monitoring the growth of the 380-nm absorption at various concentrations of added $XC_6H_4CH_2Cl$.

Relative Rate Constants. A mixture containing 30 μL (0.261 M) of $C_6H_5CH_2Cl$, 30 μL (0.237 M) of $3\text{-}ClC_6H_4CH_2Cl$, and 0.019 g (0.109 M) of $Me_3CONNOCMe_3$ in 1.0 mL of Et_3SiH in a Pyrex tube was degassed, sealed under vacuum, and heated at 40 °C for 72 h (ca. 5 half-lives of the hyponitrite). The tube was opened, a known quantity of tetradecane was added as an internal standard, and the tube's contents were then analyzed by GC. Relative rate constants were calculated[17] from the quantities of the two reactants that were consumed. Similar competition experiments were carried out with $3\text{-}ClC_6H_4CH_2Cl$ and $3\text{-}CF_3C_6H_4CH_2Cl$, with $3\text{-}ClC_6H_4CH_2Cl$ and $3,5\text{-}(CF_3)_2C_6H_3CH_2Cl$, and with $3\text{-}CF_3C_6H_4CH_2Cl$ and $3,5\text{-}Cl_2C_6H_4CH_2Cl$.

Synthesis of the Enantiomers of *endo*-Brevicomin

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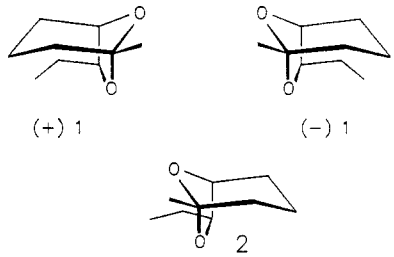
endo-Brevicomin (1) is a component of the volatiles of several economically important bark beetles in the genera *Dendroctonus* and *Dryocetes*.[1] In several species it is a minor component with undefined biological activity[1a,b] accompanying *exo*-brevicomin (2), which is often an aggregation pheromone.[2] Recently 1 has been reported to be an aggregation pheromone of *Dryocetes antographus*, a damaging pest of Norway spruce.[1c] Furthermore, (−)-1 has been reported to be an antiaggregation pheromone for the southern pine beetle *Dendroctonus frontalis*, while (+)-1 acts as to increase attractiveness of other known aggregation pheromones and kairomones (frontalin, *trans*-verbenol, and α-pinene) for this insect.[1e]



Because of the significant damage to pine caused by the southern pine beetle[3] in the southwestern U.S. and the potential for development of integrated pest management programs based on semiochemical technology,[4] we sought a synthesis of (+)- and (−)-1 that would be ammenable to the production of the (gram) quantities required for field evaluation of alternative strategies. Although many syntheses of (±)-1 have been reported,[5] only four syntheses of (+)- and (−)-1 are available. One synthesis involves threo-selective addition of Grignard reagents to chiral β-alkoxy aldehydes. This synthesis yields mixtures of 1 and 2 that must be separated by preparative gas chromatography.[6]

Two recent syntheses of (+)- and (−)-1 utilized Sharpless kinetic resolution of allylic alcohols. One involves a six-step (29% overall, 78.5% ee) route commencing with kinetic enantio- (90:10) and threo- (93:3) selective epoxidation of divinylcarbinol[7] while the second route proceeded in five steps (7% overall, 96–97% ee) from (±)-1-penten-3-ol. The higher chiral purity in the second route was achieved through crystallization of a key intermediate.[1c]

Most recently[8] the enantiomers of 1 have been prepared in high (>99% ee) enantiomeric purity and good chemical yield (60% over three steps) by a route used earlier[5i] that involves stereoselective cyclization of the ketal formed by reaction of 4-(phenylsulfonyl)-2-butanone and *erythro*-1-bromopentane-2,3-diol. The latter intermediate was available in enantiomerically pure form from degradation of α-D-(+)-glucose over L-(+)-arabinose by multistep procedures.

The present route to (+)- and (−)-1 is based on our earlier synthesis (+)- and (−)-2[9] and does not involve any chromatographic separation. It involves seven steps and proceeds in an overall yield of 20% (Scheme I).

The synthesis commenced with protection of 5-bromo-2-pentanone[5a] (3) with 2,2-dimethyl-1,3-propanediol to give 4. The bromo ketal was chain-extended by reaction with the dianion of propargyl alcohol.[9] Lithium metal reduction to the desired *E* allylic alcohol, 5, was conducted without

(1) *endo*-Brevicomin. (a) Inactive component of frass of western pine beetle, *Dendroctonus brevicomis*. Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science (Washington, D.C.)* **1968**, *159*, 889–891. (b) Minor component of volatiles of mountain pine beetle, *Dendroctonus ponderosae*, and western balsam bark beetle, *Dryocetes confusus*. Schurig, V.; Weber, R.; Nicholson, G. J.; Oehlschlager, A. C.; Pierce, H. D., Jr.; Pierce, A. M.; Borden, J. H.; Ryker, L. C. *Naturwissenshaften* **1983**, *70*, 92–93. (c) Aggregation pheromone of *Dryocetes antographus*. Mori, K.; Sew, Y.-B. *Tetrahedron* **1985**, *41*, 3429–3431. (d) (±)-Antiaggregation pheromone for southern pine beetle, *Dendroctonus frontalis*. Vité, J. P.; Renwick, J. A. A. *Naturwissenschaften* **1971**, *7*, 578–582. (e) (−)-Antiaggregation pheromone and (+) aggregation pheromone for *D. frontalis*. Vité, J. P.; Billings, R. F.; Ware, C. W.; Mori, K. *Naturwissenschaften* **1985**, *72*, 99–100.

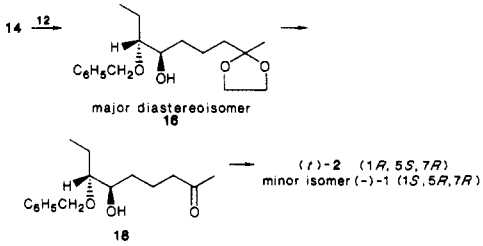
(2) Borden, J. H. "Aggregation Pheromones" in *Comprehensive Insect Physiology, Biochemistry and Pharmacology*; Kerkut, G. A., Gilbert, L. I., Eds.; Pergamon Press: 1985; Vol. 9, pp 257–285.

(3) In 1983 more than 10^8 ft^3 of timber was lost to *D. frontalis*. U.S. Forest Insect and Disease Conditions in the U.S. 1985, U.S.D.A Forest Service Report, 1985.

(4) Borden, J. H.; Conn, J. E.; Friskie, L. M.; Scott, B. E.; Chong, L. J.; Pierce, H. D., Jr.; Oehlschlager, A. C. *Can. J. For. Res.* **1983**, *13*, 325–333.

(5) (a) Bellas, T. E.; Brownlee, R. G.; Silverstein, R. M. *Tetrahedron* **1969**, *25*, 5149–5143. (b) Kocienski, P. J.; Ostrow, R. W. *J. Org. Chem.* **1976**, *41*, 398–400. (c) Look, J. *J. Chem. Ecol.* **1976**, *2*, 83–86. (d) Byrom, N. T.; Grigg, R.; Kongkathip, B. *J. Chem. Soc., Chem. Commun.* **1976**, 216–217. (e) Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1643–1653. (f) Mori, K. *Agric. Biol. Chem.* **1976**, *40*, 2499–2500. (g) Sum, P. E.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1475–1480. (h) Cohen, T.; Bhupathy, M. *Tetrahedron Lett.* **1983**, *24*, 4163–4164. (i) Meister, C.; Shen, Z.-P.; Scharf, H.-D. *Justus Liebigs Ann. Chem.* **1984**, 147–156. (j) Jatizac, M.; Amourux, R.; Chastrette, M. *Tetrahedron Lett.* **1985**, *26*, 2315–2316.

(6) Bernardi, R.; Fugani, C.; and Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021–4024. This paper erroneously illustrates erythro selectivity in addition of $ClMgCH_2CH_2(\overline{COCH_2CH_2O})CH_3$ (12) to an enantiomer of α-(benzyloxy)butyraldehyde while reporting the reaction is threo-selective. Structures 16 and 18 in this paper should be



Furthermore, as pointed out by a referee the recent statement made in the article by Yusufolgu et al. "According to our results, in the former synthesis (Bernardi, et al.) the sign of the optical rotation disagrees with the configuration of 5 (*endo*-brevicomins)". This statement is not correct. Bernardi et al. have numbered the usual C_1 as C_7 and the usual C_7 as C_1. That is the cause of confusion.

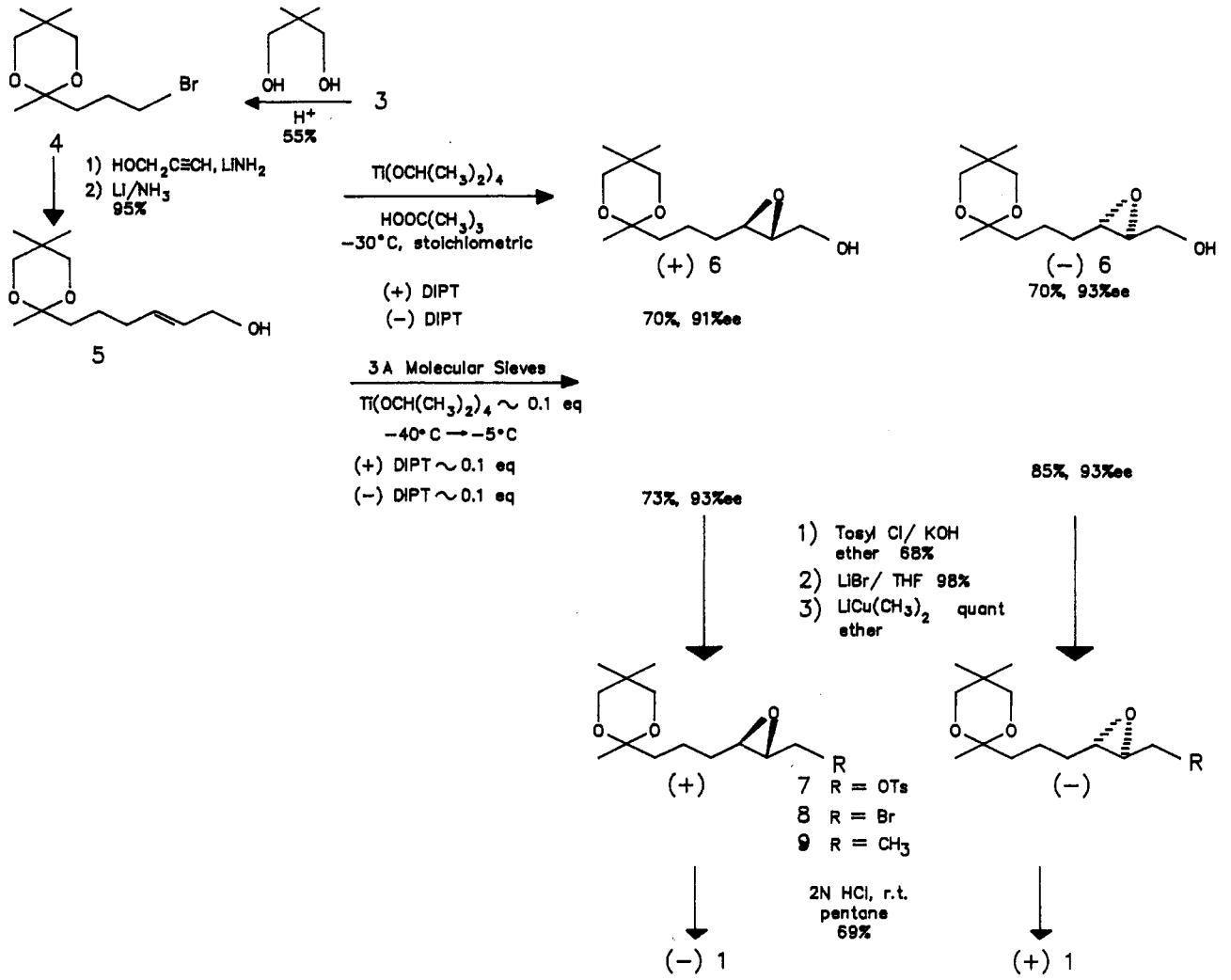
(7) Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759–1761.

(8) Yusufolgu, A.; Antons, S.; Scharf, H.-D. *J. Org. Chem.* **1986**, *51*, 3485–3487.

(9) Johnston, B. D.; Oehlschlager, A. C. *J. Org. Chem.* **1982**, *47*, 5384–5386.

0022-3263/87/1952-0940$01.50/0

Scheme I



isolation of the intermediate product.[10]

Sharpless asymmetric epoxidation of **5** using both the stoichiometric[11] method and the catalytic[12] method yielded the expected epoxy alcohol **6** in good yields. The enantiomeric excess determined by ^{1}H NMR analyses of the (*S*)-α-(trifluoromethyl)phenyl acetates[13] of **6** was in the range of 91–93% for both epoxidation methods. In our synthesis of (+)- and (−)-**2** we cyclized the analogue of **6** to a 7-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane prior to introduction of the methyl.[9] When this chemistry was carried out on **6**, we obtained a difficulty separable mixture of intramolecular ketals. We therefore converted **6** to the corresponding tosylate, **7**, and thence to the bromide, **8**, and methyl derivative, **9**,[9] prior to cyclization.

Cyclization of **9** in pentane with dilute HCl yielded (+)- and (−)-**1**. We calculate the enantiomeric excess of (+)-**1** to be 81.5% and that of (−)-**1** to be 83% based on the highest reported rotation for (+)- and (−)-**1**.[1c]

Experimental Section

NMR spectra were recorded on a Bruker WM400 spectrometer. Mass spectra were obtained by using a Hewlett-Packard 5985B GC/MS/DS system operating at 70 eV. Elemental analyses were performed by Mr. M. Yang at Simon Fraser University. GLC analyses were performed on a 0.21 mm i.d. × 30 mm SP2100 capillary column on a Hewlett-Packard 5880 gas chromatograph programmed to change the column temperature from 100 to 250 °C at 10°/min. Optical rotations were determined on a Perkin-Elmer P-22 spectropolarimeter (0.5-dm cell) and a Rudolph polarimeter Model 70 (1-dm cell).

Tetrahydrofuran (THF) and ether were distilled from lithium tetrahydridoaluminate immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored under argon over activated 3A molecular sieves.

Activation of crushed 3A molecular sieves involved heating in a vacuum oven at 160 °C and 0.05 mmHg pressure for at least 3 h. Diisopropyl tartrate was used as obtained from Aldrich Chemical Co. *tert*-Butyl hydroperoxide was made anhydrous by the procedures of ref 11 and 12.

2,5,5-Trimethyl-2-(3-bromopropyl)-1,3-dioxane (4). A mixture of 5-bromo-2-pentanone (**3**)[5c] (165 g, 1.00 mol), 2,2-dimethyl-1,3-propanediol (110 g, 1.06 mol), *p*-toluenesulfonic acid (2 g), and toluene (500 mL) was refluxed in an apparatus equipped with a Dean–Stark trap for 2.5 h. The cooled solution was washed with saturated $NaHCO_3$ solution (100 mL), water (2 × 100 mL), and saturated NaCl solution (100 mL). After drying (anhydrous $MgSO_4$), the solvent was removed in vacuo and the residue was distilled to yield **4** (139 g, 55%): bp 90–105 °C (0.05 mmHg); IR (neat film) 2960 (s), 2870 (s), 1474 (m), 1402 (m), 1398 (m), 1375 (m), 1298 (m), 1254 (s), 1217 (s), 1190 (m), 1115 (s), 1090 (m), 1044 (m), 1035 (m), 954 (m), 912 (m), 863 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 3.45 (2 H, CH_2Br, t, J = 7 Hz), 3.41 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 2.02 (2 H, CH_2, m), 1.81 (2 H, CH_2, m), 1.36 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.86

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(11) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
(12) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922–1925.
(13) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 237/235 (20, $M^+ - CH_3$), 167/165 (20), 151/149 (23), 129 (100), 85 (15), 69 (87), 56 (48), 43 (60), 41 (34); CI (isobutane) 253/251 (100, $M^+ + 1$), 171 (38), 167/165 (20), 129 (47). Anal. Calcd for $C_{10}H_{19}O_2Br$: C, 47.82; H, 7.62. Found: C, 47.88; H, 7.73.

2,5,5-Trimethyl-2-(6-hydroxy-(*E*)-4-hexenyl)-1,3-dioxane (5). Propargyl alcohol (23.0 mL, 0.40 mol) in anhydrous THF (100 mL) was added dropwise to a suspension of $LiNH_2$ (0.80 mol) in liquid NH_3 (650 mL). The reaction mixture was refluxed under a dry ice condensor for 1 h. A solution of bromide **4** (75.3 g 0.30 mol) in dry THF (100 mL) was added dropwise over 0.5 h. After a further 0.5 h, lithium metal (4.6 g 0.66 mol) was added in small portions over 0.5 h. The dark blue solution was allowed to warm to ambient temperature overnight while the NH_3 evaporated. The semisolid residue was added to ice water (800 mL) and extracted with ether (3 × 300 mL). The combined extracts were dried (anhydrous $MgSO_4$) and concentrated in vacuo. Distillation yielded **5** (65.3 g, 95%): bp 118–123 °C (0.03 mmHg); IR (neat film) 3425 (m), 2995 (m), 2960 (s), 2890 (s), 1674 (w), 1480 (m), 1467 (m), 1402 (m), 1378 (m), 1262 (m), 1247 (m), 1218 (m), 1195 (m), 1123 (m), 1093 (s), 1048 (m), 1020 (m), 977 (m), 960 (m), 915 (m), 854 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (2 H, vinyl H, m), 4.07 (2 H, —C=CCH_2O—, t, *J* = 5 Hz), 3.54 (2 H, OCH, d, J_{AB} = 11.5 Hz), 3.41 (2 H, OCH, d, J_{AB} = 11.5 Hz), 2.07 (2 H, allylic CH_2, m), 1.66 (2 H, CH_2, m), 1.51 (2 H, CH_2, m), 1.35 (3 H, CH_3, s), 1.01 (3 H, CH_3, s), 0.87 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 213 (18, $M^+ - CH_3$), 129 (100), 109 (13), 81 (24), 69 (56), 67 (16), 43 (38); CI (isobutane) 229 (52, $M^+ + 1$, 211 (83), 129 (35), 125 (100), 109 (37). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.09; H, 10.88.

2,5,5-Trimethyl-2-(6-hydroxy-4,5-epoxyhexanyl)-1,3-dioxane (6). Method A. Stoichiometric Sharpless Asymmetric Epoxidation.[11] A solution of titanium tetraisopropoxide (14.2 g, 50 mmol) in anhydrous CH_2Cl_2 (300 mL) was cooled to <–30 °C. (+)-Diisopropyl L-tartrate (12.9 g, 55 mmol) in CH_2Cl_2 (50 mL) was added. After 10 min, alkene **5** (10.0 g, 44 mmol) was added, followed in another 10 min by a 3.3 M anhydrous toluene solution of *tert*-butyl hydroperoxide in toluene (30 mL, 100 mmol). After 6 h at –30 °C, GC analysis of a sample showed the absence of starting material. Standard workup and purification by flash chromatography (hexane/ethyl acetate, 1:3) yielded (–)-**6** (7.5 g, 70%): $[\alpha]^{25}_D$ –13.4° (*c* 3.0, EtOH); IR (neat film) 3425 (br) 2960 (s), 2890 (m), 1465 (m), 1398 (m), 1377 (m), 1258 (m), 1216 (m), 1195 (m), 1094 (s), 1044 (m), 1026 (m), 956 (m), 912 (m), 860 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (1 H, C=CCHO, dd, J_{AB} = 12.5 Hz, J_{vic} = 2.5 Hz), 3.61 (1 H, C=CCH'O, dd, J_{AB} = 12.5 Hz, J_{vic} = 4.3 Hz), 3.56 (2 H, 2-OCH, d, J_{gem} = 11 Hz), 3.40 (2 H, 2-OCH, d, J_{gem} = 11 Hz), 2.93 (2 H, epoxide OCH, m), 1.70 (2 H, CH_2, m), 1.59 (5 H, 2-CH_2 plus OH, m), 1.35 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.86 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 229 (27, $M^+ - CH_3$), 129 (100), 99 (11), 97 (13), 83 (11), 81 (19), 71 (17), 69 (64), 56 (15), 55 (17), 43 (41), 41 (16); CI (isobutane) 245 (47, $M^+ + 1$), 159 (52), 141 (100), 129 (43), 123 (36). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.61; H, 10.20.

Method B. Catalytic Sharpless Asymmetric Epoxidation.[12] Powdered 3A molecular seives (5 g) were activated by gentle heating with a flame under high vacuum (<0.1 mmHg). After cooling, anhydrous CH_2Cl_2 (250 mL) was added and the mixture was stirred while cooling to –40 °C. Sequential additions of (+)-diisopropyl tartrate (4.0 g, 17 mmol), titanium tetraisopropoxide (4.0 mL, 13.4 mmol), and anhydrous *t*-BuOOH in CH_2Cl_2 (50 mL of 4 M solution) were made. After stirring for 20 min at –30 °C to –40 °C, allylic alcohol **5** (30.0 g, 123 mmol) was added. The temperature was allowed to slowly rise to –10 °C over 1.5 h and the cooling bath was switched to an ice/salt bath. The reaction mixture was stirred at –8 °C to –5 °C for a further 2 h. The reaction was quenched by the addition of tartaric acid (8.0 g) in water (40 mL). After 15 min of vigorous stirring, the mixture was filtered with suction and the aqueous phase further extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 extracts were washed with saturated NaCl solution (50 mL), dried over anhydrous $MgSO_4$, and concentrated on a rotary evaporator. Excess *t*-BuOOH was removed under high vacuum (<0.5 mmHg) at 50–60 °C. The residue was distilled to yield (–)-**6** (29.6 g): bp 135–150 °C (0.03 mmHg). This material was analyzed by GC to be ~90% pure, making the yield ~85%. An analytical sample was obtained by flash chromatography on silica gel (hexane/ethyl acetate, 1:3) and exhibited the same spectral characteristics as (–)-**6** from the stoichiometric method.

Similar stoichiometric and catalytic reactions using (–)-DIPT as the chiral auxilliary gave (+)-**6** ($[\alpha]^{25}_D$ +13.2° (*c* 2.7, EtOH)) in yields of 70% and 73%, respectively.

The preparation of (+)-α-methoxy(trifluoromethyl)phenylacetate ((+)-MTPA esters) of (–)-**6** and (+)-**6** by the published method[13] and analysis by ^1H NMR integration of the low field differentially shifted ($\Delta\delta$ = 0.05 ppm) diastereotopic -CHOMTPA signals gave the enantiomeric excess (ee) values indicated in the text.

2,5,5-Trimethyl-2-[6-(tosyloxy)-4,5-epoxyhexanyl]-1,3-dioxane (7). A solution of (–)-**6** (29.1 g, 119 mmol) in dry Et_2O (300 mL) was cooled with an ice/salt bath to <0 °C. *p*-Toluenesulfonyl chloride (23.0 g, 120 mmol) was added and the reaction mixture stirred vigorously while powdered KOH (12.0 g, 214 mmol) was added in small portions over 0.5 h. After 4 h the reaction mixture was poured into ice water (300 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined Et_2O extracts were washed with water (100 mL). Drying (anhydrous $MgSO_4$) and solvent removal yielded a colorless syrup which slowly crystallized. After two recrystallizations from hexane/EtOAc (10:1), (–)-**7** (32.1 g, 68%) was obtained as colorless crystals: mp 50–52 °C; $[\alpha]^{25}_D$ –22.7 ° (*c* 2.8, EtOH); IR (KBr pellet) 2995 (m), 2965 (m), 2940 (m), 2880 (m), 2865 (m), 1605 (w), 1483 (m), 1450 (m), 1400 (m), 1373 (s), 1270 (m), 1255 (m), 1218 (m), 1203 (s), 1188 (m), 1136 (m), 1104 (m), 980 (s), 970 (m), 878 (m), 846 (m), 825 (m), 677 (m), 563 (m), 520 (m), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, aromatic, d, *J* = 8 Hz), 7.34 (2 H, aromatic, d, *J* = 8 Hz), 4.18 (1 H, CHOTs, dd, J_{gem} = 11.3 Hz, J_{vic} = 3.7 Hz), 3.94 (1 H, CH'OTs, dd, J_{gem} = 11.3 Hz, J_{vic} = 5.9 Hz), 3.56 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 3.39 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 2.95 (1 H, epoxide H, m), 2.78 (1 H, epoxide H, m), 2.44 (3 H, tosyl CH_3, s), 1.65 (2 H, CH_2, m), 1.54 (4 H, 2-CH_2, m), 1.34 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.85 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 73 (60), 57 (35), 56 (100), 45 (25), 43 (40), 41 (30); CI (isobutane) 399 (100, $M^+ + 1$), 313 (90), 295 (47), 227 (20), 141 (35), 123 (20), 105 (15). Anal. Calcd for $C_{20}H_{30}O_6S$: C, 60.28; H, 7.59. Found: C, 60.38; H, 7.71.

A similar tosylation of (+)-**6** yielded (+)-**7** $[\alpha]^{25}_D$ +23.0° (*c*, 2.7, EtOH).

2,5,5-Trimethyl-2-(6-bromo-4,5-epoxyhexanyl)-1,3-dioxane (8). A mixture of (–)-**7** (30.0 g, 75.4 mmol) and LiBr (25.0 g, 288 mmol) in anhydrous THF (300 mL) was stirred at room temperature for 5 h and at 40–50 °C for 1 h. The THF was removed in vacuo and the residue partitioned between Et_2O (500 mL) and water (75 mL). The ether layer was washed with water (50 mL) and saturated NaCl solution (50 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo to give (–)-**8** as a colorless syrup (22.7 g, 98%). An analytical sample was obtained by bulb-to-bulb distillation: bp 120–130 °C (bath temperature) (0.05 mmHg); $[\alpha]^{25}_D$ –3.2° (*c* 2.2, Et_2O); IR (neat film) 2990 (s), 2975 (s), 2865 (s), 1460 (m), 1397 (m), 1373 (m), 1250 (m), 1214 (m), 1193 (m), 1100 (m), 1043 (m), 1022 (m), 955 (m), 910 (m), 857 (m), 655 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 3.42 (3 H, OCH and CHBr, m), 3.28 (1 H, epoxide H, dt, *J* = 2 Hz, 6 Hz), 2.86 (1 H, epoxide H, m), 1.71 (2 H, CH_2, m), 1.62 (4 H, 2-CH_2, m), 1.36 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.87 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 291/293 (10, $M^+ - CH_3$), 129 (100), 97 (17), 83 (23), 81 (20), 69 (67), 56 (22), 55 (24), 43 (48), 41 (20); CI (isobutane) 307/309 (65, $M^+ + 1$), 221/223 (50), 203/205 (55), 129 (100). Anal. Calcd for $C_{13}H_{23}O_3Br$: C, 50.82; H, 7.55. Found: C, 50.92; H, 7.80.

A similar reaction of (+)-**7** with LiBr yielded (+)-**8** $[\alpha]_D$ +2.9° (*c* 2.5, Et_2O).

2,5,5-Trimethyl-2-(4,5-epoxyheptanyl)-1,3-dioxane (9). An ether solution of $LiCuMe_2$ was prepared from CuI (19.0 g, 100 mmol) and MeLi (200 mmol). The light yellow solution (300 mL) was stirred with ice/salt bath cooling while (–)-**8** (22.2 g, 72.3 mmol) in Et_2O (50 mL) was added dropwise over 15 min. After a further 30 min, the reaction mixture was poured into cold saturated NH_4Cl solution (300 mL) and stirred for 30 min. The mixture was filtered and the aqueous phase extracted with Et_2O (3 × 100 mL). The combined ether extracts were dried (anhydrous

$MgSO_4/Na_2CO_3$) and the solvent was removed to give a near quantitative yield of (−)-**9**. An analytical sample was obtained by bulb-to-bulb distillation: bp 80–110 °C (bath temperature) (0.1 mmHg); $[\alpha]^{25}_D$ −22.9° (*c* 2.3, Et_2O); IR (neat film) 2960 (s), 2880 (s), 1465 (m), 1400 (m), 1378 (m), 1312 (m), 1260 (m), 1218 (m), 1100 (m), 1048 (m), 1027 (m), 962 (m), 916 (m), 901 (m), 867 (m), 828 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 3.42 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 2.65 (2 H, epoxide H, m), 1.71 (2 H, CH_2, m), 1.55 (4 H, 2-CH_2, m), 1.37 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.98 (3 H, CH_3, t, *J* = 7 Hz), 0.86 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 227 (12, $M^+ - CH_3$), 129 (100), 99 (15), 97 (10), 95 (13), 81 (15), 71 (17), 70 (10), 69 (55), 57 (15), 55 (13), 43 (38); CI (isobutane) 243 (53, $M^+ + 1$), 225 (14), 157 (62), 141 (18), 140 (10), 139 (100), 129 (35), 123 (12). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.64; H, 11.01.

A similar reaction of (+)-**8** with $LiCuMe_2$ yielded (+)-**9**: $[\alpha]^{25}_D$ +21.0° (*c* 2.2, Et_2O).

(+)-*endo*-Brevicomin (1). A solution of (−)-**9** (17.2 g, 71.1 mmol) in pentane (250 mL) was stirred with 2 N HCl (60 mL) for 16 h at room temperature. The organic phase was washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL). After drying (anhydrous $MgSO_4$) and removal of solvent on a rotary evaporator without heating, the residue was distilled to yield (+)-**1** (7.73 g, 69%): $[\alpha]^{25}_D$ +64.2° (*c* 2.3, Et_2O), lit.[5b] $[\alpha]^{21}_D$ +78.8° (*c* 0.5, Et_2O), lit.[5c] $[\alpha]^{25}_D$ −65.4° (*c* 2.1, Et_2O).

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On the Deuterium Thermodynamic Isotope Effect on the Equilibration of 2-Cyclohexenol-α-*d* and 2-Cyclohexenol-γ-*d*

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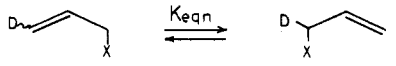
In connection with other work we needed to know the equilibrium distribution of a deuterium label for equilibration of allylic-α-*d* and -γ-*d* derivatives (eq 1) in systems

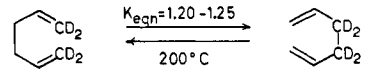


(1)

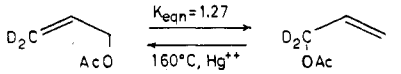
in which the rearrangement is degenerate except for the deuterium label. In such systems the equilibrium constant is the so-called[1] deuterium thermodynamic isotope effect (TIE) as shown by eq 2.

$$K_{eqn} = sp^3\alpha\text{-}d/sp^2\gamma\text{-}d = \text{TIE} \quad (2)$$

Deuterium isotope effects have been reported for equilibration of 1,1,6,6- and 3,3,4,4-tetradeuterio-1,5-hexadiene (eq 3)[1] and 1,1- and 3,3-dideuterioallyl acetate (eq 4).[2] However, these thermal equilibrations require higher temperatures than the range of interest to us, and isotope effects are complicated by the presence of more than one deuterium.

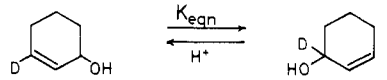


(3)



(4)

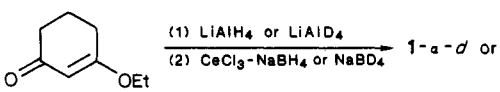
In this work we determined the equilibrium deuterium distribution for the acid-catalyzed ($HClO_4$) equilibration of 2-cyclohexenol-α-*d* and -γ-*d* (*1*) in aqueous acetone (eq 5). This equilibration was selected because from earlier



1-γ-*d* 1-α-*d* (5)

studies[3] it was known that the pseudo-first-order rates for such equilibrations are directly proportional to the acid concentration. Thus convenient rates can be arranged by adjusting acid concentration. Moreover, the equilibrium distribution can easily be determined for different temperatures because equilibration is quenched instantly by neutralization of the acid. Also, in this system the 1-α-*d*/1-γ-*d* ratio can readily be determined directly by ^2H NMR spectroscopy.[4]

The labeled alcohols 1-α-*d* and 1-γ-*d* were prepared from 3-ethoxy-2-cyclohexenone by a method similar to that reported earlier.[4] These preparations involve two hydride reductions (eq 6). The first gives 2-cyclohexenone (or



(6)

2-cyclohexenone-3-*d* and this is converted to 1-α-*d* or 1-γ-*d* by the second reduction. In this work we used sodium borohydride with cerium chloride[5] instead of lithium aluminum hydride for the second reduction. With lithium aluminum hydride the product contain 3–7% cyclohexanol (or deuteriated cyclohexanol) that results from conjugate addition to the enone. Conjugate addition is lowered to ~2% with the $CeCl_3$–$NaBH_4$ (or $NaHD_4$) reduction. Thus 1-α-*d* contained ~2% 1,3-dideuteriocyclohexanol. This saturated contaminant is inert under the conditions of the

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Table I. Equilibrium Studies of the Acid-Catalyzed Equilibrium of 2-Cyclohexenol-α-*d* and -γ-*d*

compd	% acetone[a]	temp °C	10^2-[$HClO_4$], M	k_{eqn},[b] h^{-1}	K_{eqn}[c]
1-α-*d*	35	30.2	9.51	0.298	1.17 ± 0.02
1-γ-*d*	35	30.2	9.51	0.310	1.17 ± 0.02
1-α-*d*	35	50.68	3.04	1.00	1.14 ± 0.02
1-γ-*d*	35	50.65	3.04	1.14	1.17 ± 0.02
1-γ-*d*	60	50.00	6.40	0.60	1.18 ± 0.02
1-γ-*d*	60	90.02	0.64	0.61	1.14 ± 0.02

[a] Solvent composition refers to volumes of pure components at room temperature prior to mixing. [b] Observed pseudo-first-order rate constants for equilibration. [c] Average and average deviation of three independent determinations of the equilibrium ratio of 1-α-*d*/1-γ-*d*.

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