were recorded for each spectrum which took approximately a minute (acquisition time 0.02 s).

Theoretical Calculations

Calculations were carried out with the GAUSSIAN 82 package of programs developed by Pople et al.[15a]

Acknowledgment. Support of the work at USC by the National Science Foundation is gratefully acknowledged.

Registry No. D_2HO^+, 12517-69-0; DH_2O^+, 12517-68-9; $HSbF_6$, 16950-06-4; $DSbF_6$, 54764-32-8; H_4O^{2+}, 12344-06-8; H_2, 1333-74-0; D_2, 7782-39-0.

Total Synthesis of (+)-Desepoxyasperdiol

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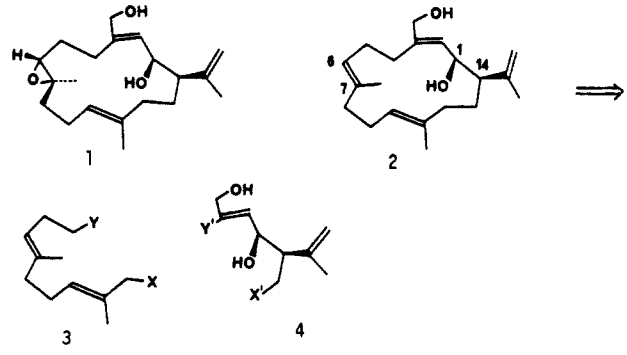
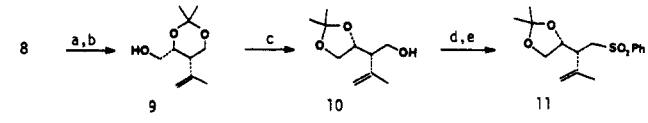
Abstract: A convergent enantioselective synthesis of desepoxyasperdiol is described. Key steps in the synthesis are the introduction of asymmetry by the regioselective ring opening of an optically active epoxy alcohol by isopropenylmagnesium bromide and the cyclization to the 14-membered ring using the conditions for the Horner–Emmons reaction which were developed by Masamune and Roush. The present work expands the scope of this reaction by demonstrating that it will simultaneously tolerate both a tertiary carbon nucleophile and an aldehyde with α-branching. During the course of this synthesis unusual behavior was noted for the reactions of (phenylthio)acetic acid dianion.

In recent years a plethora of cembrane natural products have been isolated and characterized, most of them from marine soft corals.[1] Although most of these are structurally unique and many show marked cytotoxic, antiinflammatory, carcinostatic, or other potentially useful physiological activity, relatively few have been prepared through total synthesis.

Asperdiol (**1**), a marine cembranoid isolated by Weinheimer in 1977 from a Caribbean gorgonian, is cytotoxic in vivo against several cancer cell lines.[2] Asperdiol is the only cembranoid in which antitumor activity occurs in the absence of an α-methylenebutyrolactone. Two total syntheses of the racemate of **1**, both using remote asymmetric induction, were reported in 1983.[3,4] In Still's synthesis[3] asymmetry at C-1 and C-14 was induced during the cyclization of the 14-membered ring, whereas Kato[4] used the C-1 alcohol to introduce the C-6, C-7 epoxide in (±)-desepoxyasperdiol (**2**). In this paper we describe an alternative convergent, asymmetric synthesis of (+)-desepoxyasperdiol. As a result of Kato's work,[4] this constitutes a formal total synthesis of **1**.

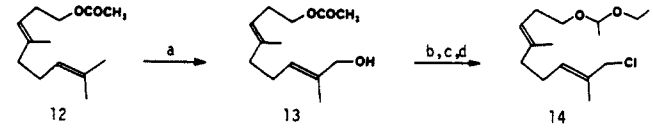


Scheme I. Synthesis of Right-Hand Fragment[a]



[a] (a) 2,2-Dimethoxypropane, TsOH catalyst, 25 °C, 95%; (b) Li, liquid NH_3, −78 °C, 85%; (c) acetone, TsOH catalyst, 25 °C, 85%; (d) 3 equiv of NBS, 2.8 equiv of PPh_3, CH_2Cl_2, 25 °C; (e) 2 equiv of $PhSO_2Na$, HMPA, 25 °C, 65% overall.

Scheme II. Synthesis of Left-Hand Fragment[a]



[a] (a) 4 equiv of *t*-BuOOH, 0.05 equiv of SeO_2, CH_2Cl_2, 25 °C, 40%; 60% after a single recycle of **12**; (b) 2 equiv of MsCl, 2.3 equiv of pyridine, pentane, 0–25 °C, 70%; (c) CH_3OH, K_2CO_3, 25 °C; (d) 1.2 equiv of ethyl vinyl ether, PPTS catalyst, CH_2Cl_2, 25 °C, 70% overall.

Retrosynthetic disconnection of the C-12, C-13 and the C-3, C-4 bonds generates fragments **3** and **4**. Fragment **3** is easily derived from geraniol whereas fragment **4** appeared to be a candidate for an aldol process.[5] All attempts to use the aldol condensation of aldehydes with the extended enolates derived from **5**[6] or **6**[7] led mainly to products derived from γ-alkylation. Therefore an alternative approach for controlling the stereochemistry at C-1 and C-14 was developed. Both enantiomers of epoxy alcohol **7**, are

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(2) Weinheimer, A. J.; Matson, J. A.; van der Helm, D.; Poling, M. *Tetrahedron Lett.* **1977**, 1295–1298.

(3) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785–4786. We thank Professor Still for a preprint of this paper.

(4) Aoki, M.; Tooyama, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1983**, 2267–2270.

(5) For reviews of the aldol reaction, see: (a) Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds. Elsevier: Amsterdam, 1984; Part B, pp 177–237. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (c) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon: Oxford, 1980; pp 197–215.

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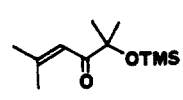
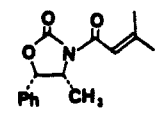
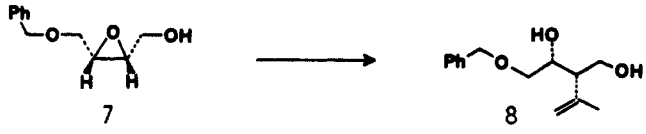


5



6

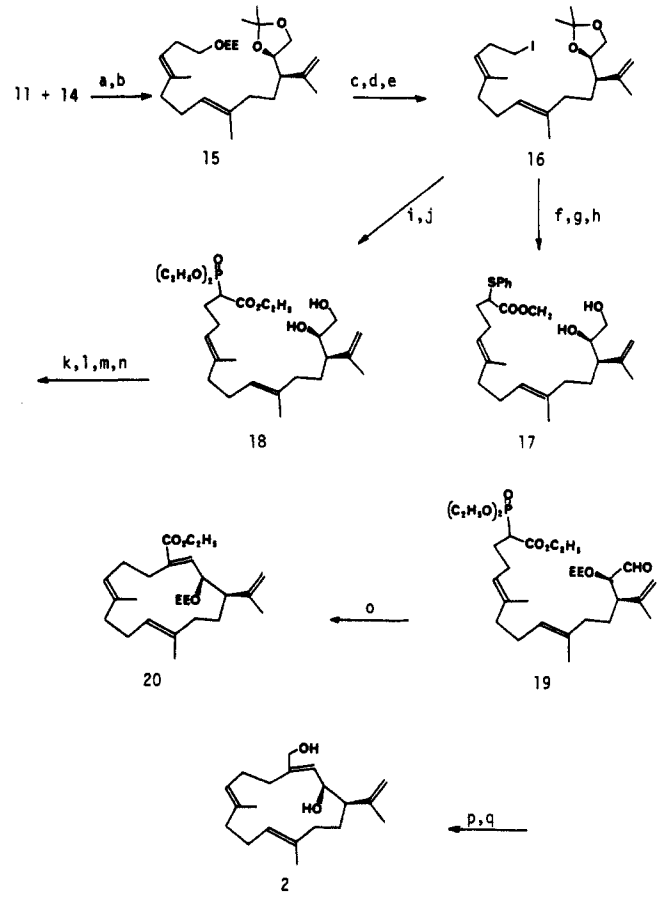


7 8

available in high optical yield through Sharpless' methodology.[8,9] Nucleophilic epoxide ring opening by an isopropenyl nucleophile would create the stereocenters at C-1 and C-14. Because of the symmetry of **7**, the regiochemical preference for nucleophilic epoxide ring opening was inconsequential to the synthetic plan. By choice of the appropriate optical isomer of **7** the required absolute configuration of the two stereocenters could be obtained whether attack took place with preference for C-2 or C-3 of **7**. Thus it was found that the cuprous iodide catalyzed addition of Grignard reagents under carefully controlled conditions took place selectively at C-2.[10] The asymmetric epoxidation of (*Z*)-2-butene-1,4-diol was catalyzed by (−)-diethyl tartrate according to Sharpless' conditions.[9] The optical purity of 2(*R*),3(*S*)-**7**, $[\alpha]^{22}_D$ +25° (*c* 1.0, $CHCl_3$), was determined to be >95% by analysis of the (+)-MTPA ester[11] and was further verified by Eu(hfc)$_3$ analysis[12] of the acetate derivative. The addition of isopropenylmagnesium bromide to 2(R),3(S)-**7** produced **8** in 84% yield along with 12% of the product of C-3 attack (Scheme I). Although it was reasonable to assume inversion of configuration at C-2, alternative mechanisms could not be ruled out. The stereochemical assignment was confirmed as follows: acid-catalyzed ketalization of **8** with 2,2-dimethoxypropane produced an acetonide. The vicinal coupling constant for the methine protons of the acetonide ring was determined to be 3.6 Hz, therefore the two substituents on the ring are cis, and epoxide ring opening must have occurred with inversion of configuration at C-2. Reductive cleavage of the benzyl group furnished primary alcohol **9**. Transketalization in acetone provided the five-membered ring acetonide **10** as a 20:1 equilibrium mixture with **9**. The overall yield of **10** from epoxy alcohol **7** was 60%. Acetonides **9** and **10** were readily separable by column chromatography on silica gel. All compounds that had the five-membered acetonide ring were easily identified by the base peak in the mass spectrum which occurred at 101 mass units. The optical purity of **10** was determined to be >95% by analysis of the MTPA ester.[11] The alcohol function of **10** was converted to the bromide with NBS/triphenylphosphine[13] and the bromide was displaced with sodium benzenesulfinate to produce sulfone **11** as a key intermediate. Homogeranyl acetate (**12**) was chosen as the starting material for the C-4, C-12 fragment. Selenium dioxide catalyzed allylic oxidation with *tert*-butyl hydroperoxide in dichloromethane[14] produced allylic alcohol **13** (Scheme II). The allylic alcohol was converted to the chloride by treatment with methanesulfonyl chloride and pyridine in pentane.[15] Acetate hydrolysis with potassium carbonate in dry methanol was followed by conversion to the ethoxyethyl ether with ethyl vinyl ether and catalytic pyridinium tosylate in dichloromethane. The overall yield of **14** from homogeranyl acetate (**12**) was 20%. The lithio anion of sulfone **11** was generated with *n*-butyllithium in HMPA/THF at −50 °C and was allowed to react with allylic chloride **14** (Scheme III). Reductive desulfonylation of the adduct was accomplished with 6% sodium amalgam in methanol[16] to produce **15** in 72% overall yield from **11**.

The selective functionalization of C-4 was performed in a straightforward manner in three steps. The ethoxyethyl ether protecting group was hydrolyzed in the presence of the acetonide with pyridinum tosylate in *n*-propanol. Mesylation of the homoallylic alcohol was followed by displacement with iodide (75%

Scheme III. Assembly of (+)-Desepoxyasperdiol from the Fragments[a]



[a] (a) Add 1.1 equiv of *n*-BuLi to 1.0 equiv of **11** in THF, −65 to −40 °C, 1 h; then add 1.0 equiv of **14**, and HMPA (15% by volume of solution), 80%; (b) 5 equiv of 6% Na–Hg, CH_3OH, 25 °C, 90%; (c) *n*-propanol, PPTS catalyst, 25 °C, 80–85%; (d) 1.15 equiv of MsCl, 1.5 equiv of triethylamine, CH_2Cl_2, 0 °C; (e) 4 equiv of NaI, acetone, reflux, 75% overall; (f) 1.05 equiv of PhSCHLiCOOLi, THF, 0–25 °C, 68%; (g) CH_3OH, PPTS catalyst, 25 °C, 73%; (h) CH_2N_2, ether, 100%; (i) 1.5 equiv of NaH, 0.1 equiv of 18-crown-6, DMF, 2 equiv of $(EtO)_2POCH_2COOEt$; then add 1 equiv of **16**, 78%; (j) $HOCH_2CH_2OH$, DME, Amberlyst IR-120 catalyst, 25 °C, 80%; (k) 1.2 equiv of *tert*-butyldimethylchlorosilane, 2.5 equiv of imidazole, DMF, 25 °C, 95%; (l) 10 equiv of ethyl vinyl ether, PPTS catalyst, CH_2Cl_2, 25 °C, 82%; (m) 1.5 equiv of *n*-Bu_4NF, THF, 25 °C, 90%; (n) 2 equiv of $(ClCO)_2$, 4 equiv of Me_2SO, 5 equiv of triethylamine, −78 °C, 95%; (o) 30 equiv of DBU, 33 equiv of LiCl, 25 °C, 4×10^{-3} M in CH_3CN, see text; (p) 2 equiv of LAH, ether, 0 °C; (q) CH_3OH, PPTS catalyst, 25 °C, 80% for two steps.

(8) Both enantiomers of **7** are available from Fluka Chemical Corp.
(9) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. See also Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373–1378.
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overall yield). Intermediate **16** incorporated all but two of the carbon atoms of the final product. The first two-carbon nucleophile chosen for reaction with **16** was the dilithio dianion of thiophenoxyacetic acid.[17] Methyl ester **17** was converted through the tosylate of the primary alcohol to the C-1, C-2 epoxide. Neither the monoanion of the thiophenoxy methyl ester nor the dilithio dianion of the corresponding carboxylic acid could be induced to undergo cyclization. The monoanion was insufficiently reactive to undergo cyclization, as indicated by recovery of the starting material. The dianion on the other hand underwent decomposition more rapidly than cyclization. The isolation of thiophenol from the reaction mixture suggested that decomposition to a carbenoid might have been taking place. Recent work by Cohen has shown that β-alkoxy-α-thiophenyl anions undergo loss of thiophenoxide to produce products derived from a carbene.[18] Although the thiophenyl carboxylate dianion bears a superficial resemblance to the systems studied by Cohen, the reactions of this nucleophile have been described with no mention of such a decomposition pathway. A reinvestigation of the alkylation reaction of thiophenoxyacetic acid lithio dianion with butyl bromide was undertaken and an intriguing observation was made. As the excess of butyl bromide was decreased, the proportion of butyl phenyl sulfide in the product mixture increased. A maximum yield of 50% (based on butyl bromide) of butyl phenyl sulfide was isolated when 0.25 equiv of butyl bromide was used. This result was duplicated with a commercial sample of thiophenoxyacetic acid which had been fused under vacuum overnight. Adventitious thiophenol was not being introduced with the dianion, yet a competition for the butyl bromide by the dianion and thiophenoxide was being observed. A ready interpretation of this result was not obvious[19] so an alternative two-carbon atom nucleophile was examined.

The intramolecular Horner–Emmons reaction has been used for macrocycle construction.[20] At high dilution this method has been used successfully to prepare macrocyclic rings of many sizes, including 14-membered rings. The precursor to cyclization was prepared from iodide **16**. Displacement with the sodium salt of triethyl phosphonoacetate was catalyzed by 18-crown-6. The acetonide protecting group was selectively hydrolyzed in a 2:1 mixture of ethylene glycol and 1,2-dimethoxyethane in the presence of Amberlyst IR-120 cation exchange resin to produce diol **18**. Differentiation of the two hydroxyl groups was easily accomplished. The primary alcohol was converted to the *tert*-butyldimethylsilyl ether.[21] The secondary alcohol was protected as the ethoxyethyl ether and the silyl protecting group was removed by treatment with fluoride. Swern oxidation[22] produced aldehyde **19**, the precursor to the intramolecular Horner–Emmons reaction. Aldehyde **19** did not suffer epimerization at C-1 during the oxidation. This was demonstrated by reducing **19** to the precursor alcohol with methanolic sodium borohydride. Two structural features distinguished **19** from all other substrates that had been reported for this reaction: the aldehyde had an α-substituent and the nucleophilic carbon was tertiary. Epimerization of the aldehyde was not anticipated to be a complicating factor because of the steric inaccessibility of the C-1 proton. The crowding at both reacting termini posed a more serious challenge. A variety of reaction conditions failed to produce cyclized material. Sodium hydride,[20a] sodium hexamethyldisilazide,[20b] lithium isopropoxide,[20b] and potassium carbonate/18-crown-6[20c] all failed to give more than a trace of the desired product. Success was realized with the Masamune–Roush conditions, DBU and lithium chloride in acetonitrile.[23] The cyclized material was obtained in 30% yield as a 2:1 mixture of *E* and *Z* isomers.

Further optimization of the reaction conditions did not improve the isolated yield of **20** beyond 20%. Reduction of the ethyl ester to the alcohol with lithium aluminum hydride in ether at 0 °C followed by hydrolysis of the alcohol protecting group with methanolic pyridinium tosylate at 25 °C produced (+)-desepoxyasperdiol, $[\alpha]^{22}_D$ +102° (*c* 0.003, CH_2Cl_2), in 90% overall yield from **20**.

The optically active material was identical by comparison of ^1H NMR, ^{13}C NMR, and IR spectra with racemic desepoxyasperdiol.

Conclusion

The first enantioselective synthesis of (+)-desepoxyasperdiol has been accomplished in 20 steps in 1% overall yield from **7**. Although the overall yield suffers because of the inefficiency of the cyclization step it is worth noting that aldehyde **19** could be obtained in gram quantities without difficulty. Model studies have demonstrated that by incorporating the C-6, C-7 epoxide in the left-hand fragment this scheme is suitable for the synthesis of (−)-asperdiol.[24] Some important findings have been made as a result of this research. A new method has been developed for the regioselective ring opening of epoxy alcohols with Grignard reagents.[10] The scope of the intramolecular Horner–Emmons reaction has been expanded to include the cyclization of a substituted phosphonate onto an α-alkoxy aldehyde. Unusual behavior was observed for the lithio dianion of α-(phenylthio)acetic acid. This may be useful for a better understanding of the substitution reactions of this nucleophile.

Experimental Section

(2*R*,3*R*)-4-(Benzyloxy)-2-isopropenyl-1,3-butanediol (8). To a stirred suspension of 0.57 g (3.0 mmol, 0.3 equiv) of cuprous iodide (Alfa, ultrapure) in 100 mL of anhydrous ether under nitrogen at −8 °C was added 0.03 mol of a solution of isopropenylmagnesium bromide in THF (0.43 M, 3 equiv). The light yellow suspension was immediately cooled to −23 °C and epoxy alcohol **7** (2.0 g, 10.3 mmol, 1 equiv) in 5 mL of ether was added slowly *via cannula*. The yellow heterogeneous mixture was stirred at −23 °C for 8 h. The reaction mixture was partitioned between ether and saturated aqueous NH_4Cl which had been basified to pH 8 by addition of concentrated ammonium hydroxide. The ethereal extract was washed with brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated. Flash chromatography on silica gel provided 2.05 g of **8** (84%) as a colorless oil and 0.29 g (12%) of the isomeric 1,2-diol. **8**: ^1H NMR (100 MHz) δ 7.32 (s, 5 H), 4.98 (br s, 1 H), 4.85 (br s, 1 H), 4.54 (s, 2 H), 3.98 (m, 1 H), 3.75–3.40 (m, 4 H), 2.42 (m, 3 H, includes both OH), 1.78 (br s, 3 H); IR (neat) 3450, 3080, 3040, 2910, 1650, 1450, 1370, 1090, 880 cm^{-1}; mass spectrum, *m/e* 236 (M^+), 205 (M^+ - CH_2OH), 149, 121, 107, 97, 91 (100%), 69, 43.

(2*R*,3*R*)-3-(1-Methylethenyl)-4-(phenylsulfonyl)-1,2-*O*-isopropylidene-1,2-butanediol (11). A solution of 21.3 g (81.2 mmol, 2.8 equiv) of triphenylphosphine in 60 mL of dichloromethane was added dropwise to a stirred suspension of 15.5 g (87.0 mmol, 3.0 equiv) of *N*-bromosuccinimide in 135 mL of dichloromethane at 25 °C. The reddish brown solution was stirred for 5 min. To the solution pyridine (2.7 g, 34.5 mmol, 1.2 equiv) was added dropwise followed by slow addition of a solution of 5.4 g (29.0 mmol, 1.0 equiv) of acetonide alcohol **10** in 60 mL of dichloromethane. The reaction mixture was stirred for 12 h and was poured onto 150 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with ether and the combined organic phase was washed sequentially with water and brine. The reaction mixture was dried ($MgSO_4$), filtered, and evaporated. Flash chromatography produced 5.8 g (80%) of bromide as a colorless oil: $[\alpha]^{23}_D$ −24.40° (neat, *d* = 1.288); ^1H NMR (300 MHz) δ 5.04 (br s, 1 H), 4.88 (br s, 1 H),

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4.22 (dd, J = 7.6, 6.2 Hz, 1 H), 4.04 (dd, J = 8.2, 6.2 Hz, 1 H), 3.70 (t, J = 7.6 Hz, 1 H), 3.51 (dd, J = 10.2, 5.8 Hz, 1 H), 3.40 (dd, J = 10.2, 8.2 Hz, 1 H), 2.60 (m, 1 H), 1.80 (br s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H); IR (neat) 2930, 1650, 1450, 1380, 1210, 1110, 1060, 890, 850 cm^{-1}; mass spectrum, m/e (no M^+), 235, 233 ($M^+ - CH_3$), 175, 173, 111, 101, 94, 73, 61, 59, 55, 53, 43 (100%); calcd for $C_9H_{14}BrO_2$ ($M^+ - CH_3$) 233.0177, found 233.0174.

A solution of 2.15 g (8.6 mmol) of the bromide in 10 mL of dry HMPA was treated with 3.45 g (17.2 mmol, 2.0 equiv) of anhydrous sodium phenylsulfinate. After 2 h at 25 °C the mixture was poured into 50 mL of water and was extracted with ether (4 × 100 mL). The ethereal phase was washed with water and brine and was dried ($MgSO_4$). Solvent evaporation followed by flash chromatography produced 1.82 g (68%) of crystalline sulfone **11**, mp 60–62 °C, along with 144 mg (9%) of alcohol **10** and 150 mg (7%) of the bromide. **11**: $[\alpha]^{23}_D$ −7.2° (c 0.388, CH_2Cl_2); ^1H NMR (300 MHz) δ 7.90 (m, 2 H), 7.63 (m, 1 H), 7.55 (m, 2 H), 4.90 (br s, 1 H), 4.78 (br s, 1 H), 4.20 (dd, J = 12.0, 6.2 Hz, 1 H), 3.90 (dd, J = 8.1, 6.2 Hz, 1 H), 3.60 (dd, J = 8.1, 7.3 Hz, 1 H), 3.37 (dd, J = 14.4, 8.4 Hz, 1 H), 3.27 (dd, J = 14.4, 4.2 Hz, 1 H), 2.84 (m, 1 H), 1.70 (br s, 3 H), 1.36 (s, 3 H), 1.28 (s, 3 H); IR (CH_2Cl_2) 2930, 1640, 1370, 1300, 1130, 1055 cm^{-1}; mass spectrum, m/e 310 (M^+), 295 ($M^+ - CH_3$), 292, 193, 125, 111, 101, 97, 93, 77, 43 (100%); calcd for $C_{15}H_{19}SO_4$ ($M^+ - CH_3$) 295.1004, found 295.1016.

Anal. Calcd for $C_{15}H_{19}SO_4$: C, 61.91; H, 7.14; S, 10.32. Found: C, 61.86; H, 7.29; S, 10.37.

(2*R*,3*R*,4*RS*,6*E*,10*E*)-6,10,15-Trimethyl-3-(1-methylethenyl)-4-(phenylsulfonyl)-1,2-*O*-isopropylidene-6,10-octadecadiene-1,2-diol (15). A solution of 5.16 g (16.65 mmol, 1.0 equiv) of sulfone **11** in 65 mL of THF was treated with 6.78 mL of a 2.7 M solution n-butyllithium (18.30 mmol, 1.1 equiv) at −65 °C. The reaction mixture was warmed to −40 °C over a period of 1 h, then 9.7 mL of dry HMPA was added and the reaction mixture was cooled to −65 °C. After 10 min 4.57 g of chloride **14** (16.65 mmol, 1 equiv) in 12 mL of THF was added to the solution of the anion. The reaction mixture was allowed to warm to 25 °C during 3 h and was quenched with aqueous NH_4Cl. Partitioning between ether and water produced an organic phase which was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash chromatography to afford 7.75 g (85%) of a colorless oil as a mixture of diastereomeric sulfones. ^1H NMR (100 MHz) δ 7.80 (m, 2 H), 7.65 (m, 3 H), 5.10 (m, 3 H), 4.95 (m, 1 H), 4.65 (m, 1 H), 4.20 (m, 1 H), 3.80–3.10 (m, 7 H), 3.00–2.15 (m, 9 H), 1.95 (br s, 6 H), 1.60 (br s, 3 H), 1.30–1.20 (m, 12 H); IR (neat) 3000, 2950, 1650, 1450, 1305, 1210, 1140, 740 cm^{-1}; mass spectrum, m/e (no M^+), 533 ($M^+ - CH_3$), 445, 259, 215, 179, 171, 160, 135, 133, 125, 109, 101 (100%) 95, 93, 83, 81, 73, 45, 43.

A solution of 3.18 g (5.8 mmol, 1 equiv) of sulfone diastereomers in 60 mL of anhydrous methanol was treated with 11.40 g (29.0 mmol of Na, 5 equiv) of 6% sodium amalgam at 25 °C. The heterogeneous reaction mixture was sonicated for 2 h. Most of the methanol was evaporated from the reaction mixture, the residue was diluted with ether, and the excess reducing agent was destroyed by cautious addition of water. The ether–water mixture was decanted from the mercury. The ethereal layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography to furnish 2.02 g (85%) of **15** as a colorless oil. ^1H NMR (100 MHz) δ 5.16 (m, 2 H), 4.90 (br s, 1 H), 4.75 (br s, 1 H), 4.64 (q, J = 5.4 Hz, 1 H), 4.20–3.90 (m, 2 H), 3.70–3.30 (m, 5 H), 2.25 (m, 2 H), 2.03 (m, 7 H), 1.71 (br s, 3 H), 1.62 (br s, 3 H), 1.57 (br s, 3 H), 1.40–1.15 (m, 8 H), 1.23 (s, 3 H), 1.18 (s, 3 H); IR (neat) 3090, 3000, 2950, 1640, 1450, 1375, 1370, 1250, 880, 850 cm^{-1}; mass spectrum, m/e 408 (M^+), 393 ($M^+ - CH_3$), 362, 335, 320, 318, 305, 277, 261, 236, 219, 178, 161, 135, 101, 73 (100%), 43.

Ethyl (2*R*,3*R*,5*E*,9*E*)-2-(Diethoxyphosphinyl)-14,15-dihydroxy-6,10-dimethyl-13-(1-methylethenyl)-5,9-pentadecadienoate (18). A stock solution of the sodium salt of triethyl phosphonoacetate was prepared by stirring 1.07 g (4.77 mmol) of triethyl phosphonoacetate with 224 mg (9.33 mmol) of oil-free sodium hydride in 9.5 mL of DMF at 25 °C for 1 h. The stock solution, 4.7 mL (1.53 mmol), was added by syringe to a solution of 457 mg (1.02 mmol) of iodide **16** and 100 mg of 18-crown-6 in 4 mL of DMF. The solution was stirred for 2 h at 50 °C. Water (20 mL) was added and the mixture was extracted with ether (3 × 50 mL). The ether extract was washed with water and brine and was dried ($MgSO_4$). Evaporation of the solvent furnished the crude product which was chromatographed to afford 450 mg (81%) of acetonide phosphonate as a clear oil: ^1H NMR (300 MHz) δ 5.17 (m, 2 H), 4.92 (br s, 1 H), 4.76 (br s, 1 H), 4.25–4.15 (m, 6 H), 4.15–4.00 (m, 2 H), 3.62 (m, 1 H), 2.94 (m, 1 H), 2.15 (m, 1 H), 2.10–1.60 (m, 8 H), 1.72 (br s, 3 H), 1.57 (br s, 6 H), 1.42–1.20 (m, 19 H); IR (neat) 2920, 1730, 1370, 1150, 1030, 950 cm^{-1}; mass spectrum, m/e 542 (M^+), 527 ($M^+ - CH_3$), 454, 442, 386, 331, 305, 237, 224, 197, 152, 101, 93, 81, 71, 57, 43 (100%); calcd for $C_{29}H_{51}PO_7$ 542.3379, found 542.3369.

A suspension of the acetonide phosphonate (450 mg, 0.83 mmol) and 200 mg of Amberlite IR-120 (H^+ form) in 8 mL of 2:1 ethylene glycol/DME was heated at 45 °C for 5 h. The mixture was filtered and the DME was removed under vacuum. The residue was dissolved in water and was extracted with ether (5 × 50 mL). The ethereal extract was washed with water and brine and dried (Na_2SO_4). Evaportion of the solvent furnished a colorless residue which was filtered through a short silica gel column eluting with ethyl acetate. Evaporation of the solvent furnished **18** as a colorless oil (422 mg, 93%): $[\alpha]^{23}_D$ −3.30° (c 0.654, CH_2Cl_2); ^1H NMR (300 MHz) δ 5.06 (m, 2 H), 4.95 (br s, 1 H), 4.81 (br s, 1 H), 4.22–4.07 (m, 6 H), 3.74 (br d, J = 9.6 Hz, 1 H), 3.60–3.40 (m, 2 H), 2.92 (ddd, J = 23.0, 10.7, 3.3 Hz, 1 H), 2.45 (m, 1 H), 2.10–1.70 (m, 10 H; includes two OH protons), 1.69 (br s, 3 H), 1.56 (br s, 6 H), 1.42–1.18 (m, 13 H); IR (neat) 3380, 2930, 1736, 1640, 1368, 1286, 1041, 964, 880 cm^{-1}; mass spectrum, m/e 502 (M^+), 487 ($M^+ - CH_3$), 471, 442, 427, 387, 331, 307, 261, 237, 224 (100%), 197, 178, 152, 135, 123, 109, 93, 81, 43; calcd for $C_{26}H_{47}PO_7$ 502.3059, found 502.3085.

Ethyl (13*R*,14*R*,5*E*,9*E*)-2-(Diethoxyphosphinyl)-6,10-dimethyl-14-(1,3-dioxa-2-methylprop-1-yl)-13-(1-methylethenyl)-15-oxo-5,9-pentadecadienoate (19). To a solution of 442 mg (3.48 mmol, 2 equiv) of oxalyl chloride in 8 mL of CH_2Cl_2 was added dropwise 544 mg (6.97 mmol, 4 equiv) of Me_2SO in 0.6 mL of CH_2Cl_2 at −68 °C. After 6 min a solution of 1.00 g (1.74 mmol, 1 equiv) of the C-2 primary alcohol **18** in 4 mL of CH_2Cl_2 was added to the complex. After 25 min, 880 mg (8.70 mmol, 5 equiv) of triethylamine was added. After 10 min the cooling bath was removed and the reaction was quenched with 10 mL of water. The reaction mixture was partitioned between water and CH_2Cl_2; the organic extracts were washed with water and brine and were dried ($MgSO_4$). Solvent evaporation followed by chromatography furnished 0.96 g of **19** as a colorless oil (95%): (diastereomers) ^1H NMR (300 MHz) δ 9.50, 9.47 (two doublets, J = 3.4, 3.0 Hz, 1 H), 5.01 (m, 2 H), 4.81 (br s, 1 H), 4.70 (br s, 1 H), 4.67, 4.51 (two quartets, J = 5.4, 5.4 Hz, 1 H), 4.12 (m, 6 H), 3.63–3.55 (m, 1 H), 3.50–3.35 (m, 2 H), 2.81 (m, 1 H), 2.38 (m, 1 H), 2.10–1.80 (m, 8 H), 1.65 (br s, 3 H), 1.51 (br s, 6 H), 1.45–1.20 (m, 16 H), 1.15 (m, 3 H); IR (neat) 2937, 1723, 1640, 1440, 1254, 1022, 980 cm^{-1}; mass spectrum, m/e no M^+, 526 ($M^+ - CH_3CH_2OH$), 550, 482, 443, 387, 305, 261, 237, 231, 224 (100%), 197, 178, 152, 81, 73.

(1*R*,2*E*,6*E*,10*E*,14*R*)-1-Hydroxy-7,11-dimethyl-14-(1-methylethenyl)-2,6,10-cyclotetradecatriene-3-carboxylic Acid Ethyl Ester (20). A flame-dried flask was charged with 37 mL of anhydrous acetonitrile (distilled from calcium hydride) and 318 mg (7.6 mmol, 33 equiv) of dry lithium chloride (heated to 60 °C overnight under vacuum over phosphorus pentoxide). Solutions of 130 mg (0.23 mmol, 1 equiv) of aldehyde **19** in 10 mL of acetonitrile and 1.030 g (6.90 mmol, 30 equiv) of DBU in 10 mL of acetonitrile were added simultaneously during 8 h to the stirred suspension at 25 °C. After 30 h the acetonitrile was evaporated from the reaction mixture. With the minimum amount of benzene, the residue was transferred to a flash chromatography column charged with 30 g of silica gel. Elution with 8% ethyl acetate in hexane separated **20** from the lower R_f Z isomer. The combined yield of both isomers was 30 mg (32%). Further purification by HPLC (μ-Porasil) eluting with 15% ethyl acetate in hexane provided 19 mg (20%) of **20** (ethoxyethyl diastereomers): ^1H NMR (300 MHz) δ 6.67, 6.56 (two doublets, J = 9.7, 9.7 Hz, 1 H), 5.05–4.90 (m, 2 H), 4.82 (br s, 1 H), 4.64 (br s, 1 H) 4.59–4.42 (overlapping quartets, 1 H), 4.39 (dd, J = 9.7, 5.0 Hz, 1 H), 4.20 (overlapping quartets, 2 H), 3.51 (overlapping quartets, 2 H), 2.61 (m, 1 H), 2.40–2.20 (m, 2 H), 2.20–1.90 (m, 8 H), 1.67 (br s, 3 H), 1.59 (two br singlets, 6 H), 1.30–1.10 (m, 11 H); IR ($CDCl_3$) 2968, 1707, 1643, 1601, 1440, 1373, 1265 cm^{-1}; mass spectrum, m/e 418 (M^+), 372 ($M^+ - CH_3CH_2OH$), 345, 328, 283, 255, 230, 191, 163, 135, 119, 109, 97, 73 (100%). Z isomer (ethoxyethyl diastereomers): ^1H NMR (300 MHz) δ 5.68, 5.52 (two br doublets, J = 9.7, 9.7 Hz, 1 H), 5.06 (m, 2 H), 4.81 (br s, 1 H), 4.71 (br s, 1 H), 4.80–4.60 (overlapping quartets, 1 H), 4.51 (m, 1 H), 4.17 (m, 2 H), 3.60–3.20 (overlapping quartets, 2 H), 2.60–1.80 (m, 11 H), 1.67 (br s, 3 H), 1.56 (br s, 6 H), 1.40–1.10 (m, 11 H); IR ($CDCl_3$) 2965, 1707, 1645, 1441, 1375, 1266 cm^{-1}.

(1*R*,2*E*,6*E*,10*E*,14*R*)-1-Hydroxy-7,11-dimethyl-14-(1-methylethenyl)-2,6,10-cyclotetradecatriene-3-methanol (2). A solution of 19 mg (0.043 mmol) of ester **20** in 0.2 mL ether was treated at 0 °C with 100 μL of a 1 M solution of LAH in ether. After 5 min the solution was quenched with water and was extracted with ether. The solvent was evaporated and the residue was dissolved in 0.5 mL of methanol containing a few crystals of PPTS. The solution was stirred at 25 °C for 2 h. The methanol was evaporated and the residue was dissolved in ether. The combined organic extract was washed with saturated aqueous sodium bicarbonate and the aqueous phase was back extracted with ether. The ether extracts were combined, washed with brine, dried (Na_2SO_4), and

concentrated. The solid product was purified by HPLC (μ-Porasil) to furnish 13 mg (90% overall) of desepoxyasperdiol as an oil: TLC R_f 0.15 (30% ethyl acetate in hexane); ^{1}H NMR (300 MHz) δ 5.46 (d, J = 8.7 Hz, 1 H), 5.02–4.81 (m, 2 H), 4.91 (br s, 1 H), 4.72 (br s, 1 H), 4.32 (dd, J = 8.7, 4.0 Hz, 1 H), 4.05 (AB q, J = 13.2 Hz, 2 H), 2.38–1.80 (m, 11 H), 1.72 (br s, 3 H), 1.56 (br s, 3 H), 1.49 (br s, 3 H), 1.61–1.20 (m, 4 H; includes two OH protons); ^{13}C NMR (75 MHz) δ 145.50, 138.98, 134.04, 133.54, 129.73, 125.55, 124.18, 113.71, 69.41, 65.75, 49.39, 40.21, 35.98, 28.16, 28.08, 24.54, 24.52, 23.19, 15.68, 15.32; IR ($CDCl_3$) 3344, 2938, 1662, 1638, 1441, 1367, 1251, 1050, 910 cm^{-1}; mass spectrum, m/e 305 (M^+ + 1), 304 (M^+), 286 ($M^+ - H_2O$), 274, 256, 244, 217, 204, 189, 175, 161, 149, 136, 123, 109, 100, 92, 81 (100%), 69; calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2409.

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Studies on the Synthesis of Vitamin B_{12}. 4

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Abstract: Chiral syntheses of the four precursors (**A1–D1**) to cobyric acid (**1**) and their assembly into the triisoxazole **4** are presented.

A novel strategy for the synthesis of cobyric acid (**1**) (Scheme I) was outlined in previous accounts from this laboratory.[1] The key feature of this design was the use of a triisoxazole scaffold (e.g., **3** or **4**) as a latent synthon for the crucial secocorrin intermediate **2**. This Cd complex **2** was used by the Eschenmoser group and undergoes a remarkably stereoselective photochemically induced A/D cycloisomerization.[2]

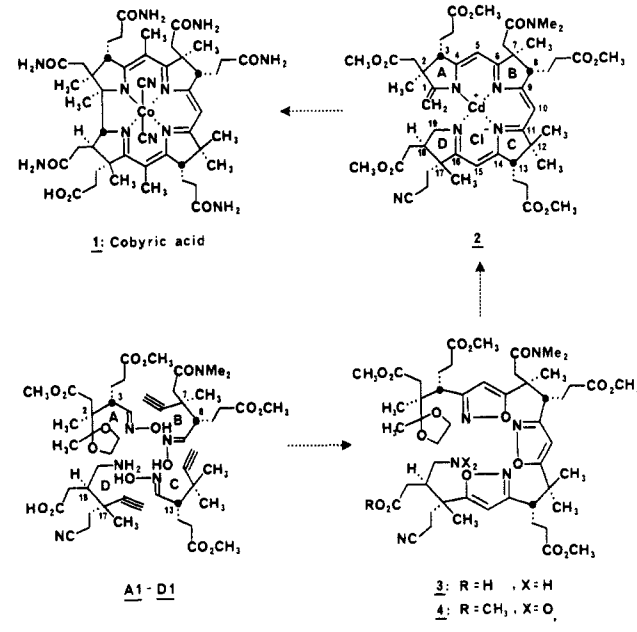
In an earlier report, an enantiospecific approach to the synthesis of four precursors (**A1–D1**) from dextro- and levorotatory camphor was described.[3] Unfortunately, with but one exception (shown in Scheme II), the Tanabe–Eschenmoser fragmentation (e.g., **6** → **C7**), which would have led to the four necessary acetylenes **A1–D1**, did not occur. Although cyclopentenone oxide **5** fragmented via the epoxyhydrazone **6** to the acetylenic aldehyde **C7**, the yield was modest and, as will be shown later, racemization took place.

"Nevertheless, the synthesis of the vitamin remained a dream unfulfilled, and as experiment after experiment failed, we thought seriously of abandoning our dream. However, rather than giving up we decided to undertake an entirely different approach".[4] Herein we describe the syntheses of the four precursors **A1–D1** in enantiomerically pure form and their assembly into the triisoxazole **4** via nitrile oxide cycloaddition methodology.

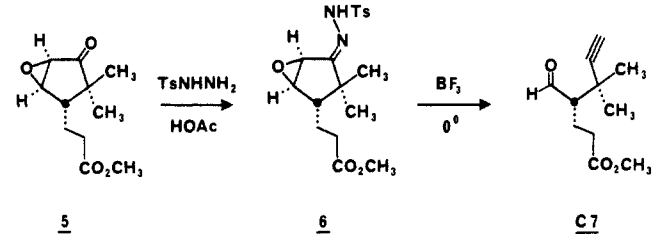
Synthesis of the A Ring. The first five steps of the synthesis remained unchanged from our previous approach[3] (Scheme III). Starting from (−)-camphor, the C-9 methyl group was functionalized via bromide **A3**[5,6] to the nitrile **A4**. Sodium borohydride reduction of the keto group gave predominantly the *exo*-alcohol **A5** that was subjected to oxidative fragmentation with ceric ammonium nitrate (CAN)[7] to afford cyclopentene **A6**. At this point, we were able to shorten the synthesis by a modified route and homologate the aldehyde side chain to the nitrile **A8**. This was accomplished by sodium borohydride reduction followed by tosylation and displacement of the tosylate with sodium cyanide in dimethylformamide (DMF). Oxidative ring opening with ozone afforded the crystalline keto aldehyde **A9** in 14% overall yield starting from (−)-camphor.

As shown in Scheme IV, reductive amination of **A9** with dimethylamine and sodium cyanoborohydride[8] gave the amino ketone **A10** in high yield. Oxidation with *m*-chloroperbenzoic acid (MCPBA) to the *N*-oxide **A11** followed by Cope elimination yielded the keto olefin **A12** which was protected as the ethylene

Scheme I



Scheme II



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