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CAMPHORAE: CHIRAL INTERMEDIATES FOR THE TOTAL SYNTHESIS OF STEROIDS. PART 2. AN ENANTIOSPECIFIC APPROACH TOWARD VITAMIN D METABOLITES

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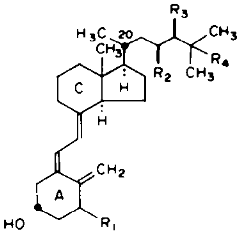
Abstract: The methylation of camphor and its derivatives has been investigated. The endo/exo stereochemistry of the methyl group has been established by ^{1}H NMR. These studies provide the basis for an enantiospecific approach to the synthesis of vitamin D and its metabolites from readily available dextrorotatory camphor.

Recently, a number of advances have been made in elucidating the metabolic fate of vitamin D_3 (1) which have led to improved treatment of patients with calcium homeostasis dysfunction.[1-3] For example, when kidney function is impaired, 1,25-dihydroxyvitamin D_3, the active form of the vitamin, is insufficiently produced. Daily administration of this metabolite to the patient prevents renal osteodystraphy. However, the isolation of this metabolite, as well as other metabolites (3-6) is a tedious process and furnishes only minute quantities of material. Accordingly, studies on the production of these substances by total synthesis have been intensive.[4]



1 R_1-R_4=H
2 R_1=R_4=OH, R_2=R_3=H
3 R_1-R_3=H, R_4=OH
4 R_1=R_2=H, R_3=R_4=OH
5 R_1=R_3=R_4=OH, R_2=H
6 R_2=R_4=OH, R_1=R_3=H

The most obvious convergent approach to the synthesis of these substances requires the development of methodology for (a) elaboration of the acyclic side chain,[4,5] (b) the A-ring,[4,6] and (c) a suitable CD hydrindane derivative for the attachment of the former moieties. Since all three components incorporate one or more chiral centers it is essential that each be manufactured in enantiomerically-pure form to avoid complex mixtures of diastereomers. This paper outlines an approach to the hydrindane portion of the molecule in which the crucial question of chirality is addressed. It should be noted that this portion of the molecule

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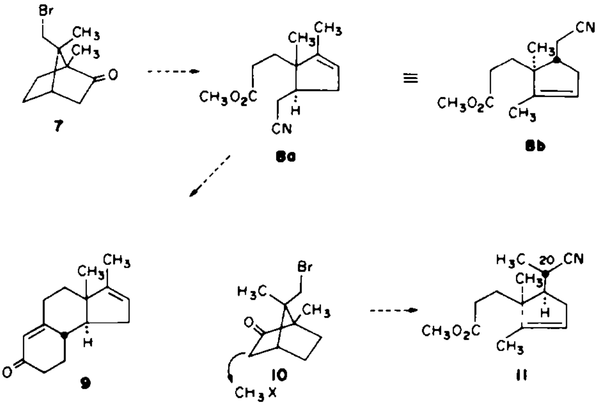
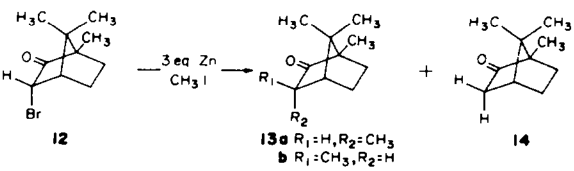
contains four contiguous chiral centers. Of these, the acyclic center at C-20 is potentially the most difficult to control. In the preceeding paper[7] we disclosed an enantiospecific synthesis of the tricyclic steroid intermediate 9 from laevorotatory 9-bromocamphor (7). During the course of that investigation it occurred to us that one of the intermediates (8a) when rotated within the plane of the paper (cf. 8b) has certain structural features in common with the vitamin. Furthermore, the chiral centers at C-13 and C-17 (steroid numbering) are established in the correct *relative* configuration. In order to establish them in the correct *absolute* sense as well simply required employment of readily available dextrorotatory 9-bromocamophor (10). Finally, it was noted that the potentially difficult asymmetric center at C-20 (*cf.* 11) is derived from the C-3 position of camphor. Accordingly, *endo*-methylation of 10 would provide an unambiguous method for establishing this potentially troublesome center stereospecifically.[8]

Diagram I



Since 3,9-dibromocamphor (15)[9] is an obligatory intermediate in the synthesis of chirally pure 9-bromocamphor (10) it occurred to us that reductive alkylation of 15 to afford 16 might be an expeditious method for incorporating the requisite methyl group and chirality associated with C-20. To our knowledge this reaction has not been reported for any camphor derivative. Therefore, we selected commercially available 3-bromocamphor (12) as a suitable model. Spencer *et al.* have reported[10] that zinc enolates, derived from the corresponding α-bromoketone, can be alkylated *in situ* with alkyl halides. When *d*-3-bromocamphor (12) was subjected to the reported conditions the predominant product was camphor (14, see Diagram II, run 1). However, manipulation of solvent polarity (run 3) and an increase in methyl iodide concentration (runs 2 and 4) provided more encouraging results. An acceptable ratio of 3-methylcamphor to camphor (*exo* and *endo* isomers 13a,b) was achieved eventually when the reaction mixture was heated to 60 °C in a pressure bottle (run 6).

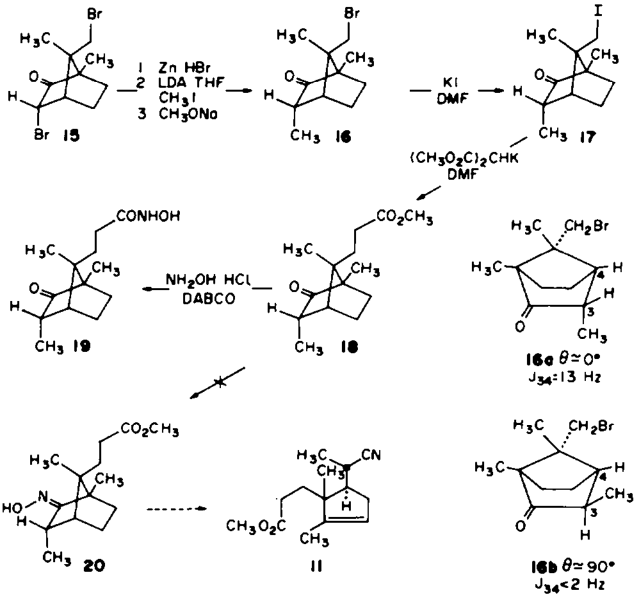
Diagram II



	Conditions				Products-glc	
Run	C_6H_6	DMSO	CH_3I equiv	Temp °C	13	14
1	10	1	2	rt	10	90
2	10	1	14	rt	41	59
3	1	1	10	rt	48	52
4	3	1	20	rt	48	52
5	0	100	10	rt	0	100
6	10	1	20	60	95	5

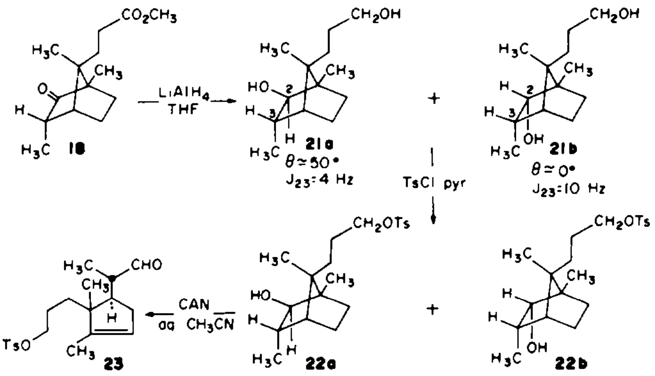
Armed with these encouraging results we turned our attention to 3,9-dibromocamphor (15). Reductive alkylation of this substance employing activated zinc[11] gave variable results depending on the particular batch of zinc. The ratio of alkylated to unalkylated ketone (16 to 10) varied from 6:1 to 1:1. A more reliable procedure was eventually developed which involved first selective debromination of 15 to 10. Treatment of 10 with lithium diisopropylamide in tetrahydrofuran at -78 °C followed by quenching of the resultant enolate with methyl iodide provided a 10:1 ratio of 16 to 10. Although the yield for this reaction was not high (34%)[12], the high predominance of alkylated material was reproducible. Accordingly, this procedure was generally employed. As noted above, the stereochemistry of the methyl group must be endo in order to correspond to the natural stereochemistry at C-20 in the vitamin. In fact, ^{1}H NMR revealed that the alkylated material was a mixture of both endo and exo isomers favoring the latter (16a:16b, 1:2). Homonuclear decoupling of the protons of the C-3 methyl group allowed observation of the coupling constant between the protons attached directly to C-3 and C-4. The dihedral angle (Θ) between the CH bonds is approximately 0° in 16a and 90° in 16b. The observed coupling constants correspond well to that predicted by the Karplus equation.[13] Fortunately, treatment of the endo-exo mixture with sodium methoxide in methanol provided the pure endo-isomer (16a) in quantitative yield. Homologation of 16 to 18 was accomplished by the same procedure developed previously[7] and proceeded in good overall yield (66%). The integrity of the endo-stereochemistry at C-3 throughout this process was verified by ^{1}H NMR as discussed above. The next stage of the planned synthesis required conversion of 18 to the corresponding oxime 20 for Beckman fragmentation to 11. Unfortunately, 18 failed to react with hydroxylamine under the usual conditions. Under forcing conditions 18 underwent reaction at the ester site to afford 19. Accordingly, our strategy had to be modified.

Diagram III



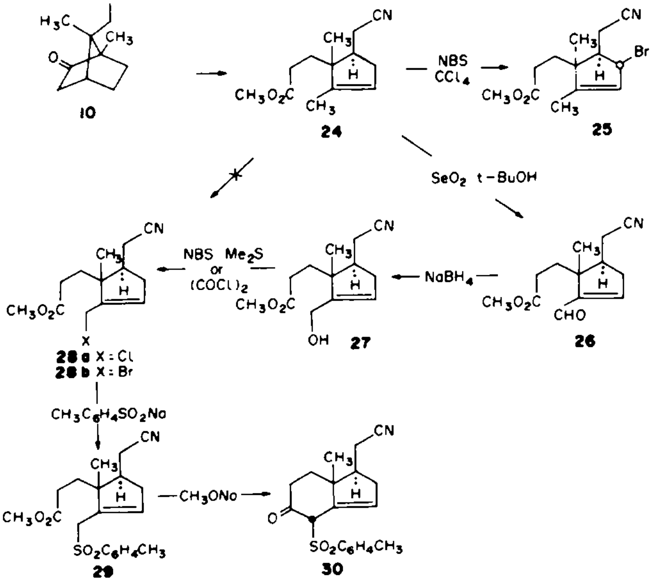
Reduction of ketoester 18 with lithium aluminum hydride provided a 1:1 mixture of exo and endo diols 21a and 21b in 96% yield. The stereochemistry of each isomer was easily confirmed from its ^{1}H NMR spectrum. The coupling constant between the protons attached to C-2 and C-3 was found to be 4 Hz for 21a (50° dihedral angle) and 10 Hz for 21b (0° dihedral angle). Interestingly, when lithium borohydride in diglyme was employed as the reducing agent only the exo-alcohol (21a) was produced. The mixture of diols was converted to the corresponding p-toluenesulfonate esters (22a, b) and fragmented with ceric ammonium nitrate[14] in aqueous acetonitrile at 0° to afford aldehyde 23 in 82% yield. The complete absence of epimerization during this fragmentation process was demonstrated by ^{1}H NMR spectroscopy. The aldehyde proton of pure 23 appears as a sharp doublet at δ 9.55. When the sequence deliniated in Diagram IV was repeated with an epimeric mixture at C-3, two aldehyde doublets were observed. Thus, a method has been developed which insures the proper relative and absolute stereochemistry at all three contiguous asymmetric centers.

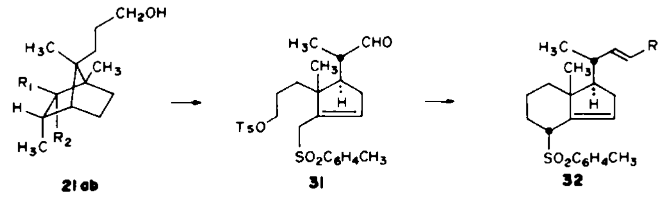
Diagram IV



Encouraged by these results, we next focused our attention on developing a method for the elaboration of the hydrindane system. For this purpose we selected the somewhat less complicated cyanoester 24 derived from dextrorotatory 9-bromocamphor 10 by the same procedure established previously in the laevorotatory series.[7] The direct conversion of 24 to 28b was attempted with N-bromosuccinimide. However, the only products isolated were the epimeric mixtures of bromides 25. On the other hand 24 could be oxidized regiospecifically with selenium dioxide to afford the unstable aldehyde 26 which was reduced immediately with sodium borohydride to the allylic alcohol 27. The latter substance was converted to the bromide 28b with N-bromosuccinimide and dimethylsulfide in dimethylformamide[15] in 70% yield. A higher yield (96%) of allylic chloride (28a) was obtained when 27 was exposed to oxalyl chloride in dimethylformamide. Displacement of the chloride with sodium *p*-toluenesulfinate proceeded smoothly in dimethylformamide to provide the sulfone 29 in 83% yield. The desired hydrindanone 30 was obtained by treating 29 with two equivalents of sodium methoxide in benzene-methanol

Diagram V





solution. Thus, an efficient method for construction of the hydrindane moiety has been established. These two studies establish a clear pathway (*cf.* 21a,b to 31 to 32) for an enantiospecific total synthesis of vitamin D_3 (1) and its medicinally important metabolites (2-6).

Experimental Section

^1H NMR spectra were measured at 200 MHz on a Bruker WP-200 spectrometer. ^{13}C NMR spectra were measured at 22.5 MHz on a Jeol FX 900 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Infrared spectra were recorded on a Beckman 4210 spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were recorded on an AEI-MS9 mass spectrometer. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are corrected.

All solvents were purified before use: ethyl ether, tetrahydrofuran, and benzene were distilled from sodium benzophenone ketyl; diisopropylamine was distilled from calcium hydride, methanol was distilled from magnesium metal. Dimethylformamide was percolated through 3 Å molecular sieves. Trifluoroacetic acid and trifluoroacetic anhydride were distilled from phosphorous pentoxide.

Medium pressure liquid chromatography was performed with Altex equipment using E. Merck silica gel (particle size 0.040 - 0.063 mm). High performance liquid chromatography was performed on a Waters Associates Prep LC/System 500. All chromatography solvents were distilled prior to use.

(+)-3-Methyl-9-bromocamphor (16a and b).

Method A. In an oven dried pressure bottle (magnetic stirring bar, Ar atmosphere) were placed 3,9-dibromocamphor[9] (4.63 g, 0.015 mol), benzene (30 mL), DMSO (3 mL), CH_3I (18.6 mL, 0.21 mol), and activated zinc dust[11] (3 g, 0.046 g-atoms). The mixture was heated to 60 °C for 11 hr and then allowed to cool to room temperature. The reaction mixture was then filtered, washed successively with water and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure provided an 85:15 mixture of 3-methyl-9-bromocamphor:9-bromocamphor. These compounds were separated, as indicated in Method B, to furnish (+)-3-methyl-9-bromocamphor as a mixture of *endo* and *exo* isomers (2.75 g, 75% yield).

Method B. THF (500mL) and *i*-Pr_2NH (33.1 mL, 0.216 mol) were placed in a 1 L three neck round-bottomed flask (flame dried, magnetic stirring bar, addition funnel, N_2). The solution was cooled to -78 °C and 88.5 mL of 2.45 M n-BuLi/hexane solution added dropwise. A solution of 9-bromocamphor[9] (50 g, 0.206 mol) in THF (72 mL) was placed in the addition funnel and added dropwise over a period of 0.33 hr. The reaction mixture was allowed to stir for an additional 0.33 hr. A solution of CH_3I (108 mL, 1.73 mol) in THF (100 mL) was placed in the addition funnel and added dropwise over a period of 0.33 hr. After the addition was complete, the reaction vessel was allowed to warm to room temperature. Upon warming the solution became yellow in color and then orange. Finally, upon reaching room temperature a precipitate formed (LiI). Gas-liquid chromatography on OV-101 at 160 °C indicated a 10:1 predominance of the alkylated:unalkylated material. The reaction mixture was filtered and the precipitate washed thoroughly with THF. The organics were combined and the solvent removed under reduced pressure. The solid product was purified via HPLC using 10% ethylacetate/hexane as the solvent. The chromatography provided (+)-3-methyl-9-bromocamphor (18.15 g, 34% yield) as a 2:1 mixture of *exo*:*endo* C-3 methyl isomers. ^1H NMR ($CDCl_3$) δ 3.20-3.75 (q, CH_2Br, *endo* isomer), 3.10-3.65 (q, CH_2Br, *exo* isomer), 2.30-2.55 (m, CHC=O, *endo* isomer), 1.90-2.25 (m, CHC=O, *exo* isomer), 1.05-1.15 (d, CH_3, *endo* isomer), 1.20-1.28 (d, CH_3, *exo* isomer).

(+)-3-Methyl-9-bromocamphor (16)

Methanol (50 mL) and small chunks of sodium metal (0.5 g) were placed in a 100 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, N_2 atmosphere). After the sodium metal had completely reacted, the *exo-endo* mixture of the title compound (245 mg, 1 mmol) was added and stirred at room temperature for 24 hr. The solvent was removed under reduced pressure and the residue taken up in ether. The organic layer was washed successively with water and brine and then dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the *endo* isomer of (+)-3-methyl-9-bromocamphor in quantitative yield. mp, 97-99 °C; IR (CCl_4) 1740, 1450, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.2-3.75 (q, 2H, CH_2Br), 2.3-2.5 (m, 1H, CHC=O), 1.2-1.9 (m, 5H), 1.08-1.15 (d, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 219.9, 59.2, 50.5, 46.1, 43.7, 39.9, 30.6, 19.4, 16.6, 11.8, 9.9; mass spectrum observed m/e = 244.0464, calculated for $C_{11}H_{17}O^{79}Br$ = 244.0463, $[\alpha]_D^{25}$ = 54.3° (C = 0.1, $CHCl_3$).

(+)-3-Methyl-9-iodocamphor (17)

Dry pulverized KI (61 g, 0.36 mol) in 220 mL DMF was placed into a 500 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, condenser, addition funnel, N_2 atmosphere). The reaction mixture was heated to 100 °C and a clear yellow solution resulted. Bromide 12a (18.2 g, 0.74 mol) in DMF (20 mL) was placed in the addition funnel and added fairly rapidly to the reaction vessel. After 6 hr an additional 5 g of KI (0.03 mol) was added. After a total of 12 hr the reaction mixture was cooled to room temperature and poured into a separatory funnel containing 200 mL of water. The remaining solid in the reaction vessel was dissolved with additional water and added to the separatory funnel. The aqueous mixture was extracted three times with petroleum ether, the organic layers combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide 20.65 g (95.8%) of endo (+)-3-methyl-9-iodocamphor. mp, 112-114 °C; IR (CCl_4) 1740, 1450, 1374-1385 cm^{-1}, ^1H NMR ($CDCl_3$) 3.02-3.54 (q, 2H, CH_2I), 2.20-2.50 (m, 1H, CHC=O), 1.18-1.75 (m, 5H), 1.05-1.15 (d, 3H, CH_3), 1.0 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 220.4, 58.4, 49.8, 48.2, 43.9, 30.5, 19.6, 18.0, 16.0, 11.8, 9.8; mass spectrum observed m/e = 292.0331, calculated for $C_{11}H_{17}OI$ = 292.0325; $[\alpha]_D^{25}$ = 52.5° (C = 0.1, $CHCl_3$).

(+)-Ketoester (18)

Into a 2 L three neck round-bottomed flask (flame dried, condenser, overhead mechanical stirrer, Ar atmosphere) was placed KH (25 g, 0.265 mol), the oil being previously decanted. The KH was freed of the remaining oil by washing with 4 x 150 mL of 20-40 petroleum ether. Anhydrous ether (800 mL) was then added followed by the addition of freshly distilled dimethyl malonate (100 g, 0.76 mol) via syringe pump over a 2 hr period. The resultant suspension was heated to reflux for 2 hr and then approximately 600 mL of ether distilled off. DMF (400 mL) was then added to the reaction mixture and the temperature raised to remove the remaining ether. Upon addition of DMF the reaction mixture became homogeneous. Then (+)-3-methyl-9-iodocamphor (17.0 g, 0.058 mol) in DMF (25 mL) was added and the reaction temperature raised to 130 °C. After 24 hr, KI (20 g, 0.12 mol) and water (1 mL - dropwise) were added successively to the reaction vessel. The temperature was raised to 140 °C to effect complete decarbomethoxylation. After 24 hr the reaction mixture was cooled to room temperature. Water (10 mL) was carefully added and then most of the volatile material (DMF, dimethylmalonate) removed via high vacuum rotary evaporation. The resultant residue was taken up in 300 mL of water and, with vigorous stirring, carefully acidified to pH 3 with concentrated hydrochloric acid. The acidified residue was continuously extracted for 48 hr with 20-40 petroleum ether. The extract was washed once with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a yellow oil which was dissolved in a small amount of petroleum ether and filtered through 25 g of basic alumina. Removal of the solvent and distillation of the resultant oil under high vacuum provided the ketoester 18 (9.84 g, 68.4%) as a solid. mp, 41-43 °C; IR (CCl_4) 1738, 1440, 1370, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, CO_2CH_3), 2.3-2.5 (m, 1H, CHC=O), 1.25-2.15 (m, 9H), 1.05-1.15 (d, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 221.2, 174.3, 59.4, 51.7, 48.2, 45.1, 43.8, 30.8, 28.9, 27.5, 19.7, 16.7, 11.8, 9.7; mass spectrum observed m/e = 238.1582, calculated for $C_{14}H_{22}O_3$ = 238.1570; $[\alpha]_D^{25}$ = 28.6° (C = 0.1, $CHCl_3$).

Diols (21a and 21b)

Lithium aluminum hydride (0.38 g, 10.0 mmol) and THF (10.0 mL) were placed in a 25 mL three neck round-bottomed (flame dried, efficient magnetic stirring bar, N_2 atmosphere). Ketoester 18 (1.0 g, 4.2 mmol) in THF (5 mL) was added to the reaction mixture via syringe. An exothermic reaction ensued. After 24 hr at room temperature the reaction mixture was quenched with the successive addition of water (0.38 mL), 15% NaOH (0.38 mL), and water (1.1 mL). The mixture was filtered and the recovered precipitate was washed several times with ether. The combined organics were dried (Na_2SO_4) and the solvents removed under reduced pressure to furnish a mixture of endo and exo alcohols 21a,b in 94.3% yield. (0.89 g). mp, 109-112 °C; IR (nujol mull) 3100-3500, 1000-1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85-3.95 (d), 3.60-3.75 (t), 3.05-3.10 (d), 1.20-2.40 (m), 1.10 (s), 1.08 (s), 1.05 (s), 0.9 (s), 0.85 (s), 0.83 (s); ^{13}C NMR ($CDCl_3$) δ 88.2, 88.1, 68.0, 64.0; mass spectrum observed m/e = 153.1263, calculated for $C_{13}H_{24}O_2 - C_3H_7O$ = 153.1280.

Tosylates (22a and 22b)

The diols 21a, b (0.212 g, 1.1 mmol) and pyridine (10 mL) were placed in a 25 mL round-bottomed flask (oven dried, magnetic stirring bar). The reaction vessel was stoppered and cooled to 4 °C. Freshly recrystallized toluenesulfonyl chloride (0.209 g, 1.1 mmol) was then added with stirring to the pyridine solution. The reaction mixture was allowed to stand for 48 hr at 4 °C and then poured into 25 mL of 10% aqueous hydrochloric acid. The aqueous mixture was extracted with 3 x 15 mL of ether. The combined ether layers were washed with brine, dried (Na_2SO_4), and removed via rotary evaporation. Thin layer chromatography revealed a major spot which was UV active (40% ethylacetate/hexane). There were also three products of higher R_f. This mixture was separated by medium pressure liquid chromatography to furnish the tosylates 22a,b in 50% yield (0.183 g) as an oil. IR (CCl_4) 3400-3600, 1375, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.80 (dd, 4H, aromatic H), 3.90-4.0 (t, 2H, CH_2OTs), 2.95-3.00 (d, 1H, CHOH), 2.38 (s, 3H, aromatic CH_3), 1.0-2.05 (m, 10H), 0.95-1.0 (d, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.81 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.8, 133.5, 130.0, 128.1, 88.1, 71.9, 51.0, 50.5, 47.1, 42.6, 34.6, 29.9, 24.8, 21.8, 19.6, 16.3, 15.7, 11.7; mass spectrum observed m/e = 366.1882, calculated for $C_{20}H_{30}O_4{}^{32}S$ = 366.1866.

Aldehyde (23)

The tosylate 22 (40 mg, 0.11 mmol), acetonitrile (2.0 mL), and water (2.0 mL) were placed in a 10 mL round-bottomed flask (magnetic stirring bar) and cooled to 0 °C. Ceric ammonium nitrate (152 mg, 0.28 mmol) and water (1.0 mL) were placed in a second round-bottomed flask and likewise cooled to 0 °C. The second solution was then added to the first in one portion. The reaction vessel was removed from the ice bath and then stirred for 10 minutes. The solution was then poured into a separatory funnel and extracted three times with ether. The combined ethereal layers were washed with brine , dried (Na_2SO_4), and removed via rotary evaporation to provide the aldehyde 23 (32.6 mg, 82.0% yield) as an oily solid. IR (CCl_4) 3040, 2700-2740 (fermi doublet), 1725, 1595, 1450, 1370, 1275, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.55 (d, 1H, HC=O), 7.28-7.78 (dd, 4H, aromatic H), 5.1-5.3 (m, 1H, vinyl H), 3.85-4.10 (broad t, 2H, CH_2OTs), 2.35

(s, 3H, aromatic CH_3), 1.1-2.35 (m, 11H), 1.05 (d, 3H, CH_3), 0.9 (s, 3H, CH_3); mass spectrum observed m/e = 172.0195, calculated for $C_{20}H_{28}O_4{}^{34}S - C_{13}H_{21}O$ = 172.0194.

Unsaturated aldehyde (26)

Cyanoester 24 (1.0 g, 4.52 mmol) and t-butanol (15 mL) were placed in a 25 mL three neck round-bottomed flask (magnetic stirring bar, condenser). This solution was heated to reflux and then four 150 mg portions of SeO_2 (5.41 mmol) were added over a period of 4 hr. The course of the reaction was monitored via gas-liquid chromatography (OV101, 200 °C). The selenium which precipitated was centrifuged off and the solvent evaporated *in vacuo*; 20 mL of benzene were added and the mixture centrifuged again. The benzene layer was extracted with hydrogen peroxide (30%, 3 x 5 mL) and evaporated *in vacuo* after drying (Na_2SO_4) to yield a dark oil, which was kugelrohr-distilled (0.003 mm, 135-145 °C). The unstable aldehyde 26 was isolated in 55% yield (0.58 g) as a yellow oil. It was not completely characterized at this stage; instead it was immediately reduced to the allylic alcohol 27.

Allylic alcohol (27)

The unsaturated aldehyde 26 (2.0 g, 9.2 mmol) and CH_3OH (35 mL) were placed into a 100 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, N_2 atmosphere). The reaction vessel was cooled to -30 °C and $NaBH_4$ (0.45 g, 11.9 mmol) was added in portions. The reaction mixture was then stirred for 0.75 hr and finally poured into a separatory funnel containing 50 mL of brine. The remaining precipitate in the reaction vessel was dissolved in additional water and this was added to the separatory funnel. Extraction was effected with ether (2 x 25 mL) and CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4), and removed via rotary evaporation to give a yellowish oil, which was kugelrohr-distilled to provide 1.85 g (92% yield) of the allylic alcohol 27 as an almost colorless oil. bp 155 °C (0.003 mm); IR (film) 3200-3600, 2250, 1735, 1650, 1440, 1370, 1200, 1025, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.69 (m, 1H, vinyl H), 4.12-4.15 (m, 2H, CH_2OH), 3.68 (s, 3H, CO_2CH_3), 1.78-2.75 (m, 9H), 1.0 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.2, 149.0, 124.6, 119.5, 59.2, 51.8, 49.7, 41.8, 35.9, 32.7, 29.8, 19.8, 18.3; mass spectrum observed m/e = 219.1259, calculated for $C_{13}H_{19}NO_3 - H_2O$ = 219.1270.

Allylic chloride (28a)

The allylic alcohol 27 (0.5 g, 2.11 mmol) and DMF (15 mL) were placed in a 50 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, N_2 atmosphere). The reaction mixture was cooled to 0 °C and oxalyl chloride (0.32 g, 2.5 mmol) slowly introduced via syringe. The reaction mixture was then warmed to room temperature. After 6 hr it was once again cooled to 0 °C and more oxalyl chloride (0.32 g, 2.5 mmol) added. The reaction vessel was allowed to reattain room temperature and after 3 hr was poured into a separatory funnel containing a three-fold volume excess of brine. This aqueous solution was extracted three times with ether, and then the combined ethereal layers were dried (Na_2SO_4) and removed *in vacuo* to yield allylic chloride 28a and starting material. These were separated via flash chromatography to yield 0.18 g of starting material and 0.33 g of allylic chloride 28a (95.6% based on consumed starting material). IR (film) 2240, 1740, 1640, 1435, 1370, 1200, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85-5.90 (m, 1H, vinyl H), 4.00-4.05 (m, 2H, CH_2Cl), 3.68 (s,3H, CO_2CH_3), 1.8-2.8 (m, 9H), 1.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.6, 144.8, 129.9, 119.2, 51.8, 50.3, 41.8, 39.8, 35.7, 32.5, 29.6, 19.9, 18.4; mass spectrum observed m/e = 219.1290, calculated for $C_{13}H_{18}NO_2Cl$ = 219.1260.

Allylic sulfone (29)

Allylic chloride 28a (0.255 g, 1.0 mmol), DMF (10 mL), and sodium p-toluenesulfinate (0.250 g, 1.4 mmol) were placed in a 25 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, N_2 atmosphere). The reaction mixture was heated to 70 °C for 13 hr, cooled, and poured into a separatory funnel containing 30 mL of brine. The aqueous phase was extracted with ether (3 x 15 mL), the organics combined, dried (Na_2SO_4), and removed *in vacuo* to furnish an oil. The oil was purified via medium pressure liquid chromatography using 15% ethylacetate/hexane as solvent. The desired allylic sulfone 29 was obtained in 83% yield (0.31 g) as a colorless oil. IR (film) 3020, 2250, 1735, 1595, 1495, 1450, 1320, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30-7.84 (dd, 4H, aromatic H), 5.95-6.02 (m, 1H, vinyl H), 3.55-3.90 (dd, 2H, CH_2SO_2), 3.66 (s, 3H, CO_2CH_3), 1.65-2.85 (m, 9H), 2.5 (s, 3H, aromatic CH_3), 0.85 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173, 145, 138, 137, 136, 135, 134, 55, 51; mass spectrum observed m/e = 345.1329, calculated for $C_{20}H_{25}O_4NS - CH_3O$ = 345.1316.

CD-bicycle (30)

The allylic sulfone 29 (0.15 g, 0.4 mmol), $NaOCH_3$ (0.043 g, 0.8 mmol), and benzene (15 mL) were placed into a 50 mL three neck round-bottomed flask (oven dried, magnetic stirring bar, condenser, N_2 atmosphere). The reaction mixture was heated to reflux and 5 mL of methanol was introduced. After 48 hr the reaction mixture was cooled to room temperature and extracted with water. The organic layer was dried (Na_2SO_4) and removed *in vacuo* to provide the desired CD-bicycle 30 as an oil. ^1H NMR ($CDCl_3$) δ 7.3-7.8 (dd, 4H, aromatic H), 6.0 (m, 1H, vinyl H), 5.8 (m, 1H, $CHSO_2$), absence of CO_2CH_3 noted; mass spectrum observed m/e = 343, observed for $C_{19}H_{21}NO_3S - C_7H_7O_2S$ (loss of toluenesulfonyl) m/e = 188.

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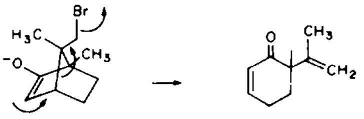

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