until all of the yellow color was in the filtrate. The latter was evaporated (VRE) to yield a honey-like oil that was chromatographed (LC: column 8-mm inner diameter and 100-cm length) and yielded 950 mg (55%) of a colorless oil that crystallized upon scratching. The crystals melted at 88–91 °C (cor): IR (KBr pellet) 3460, 2950, 2241, 1735, 1720, 1569, 1575, 1475, 1450, 1435, 1425, 1390, 1375, 1351, 1330, 1301, 1277, 1260, 1236, 1208, 1174, 1050, 1019, 998, 930, 909, 870, 741, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55–7.51 (m, 2 H, aryl), 7.29–7.26 (m, 3 H, aryl), 4.54 (d, 1 H, *J* = 11.6 Hz, CHOAc), 4.20 (d, 1 H, *J* = 11.6 Hz, CHOAc), 3.67 (s, 3 H, $COOCH_3$), 3.61 (t, 1 H, *J* = 7.8 Hz, CHSe), 2.96–1.60 (complex, 9 H, 4CH_2, CH), 1.80 (s, 3 H, CH_3COO), 1.26 (s, 1 H, OH exchangeable with D_2O), 0.89 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.36 (s, C-11), 170.75 (s, C-14), 133.33 (d, C-17, C-17a), 130.94 (s, C-16), 129.30 (d, C-18, C-18a), 127.60 (d, C-19), 118.96 (s, C-2), 85.18 (s, C-1), 67.38 (t, C-13), 51.76 (q, C-12), 50.19 (d, C-6), 48.55 (s, C-7), 41.85 (d, C-4), 38.60 (t, C-5), 30.60 (t), 30.05 (t, C-9, C-10), 20.62 (q, C-15), 17.86 (t, C-2), 15.80 (q, C-8); UV spectrum λ_{max}^1 271 nm (ε 2949), λ_{max}^2 241 nm (ε 3619); mass spectrum *m/e* 453.1042, calculated for $C_{21}H_{27}NO_5Se$ = 453.1055; specific rotations ($CHCl_3$, *c* 1) $[\alpha]^{25}_{589}$ +34.4°, $[\alpha]^{25}_{578}$ +35.7°, $[\alpha]^{25}_{456}$ +41.8°, $[\alpha]^{25}_{436}$ +84.2°.

Allylic Alcohol D12. A solution of 3.40 g (11.4 mmol) of epoxide D10b in 50 mL of ethanol containing 4 mL of benzeneselenol and 150 μL of triethylamine was heated at reflux for 3 days under a nitrogen atmosphere. A stream of air was passed through the vessel to evaporate most of the methanol and to convert unreacted benzeneselenol ti diphenyl diselenide. The residue was dissolved in 50 mL of benzene and this process continued. Excess diphenyl diselenide was then removed by filter chromatography and the crude β-hydroxy selenide was dissolved in 50 mL of dichloromethane, cooled to 0 °C, and treated with 5 mL of pyridine and an equal volume of 30% hydrogen peroxide. After being stirred 1 h at 0 °C and 2 h at ambient temperature, the mixture was diluted with 100 mL of dichloromethane, washed successively with H_2O, ($COOH_2$) (aqueous), $NaHCO_3$ (aqueous), and brine. Medium-pressure liquid chromatography of the residue from concentration of the dried organic layer, eluting with 50% EtOAc–hexane, afforded 500 mg of epoxide D10b and 2.57 g (88% based on unrecovered starting material) of D12 as an oil: IR ($CHCl_3$) 3600, 3450, 2980, 2880, 2250, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.903 (3 H, s, CH_3), 1.5–2.7 (8 H, m), 2.13 (3 H, s, $OCOCH_3$), 3.69 (3 H, s, CO_2CH_3), 4.09 (1 H, A part of AB,

J_{AB} = 10.7 Hz, CH_AH_BOAc), 4.17 (1 H, B part of AB, J_{AB} = 10.7 Hz, CH_AH_BOAc), 5.8–6.0 (2 H, m, CH=CH); ^{13}C NMR ($CDCl_3$) δ 174.4, 170.9, 134.5, 134.3, 119.1, 85.4, 67.5, 51.7, 50.4, 48.6, 31.4, 30.2, 20.9, 17.4, 16.4; mass spectrum *m/e* 222.1136, calculated for $C_{12}H_{16}NO_3$ (M – CH_3OAc) = 222.1130; specific rotation ($CHCl_3$, *c* 1.1) $[\alpha]^{25}_D$ +84.2°.

Epoxide D13. A solution of 900 mg of 70% *tert*-butyl hydroperoxide in 50 mL of benzene was dried over 4-Å molecular sieves and added to 1.19 g (4.0 mmol) of the allylic alcohol D12, 10 mg of $VO(AcAc)_2$ was added, and the solution was stirred at 40 °C for 14 h. The crude reaction mixture was passed through a column of Florisil, eluting with hexane to remove excess hydroperoxide and then with CH_2Cl_2–EtOAc to afford the crude product. Recrystallization from CH_2Cl_2–hexane yielded 1.07 g (85%) of pure epoxide D13: mp (cor) 108.0–108.5 °C; IR ($CHCl_3$) 3020, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.916 (3 H, s, CH_3), 1.7–2.7 (8 H, m), 2.143 (3 H, s, $OCOCH_3$), 3.583 (1 H, A part of AB, J_{AB} = 2.8 Hz, epoxide OCH), 3.648 (1 H, B part of AB, J_{AB} = 2.8 Hz, epoxide OCH), 3.677 (3 H, s, CO_2CO_3), 4.086 (1 H, A part of AB, J_{AB} = 11.8 Hz, CH_AH_BOAc), 4.294 (1 H, B part of AB, J_{AB} = 11.8 Hz, CH_AH_BOAc); ^{13}C NMR δ 174.7, 171.1, 118.7, 79.8, 79.6, 66.0, 62.5, 59.3, 51.5, 49.5, 43.6, 32.5, 29.5, 20.4, 15.7; mass spectrum *m/e* 238.1065, calculated for $C_{12}H_{16}NO_4$ (M – CH_2OAc) = 238.1079; specific rotation ($CHCl_3$, *c* 1) $[\alpha]^{25}_D$ 32.0°.

Epoxy Ketone D1. The hydroxy acetate D13 (470 mg, 1.5 mmol) in 20 mL of MeOH was treated with 200 mg of K_2CO_3 and 0.5 mL of H_2O. After 5 min, a solution of 400 mg of $NaIO_4$ in 5 mL of H_2O was added, followed after 16 h by another 100 mg of periodate. After 3 h, the methanol was evaporated, the aqueous solution was extracted with EtOAc, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford 320 mg of an oil that was filtered through silica gel with CH_2Cl_2 to yield epoxy ketone D1 as an oil (220 mg, 65%): IR ($CHCl_3$) 3020, 2950, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (3 H, s, CH_3), 1.8–2.7 (7 H, m), 3.545 [1 H, A part of AB, J_{AB} = 2.2 Hz, COCH(O)C*H*], 3.66 (3 H, s, CO_2CH_3), 3.905 [1 H, B part of AB, J_{AB} = 2.2 Hz, COC*H*(O)CH]; ^{13}C NMR δ 209.5, 173.2, 117.6, 58.5, 55.4, 51.8, 47.5, 40.8, 35.7, 29.1, 17.5, 17.0; mass spectrum *m/e* 206.0815, calculated for $C_{11}H_{12}NO_3$(M – OCH_3) = 206.0817; Specific rotation $[\alpha]^{25}_D$ 9.4°.

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Electronic Structure of Ferricytochrome *c* and Associated Hyperfine Interactions†

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Abstract: The electronic structure of ferricytochrome *c* has been investigated by the self-consistent charge extended Hückel procedure. By use of the spin distribution obtained from this calculation the hyperfine constants of ^{14}N and ^1H have been analyzed and found to provide satisfactory agreement with available electron nuclear double resonance data. The unpaired spin electron is found to be in a state involving a mixture of d_{XZ}- and d_{YZ}-like orbitals and the sulfur of the methionine group is found to carry a slight positive charge, in keeping with the postulates involved in the mechanism of electron transfer to and from cytochrome *c*.

In recent years, hyperfine interaction data for ^{14}N and ^1H nuclei have become available in ferricytochrome *c* through electron nuclear double resonance (ENDOR)[1] measurements.[2,3] It is therefore of interest to examine if one can explain these data through ab initio investigations of the electronic structures of this molecule, as has been possible in earlier work on other low- and high-spin heme systems.[4-6] The understanding of the electronic structure of ferricytochrome *c* is of particular interest because of the important role[7-9] it plays in electron transfer processes in a number of biological systems. In particular, in explaining the mechanism by which the ferricytochrome molecule gets reduced to the ferrous state, it has been proposed[10] that the unpaired spin orbital is in a π-like (d_{XZ} or d_{YZ}) state and that the sulfur of the methionine group carries a small positive charge that interacts electrostatically with the negative charge of an oxygen on the tyrosine molecule of the protein chain, this interaction providing a constraint on the orientation of the methionine group. It is therefore of interest to examine if these features ascribed to the ferricytochrome molecule are reproduced by ab initio investigations of its electronic structure.

Theoretical Procedures discusses briefly the structure of the model system used to represent ferricytochrome *c* in our investigations and the procedure for studying the electronic structure and hyperfine interactions. Results and Discussion presents and discusses the results for charge and spin distributions in the molecule and the ^{14}N and ^1H hyperfine interactions, making comparisons with available experimental data.[2,3] This comparison permits the assignment of the observed hyperfine constants to specific nitrogen and hydrogen atoms in the molecule.

Theoretical Procedures

Structure. The basic molecular unit that we have used to analyze the electronic structure and properties of low-spin fer-

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