Synthesis of Optically Active *endo,endo* Bicyclo[2.2.2]octane-2,5-diol, Bicyclo[2.2.2]octane-2,5-dione, and Related Compounds

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Optically active C_2-symmetric (1*S*,2*S*,4*S*,5*S*)-bicyclo[2.2.2]octane-2,5-diol ((+)-**12**; 98% ee) and several selectively protected optically active intermediates useful for synthetic transformations were synthesized via a 1,2-carbonyl transposition route starting from the easily available optically active (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one ((−)-**2**). The synthetic route also allowed the preparation of optically active (1*S*,4*S*)-bicyclo[2.2.2]octane-2,5-dione ((+)-**14**; 98% ee).

Optically pure derivatives of bicyclo[2.2.2]octane may have interesting applications in organic synthesis, e.g. for the construction of rigid template molecules suitable as mimics for various bioactive compounds and as scaffolds for placing the dents of ligands in well-defined relative positions in space. There are, however, surprisingly few reports of such compounds based on the bicyclo[2.2.2]octane system in the literature. Recently the bicyclo[2.2.2]octane system attracted interest as a structural unit suitable for application in combinatorial synthesis via tandem Michael addition reactions[1] of polymer-bound acrylates and cyclohexenones.[2]

The racemic diol (±)-**12** is in principle available by reduction of (±)-**14**,[3] but this reaction ($LiAlH_4$) resulted in a mixture of diastereomers, giving only a 7% yield of the *endo,endo* diol (±)-**12**.[4,5] Despite the low yield, this route was used for the preparation of (+)-**12** (23% yield, 84% ee) via enzymatic hydrolysis of its racemic diacetate followed by reductive deacetylation.[6,7] Transesterfication experiments with lipase YS on diol (±)-**12** did not improve the situation with the low ee's; the best result obtained for (+)-**12** was 21% ee in 31% chemical yield.[8] Enzymatic acetate hydrolysis has been used for the preparation also of (−)-**14** (25% yield, 21% ee).[7] The enzymatic results mentioned indicate that **14** would at best be synthesized with 84% ee if diol (+)-**12** were used as starting material.

Although (±)-**14** was reported already in 1939,[3] it was not until 1985 that optically pure (−)-**14** was prepared by Paquette et al.[9] The procedure used, which is a modification of that of Grob et al.,[5] gave unfortunately a low yield and involved several chromatographic separations, including separation of diastereomeric acetals. More recent work has shown that (±)-**14** is easily available via a Diels−Alder reaction of the lithium enolate of cyclohexenone and 2-(*N*-methylanilino)acrylonitrile[10] or 2-((trimethylsilyl)oxy)-1,3-cyclohexadiene and α-acetoxyacrylonitrile[11] and that (−)-**14** of high optical purity (94%) can be obtained via resolution of the corresponding olefinic dione **16** as an inclusion complex with (*S*)-(−)-10,10′-dihydroxy-9,9′-biphenanthryl, followed by catalytic hydrogenation of the double bond.[12]

It should also be noted that even if the resolution of the racemic diacid **17** gave optically active **17**, the subsequent decarboxylation resulted in complete racemization.[13] Thus, it is obviously a problem to synthesize ketone **14** and diol **12** or similar derivatives in optically pure form in quantities necessary for multistep synthesis or other applications. We here report a 1,2-carbonyl transposition route of (−)-**2** to give these and related compounds in reasonable yields and high enantiomeric purities.

Optically active (−)-**2** of high enantiomeric purity can be prepared by fermenting yeast reduction of **1**,[14] for which we previously described an improved synthesis.[15] Thus, compound (−)-**2** may be reproducibly prepared in multigram quantities and had generally an ee of >92%, which could be improved to 98% by recrystallization from ethyl acetate/heptane. The availability of (−)-**2** made a 1,2-carbonyl transposition route[16] to (+)-**12** and (+)-**14** feasible (Scheme 1). Protection of (−)-**2** as its *tert*-butyldimethylsilyl ether (+)-**3** followed by TMS−enol ether formation gave **4**, which was thiophenylated using phenylsulfenyl chloride[17] to give **5** as a 73:27 mixture of diastereomers. An inferior yield was obtained by using the alternative thiophenylation route *via* reaction of the lithium enolate of **3** with diphenyl disulfide. Subsequent reduction of **5** with sodium borohydride gave **6**, as a mixture of all four diastereomers, which was mesylated by treatment with mesyl anhydride and DMAP to give **7**. Mesyl anhydride[18] gave a much better yield here than

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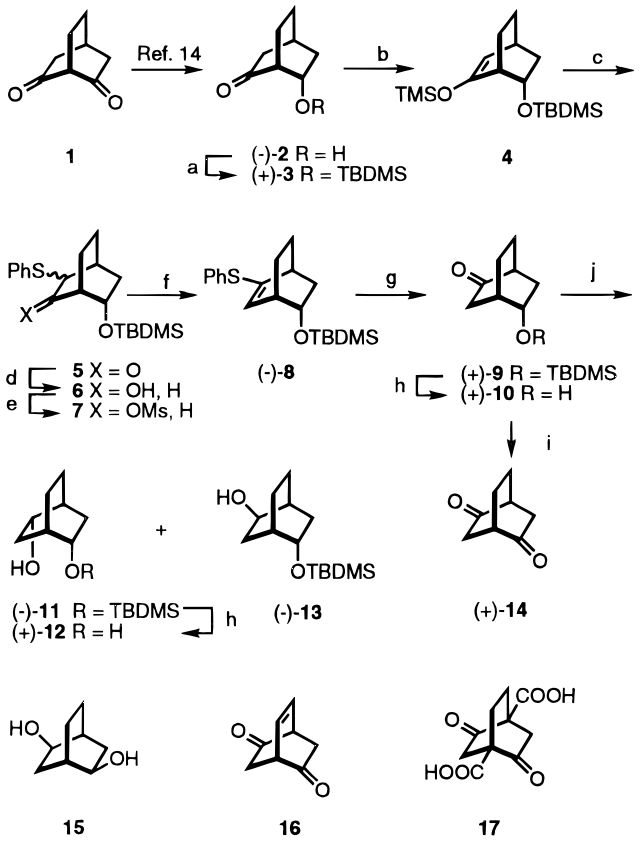
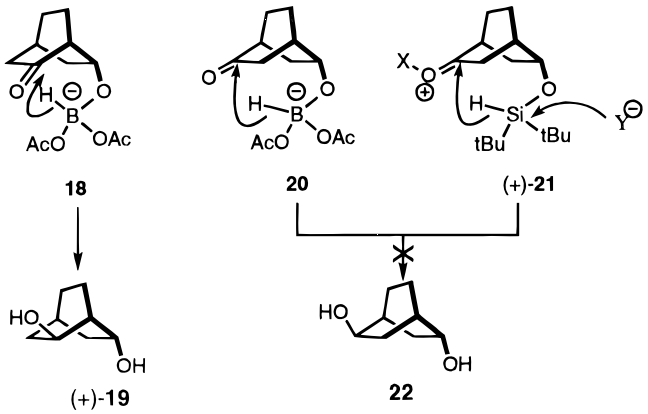
Scheme 1[a]



[a] Legend: (a) TBDMSCl, imidazole, DMF, 97%; (b) LDA, TMSCl, THF, −78 °C to room temperature; (c) PhSCl, CH_2Cl_2, −78 °C to room temperature; (d) $NaBH_4$, THF, MeOH, room temperature, 24 h; (e) $(MeSO_2)_2O$, DMAP, CH_2Cl_2, room temperature, 48 h; (f) KOtBu, DME, −30 °C to room temperature, 49% from (+)-**3**; (g) $Fe(NO_3)_3 \cdot 9H_2O$, Bentonite K-10, CH_2Cl_2, room temperature, 3 h, 93%; (h) Bu_4NF, 0 °C, room temperature, 3 h, 90%; (i) Swern oxidation, 98%; (j) DIBALH, 60% of (−)-**11**. The acronyms recommended for this journal are followed.

did mesyl chloride. Thioenol ether (−)-**8** was then obtained by elimination using KOtBu. The elimination was studied using GC analysis and showed that the major isomer was consumed at a higher rate than the other three isomers. Since a *syn* elimination should be faster than an *anti* elimination in rigid compounds,[19] this result indicates that the major isomer of **7** is (1*S*,2*S*,3*S*,4*R*,5*S*)-3-(mesyloxy)-2-(phenylsulfenyl)-5-((*tert*-butyldimethylsilyl)oxy)bicyclo[2.2.2]octane, i.e. the 2-*exo*,3-*endo*,5-*endo* product. Thus, the attack of the borohydride on **5** was only moderately *exo*-face selective. Attempts to hydrolyze the thioenol ether functionality of (−)-**8** to give the corresponding ketone (+)-**9** by the aid of $HgCl_2$, $Hg(OAc)_2$, $CuCl_2$, or NBS were sluggish and resulted in several byproducts. However, ferric nitrate absorbed on Bentonite K-10 clay[20,21] was very efficient and gave a 90% yield of (+)-**9**. Since this compound is a potentially very useful intermediate but is not too stable against acidic cleavage of the TBDMS group, it was important to keep the reaction time as short as possible and to filter the reaction mixture through neutral alumina immediately after the starting material was consumed. Diketone (+)-**14** was then obtained after deprotection and Swern oxidation.[22] According to chiral phase GC analysis using a β-cyclodextrin column the ee's of (+)-**12** and (+)-**14** were ≥98%.

Scheme 2. Reduction Attempts via Anchoring Techniques (X = H^+ or $SnCl_4$, Y = CF_3COO^- or Cl^-)



In order to make an accurate analysis of the enantiomeric purity of (+)-**14**, we prepared racemic **14** via a Diels-Alder reaction of 2-((trimethylsilyl)oxy)-1,3-cyclohexadiene and α-chloroacrylonitrile. We found that this dienophile gave only the 2,5-dione **14**, while α-acetoxyacrylonitrile was reported[11] to give a 4:1 mixture of **14** and **1**, respectively.

The stereoselctive reduction of (+)-**9** to give (−)-**11** was more problematic than expected. We anticipated that the large TBDMS group would prevent the reducing agents from attacking from the *endo* face. This turned out to be only partially true. Application of $NaBH_4$, $LiAlH(OtBu)_3$, LS-Selectride, LS-Selectride, together with 12-crown-4, catecholborane, DIBALH (CH_2Cl_2) or DIBALH (toluene) gave the *endo*,*endo*:*endo*,*exo* ratios 66:34, 54:46, 60:40, 41:59, 58:42, 76:24, and 76:24, respectively. The selectivity of the DIBALH reagent could be improved to 86:14 by using hexane as solvent. In this way (−)-**11** could be obtained in 60% yield after chromatographic separation of (−)-**13**. Reduction experiments in which sterically more demanding protecting groups such as *tert*-butyldiphenylsilyl and di-*tert*-butylsilyl (−$SiHtBu_2$) were used instead of the TBDMS group in (+)-**9** did not improve the stereoselectivity, nor did hydrosilylation using Wilkinson's catalyst together with triethylsilane.

The possibility of using the free 5-hydroxy group of (+)-**10** to direct the reduction from below *via* coordination or reaction with the reagents and thus stereoselectively give the (*R*,*S*)-*endo*,*exo* diol **22** was also investigated (Scheme 2). Unfortunately $NaBH_4$, $LiAlH_4$ or $EtMe_2N$-AlH_3[23] gave 58:42, 64:36 and 37:63 mixtures of the *endo*,*endo* (**12**) and *endo*,*exo* (**22**) isomers, respectively. Triacetoxyborohydride salts are known as hydroxyl-anchoring reagents, providing intramolecular transfer of hydride.[24,25] We used the commercially available tetramethylammonium triacetoxyborohydride,[26] which gave exclusively the isomeric 2,6-*endo*,*exo* diol (+)-**19** via **18**. This result encour-

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aged us to try the reagent on (+)-**10**, which then would give **22** via **20**, but unfortunately only starting material was detected even after several days in contact with (+)-**10**. Another possibility of delivering a hydride from the *endo* face was to use the (di-*tert*-butylsilyl)oxy functionality together with acids.[27−29] Thus, (+)-**21** was prepared, but intramolecular hydride transfer induced by trifluoroacetic acid or $SnCl_4$ did not succeed; only deprotection occurred.

The unsuccessful hydride transfer reactions may be explained by overly long distances between the carbonyl carbon and the hydrogen to be transferred. This was indeed indicated by AM1 calculations, which showed 3.3 and 3.5 Å for **20** and (+)-**21**, respectively, for their most favorable conformations having the hydrogens pointing directly toward the carbonyl carbons.

In conclusion, compounds (+)-**12** and (+)-**14** were synthesized in 40% and 25% overall yields, respectively, and high enantiomeric purities starting from (−)-**2**. The corresponding enantiomers would be available by starting the sequence from (+)-**2**, which can be prepared in six steps from its enantiomer.[30] We expect that a rather rich chemistry can be developed from several of the intermediates shown in Scheme 1, which is now being explored in our laboratory.

Experimental Section

General Considerations. GC chromatographic analyses were performed with a DBwax (J&W Scientific) capillary column (30 m, 0.25 mm i.d., 0.25 μm stationary phase) and with an β-DEX 120 (Supelco) permethylated β-cyclodextrin fused silica capillary column for determination of enantiomeric compositions. NMR spectra were recorded at 300 MHz using $CDCl_3$ ($CHCl_3$ δ 7.26 (^{1}H) and 77.0 (^{13}C)) or CD_3OD (CH_3OH δ 3.35 (OH) (^{1}H) and 49.0 (^{13}C)) as solvents. Chromatographic separations were performed on Matrex Amicon normal phase silica gel 60 (0.035−0.070 mm), and for thin-layer chromatography we used Merck precoated silica gel 60 F-254 (0.25 mm) TLC plates. After elution the TLC plates were sprayed with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL) and the compounds were visualized upon heating. All solvents were dried and distilled according to standard procedures,[31] and the reactions were performed in septum-capped, oven-dried flasks under an atmospheric pressure of argon. Organic extracts were dried using Na_2SO_4 throughout.

(1*R*,4*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)bicyclo[2.2.2]-octan-2-one ((+)-3). A solution of **2** (2.94 g, 21.0 mmol), imidazole (3.58 g, 52.6 mmol), and *tert*-butyldimethylsilyl chloride (TBDMSCl) (3.90 g, 25.9 mmol) in DMF (10 mL) was kept at room temperature for 8 h. Diethyl ether (50 mL) was then added, and the mixture was washed in sequence with water (10 mL), cold 0.1 M HCl (2 × 10 mL), saturated aqueous sodium bicarbonate (10 mL), and water (10 mL). The organic phase was dried, the solvent was removed at reduced pressure, and the residue was chromatographed (SiO_2, heptane−ethyl acetate 80:20) to give (+)-**3** (5.2 g, 98%) as an oil that crystallizes in the refrigerator but melts again on warming to room temperature: TLC R_f 0.37; $[\alpha]_D^{20}$ +3.5 (*c* 4.95, $CHCl_3$); IR (neat) 1730 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 4.09 (ddd, J = 8.3, 4.2, 1.7 Hz, 1H), 2.32 (m, 1H), 2.25 (m, 1H), 2.14−2.21 (m, 2H), 2.05 (m, 1H), 1.36−1.79 (m, 5H), 0.8 (s, 9H), −0.004 (s, 3H), −0.007 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.45, 69.23, 50.51, 44.28, 37.38, 27.69, 25.63, 23.92, 20.01, 17.82, −4.87, −4.94; MS m/z 239 ($M^+ - CH_3$, 3), 197 ($M^+ -$ tBu, 100). Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.3; H, 10.0.

2-(Phenylsulfenyl)-4-((*tert*-butyldimethylsilyl)oxy)-bicyclo[2.2.2]octan-3-one (5). LDA, prepared by treatment of diisopropylamine (3.33 g, 32.9 mmol) in THF (24 mL) at 0 °C with *n*-butyllithium (19.5 mL, 1.6 M in hexane), was added dropwise to a solution of (+)-**3** (5.34 g, 21.0 mmol) in THF (17 mL) at −78 °C, followed by TMSCl (5.6 mL, 44 mmol) after 30 min. The reaction mixture was warmed to room temperature within 2 h and then kept at this temperature for 30 min. During this time a precipitate was formed. The solvent was then removed at reduced pressure and replaced with cold pentane. The resulting mixture was filtered through Hyflo-Supercel, and then the solvent was removed at reduced pressure to give the TMS−enol ether **4** (6.36 g, 93%) as a pale yellow oil, which was used directly in the next step. IR (neat): 3060, 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.08 (dd, J = 7.4, 2.1 Hz, 1H), 3.91 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 1.80 (m, 1H), 1.12−1.49 (m, 5H), 0.87 (s, 9H), 0.21 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

Phenylsulfenyl chloride[32] (3.40 g, 23.5 mmol) diluted with CH_2Cl_2 (25 mL) was slowly added to a solution of crude **4** in CH_2Cl_2 (30 mL) at −78 °C. The reaction mixture was kept at this temperature for 45 min and then at room temperature for 30 min, whereafter it was poured into a separatory funnel containing CH_2Cl_2, crushed ice, and saturated aqueous sodium bicarbonate. The organic phase was dried, and the solvent was removed at reduced pressure to give crude **5** (7.56 g, quantitative) as an oil; TLC R_f 0.29, green spot. GC analysis (column DBwax) showed a 73:27 ratio of the *endo*,*exo* and *endo*,*endo* isomers, respectively. IR (neat): 3060, 1725, 1580 cm^{-1}. A small sample was purified using HPLC (Nucleosil Silica, 500 × 10 mm, heptane−ethyl acetate 95:5) to give a 95:5 mixture of the isomers: $[\alpha]_D^{20}$ −1.4 (*c* 1.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2H), 7.28 (m, 3H), 4.12 (m, 1H), 3.94 (m, 1H), 2.52 (m, 1H), 2.10−2.24 (m, 2H), 2.00 (m, 1H), 1.84 (m, 1H), 1.56−1.73 (m, 2H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 210.52, 136.72, 131.52, 128.96, 127.00, 68.75, 57.47, 50.91, 38.23, 33.44, 25.69, 20.56, 19.32, 17.88, −4.81, −4.90; HRMS calcd for $C_{20}H_{30}O_2SSi$ 362.1736, obsd 362.1736.

2-(Phenylsulfenyl)-5-((*tert*-butyldimethylsilyl)oxy)-bicyclo[2.2.2]octan-3-ol (6). Crude **5** (7.42 g, 20.5 mmol) was diluted with THF (725 mL) and methanol (235 mL), whereafter $NaBH_4$ (2.58 g, 68.2 mmol) was added in portions. The resulting mixture was kept at room temperature for 24 h, whereafter most of the solvent was removed at reduced pressure and replaced with ethyl acetate (400 mL). This solution was washed with saturated aqueous ammonium chloride (50 mL) and water (200 mL), and the combined aqueous phase was extracted with ethyl acetate (2 × 200 mL). The combined organic phase was dried, and the solvent was removed at reduced pressure to give oily **6** (7.44 g, quantitative) as a mixture of isomers; TLC R_f 0.29, blue spot. IR (neat): 3500 (broad, OH) 3060, 1585 cm^{-1}. A small sample was purified using HPLC (Nucleosil Silica, 500 × 10, heptane−ethyl acetate 95:5). The major and faster moving isomer had $[\alpha]_D^{20}$ +3.2 (*c* 1.64, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 7.45 (doublet of multiplets, J = 7.11 Hz, 2H), 7.29 (m, 2H), 7.19 (m, 1H), 4.42 (d, J = 10.04 Hz, 1H), 4.08 (m, 1H), 3.65 (m, 1H), 3.44 (m, 1H), 2.09 (m, 2H), 1.84 (m, 2H), 1.57 (m, 2H), 1.38 (m, 1H), 1.14 (m, 1H), 0.91 (s, 9H), 0.10 (s, broad, 6H); ^{13}C NMR ($CDCl_3$) δ 135.86, 130.54, 128.78, 126.18, 76.36, 70.72, 56.78, 39.09, 37.80, 29.66, 25.73, 20.80, 17.96, 17.82, −4.80, −5.15; HRMS calcd for $C_{20}H_{32}O_2SSi$ 364.1892, obsd 364.1891.

(1*S*,4*S*,5*S*)-2-(Phenylsulfenyl)-5-((*tert*-butyldimethylsilyl)oxy)bicyclo[2.2.2]oct-2-ene ((−)-8). 4-(Dimethylamino)pyridine (DMAP) (11.22 g, 91.84 mmol) was added to a solution of crude **6** (7.32 g, 20.1 mmol) in CH_2Cl_2 (350 mL)

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under a gentle stream of argon. After 5 min dry methanesulfonic anhydride[18] (10.61 g, 60.91 mmol) was added, during which time a precipitate was formed. The reaction mixture was kept at 40 °C for 48 h. Water was then added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried. The solvent was removed at reduced pressure to give **7** as a crude oil (8.0 g, 90%) from which a small sample, filtered through silica, showed a mixture of mesylated isomers according to NMR analysis. IR (neat): 3100, 3060, 1740, 1590 cm^{-1}. Selected ^1H NMR peaks ($CDCl_3$): δ 4.58 (m, 1H, H3), 3.97 (m, 1H, H5), 3.67 (m, 1H, H2), 2.97 (s, 3H, SO_2CH_3). Potassium *tert*-butoxide (6.07 g, 54 mmol) was added in small portions to a solution of crude **7** (7.95 g, 18.0 mmol) in 1,2-dimethoxyethane (750 mL) at −40 °C. After 2 h at −40 °C the reaction was quenched by addition of cold aqueous saturated ammonium chloride and the aqueous phase was extracted with diethyl ether. The combined organic phase was dried, followed by removal of the solvent at reduced pressure. The residue was chromatographed (SiO_2, heptane−ethyl acetate 95:5) to give (−)-**8** (3.57 g, 49% overall yield from **3**) as an oil: TLC R_f 0.64; $[\alpha]_D^{20}$ −394 (*c* 2.71, $CHCl_3$); IR (neat) 3060, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 2H), 7.25 (m, 3H), 6.27 (dd, J = 6.6, 1.2 Hz, 1H), 3.99 (dt, J = 8.1, 2.4 Hz, 1H), 2.71 (m, 1H), 2.58 (m, 1H), 1.90 (ddd, J = 13.2, 8.1, 2.5 Hz, 1H), 1.25−1.50 (m, 5H), 0.90 (s, 9H), 0.072 (s, 3H), 0.078 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 136.80, 135.09, 133.13, 130.86, 128.75, 126.50, 71.62, 40.15, 40.07, 37.33, 25.82, 24.92, 22.54, 18.00, −4.60, −4.63; MS *m*/*z* 346 (M^+, 2), 289 (M^+ − tBu, 8), 188 (100). Anal. Calcd for $C_{20}H_{30}OSSi$: C, 69.31; H, 8.72. Found: C, 69.0; H, 8.7.

(1*S*,4*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)bicyclo[2.2.2]octan-2-one ((+)-9). Freshly prepared clayfen[20] (1.08 g) was added in portions (nitrous gases were evolved) to a solution of (−)-**8** (269 mg, 0.776 mmol) in CH_2Cl_2 (27 mL). The mixture was kept at room temperature for 30 min and then filtered through a pad of neutral alumina. The alumina was washed with diethyl ether, the solvent was removed at reduced pressure, and the residue was chromatographed (SiO_2, heptane−ethyl acetate 90:10) to give (+)-**9** (178 mg, 90%) as an oil which crystallized in the refrigerator (mp 33.5−34.5 °C): TLC R_f 0.28; $[\alpha]_D^{20}$ +14.5 (*c* 5.07, $CHCl_3$); IR (neat) 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.95 (m, 1H), 2.68 (doublet of multiplets, J = 18.7 Hz, 1H), 2.23 (m, 1H), 2.14 (ddd, J = 14.2, 8.9, 2.9 Hz, 1H), 2.05 (m, 1H), 2.00 (doublet of multiplets, J = 18.6 Hz, 1H), 1.50−1.73 (m, 5H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 216.70, 67.67, 42.95, 38.06, 36.63, 35.70, 25.68, 22.22, 21.83, 17.89, −4.78, −4.85; MS *m*/*z* 254 (M^+, 0.8), 239 ($M^+ - CH_3$, 6), 197 (M^+ − tBu, 100). Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.3. Found: C, 66.1; H, 10.2.

(1*S*,2*S*,4*S*,5*S*)-2-((*tert*-Butyldimethylsilyl)oxy)bicyclo[2.2.2]octan-5-ol ((−)-11) and (1*S*,2*S*,4*S*,5*R*)-2-((*tert*-Butyldimethylsilyl)oxy)bicyclo[2.2.2]octan-5-ol ((−)-13). Diisobutylaluminum hydride (1.5 mL, 20% in hexane) was added dropwise to (+)-**9** (139 mg, 0.546 mmol) diluted with hexane (20 mL) at −78 °C. The cooling bath was removed, and after 2 h cold aqueous saturated ammonium chloride was added to the reaction mixture. The aqueous phase was extracted with ethyl acetate, the combined organic phase was dried, and the solvent was removed at reduced pressure to give an oil containing a 84:16 mixture of (−)-**11** and (−)-**13** according to GC and NMR analysis. The two isomers were separated (SiO_2, heptane−ethyl acetate 85:15), which gave (−)-**11** (84 mg, 60%) as an oil that crystallized in the refrigerator (mp 32.5−33 °C (TLC R_f 0.34)) and (−)-**13** (21 mg, 15%; mp 70−71 °C (TLC R_f 0.22)).

For (−)-**11**: $[\alpha]_D^{20}$ -46.9 (*c* 3.87, $CHCl_3$); IR (neat) 3420 cm^{-1} (OH, broad); ^1H NMR ($CDCl_3$) δ 3.88 (m, 1H), 3.76 (m, 1H), 3.02 (d, J = 10.3 Hz, 1H), 1.63−1.88 (m, 6H), 1.20−1.52 (m, 4H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 69.23, 68.35, 31.57, 31.27, 31.24, 31.20, 25.84, 21.91, 21.67, 18.05, −4.86, −4.99; CIMS (NH_3) *m*/*z* 274 ($M^+NH_4^+$, 7), 257 (M^+1, 100). Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.0. Found: C, 65.3; H, 10.8.

For (−)-**13**: $[\alpha]_D^{20}$ −13.6 (*c* 0.97, $CHCl_3$); IR (KBr) 3320 cm^{-1} (OH, broad); ^1H NMR ($CDCl_3$) δ 4.00 (m, 1H), 3.78 (m, 1H), 2.35 (m, 1H), 1.93 (ddd, J = 14.0, 8.8, 3.4 Hz, 1H), 1.80 (m, 1H), 1.53−1.66 (m, 3H), 1.48 (s, broad, 1H), 1.23−1.37 (m, 2H), 1.18 (doublet of multiplets, J = 11.5 Hz, 1H), 1.09 (doublet of multiplets, J = 14.1 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 68.71, 68.40, 36.87, 32.69, 32.52, 31.00, 25.83, 22.97, 18.01, 17.09, −4.75; CIMS (NH_3) *m*/*z* 274 ($M^+NH_4^+$, 20), 257 (M^+1, 100). Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.0. Found: C, 65.6; H, 11.0.

(1*S*,2*S*,4*S*,5*S*)-Bicyclo[2.2.2]octane-2,5-diol ((+)-12). A solution of tetrabutylammonium fluoride (TBAF) (0.5 mL, 0.5 mmol, 1 M in THF) was added dropwise to (−)-**11** (80 mg, 0.31 mmol) dissolved in THF (6 mL) at 0 °C. The mixture was then kept at room temperature for 5 h, whereafter it was concentrated under reduced pressure to a volume of approximately 1 mL. Ethyl acetate was added, and the resulting solution was washed with aqueous saturated sodium hydrogen carbonate. The aqueous phase was back-extracted three times with ethyl acetate, the combined organic phase was dried and concentrated at reduced pressure, and the residue was chromatographed (SiO_2, heptane−ethyl acetate 15:85, R_f 0.20) to give (+)-**12** (41 mg, 93%); mp 279−281 °C (lit.[8] 280−283 °C); $[\alpha]_D^{20}$ +52.6 (*c* 0.35, CH_3OH); IR (KBr) 3260 cm^{-1} (broad); ^1H NMR (CD_3OD) δ 3.84 (m, 2H), 1.74−1.89 (m, 4H), 1.65 (m, 2H), 1.48 (m, 4H); ^{13}C NMR (CD_3OD) δ 69.74, 33.72, 30.76, 23.59; HRMS calcd for $C_8H_{14}O_2$ 142.0994, obsd 142.0995.

(1*S*,4*S*,5*S*)-5-Hydroxybicyclo[2.2.2]octan-2-one ((+)-10). (+)-**9** was treated with TBAF as above to give, after chromatography (SiO_2, heptane−ethyl acetate 1:2, R_f 0.22), (+)-**10** as a white solid (105 mg, 92%): mp 151−153 °C; $[\alpha]_D^{20}$ +18.2 (*c* 5.33, $CHCl_3$); IR (KBr) 3390, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (m, 1H), 2.71 (doublet of multiplets, J = 18.9 Hz, 1H), 2.16−2.33 (m, 3H), 2.09 (ddd, J = 18.9, 2.8, 1.1 Hz, 1H), 1.88−2.01 (s, broad, 1H), 1.59−1.78 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 216.45, 67.31, 42.89, 37.99, 35.40, 35.32, 22.08, 22.06; MS *m*/*z* 140 (M^+, 17), 122 (17), 80 (100). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.5; H, 8.6.

(2*S*,6*S*)-Bicyclo[2.2.2]octane-2,6-diol ((+)-19). A solution of the hydroxy ketone (−)-**2** (20 mg, 0.14 mmol) in acetone (0.2 mL) was added to a solution of tetramethylammonium triacetoxyborohydride (92 mg, 0.35 mmol) and acetic acid (40 μL, 0.70 mmol) in acetone (1.6 mL). The reaction mixture was stirred for 6 h at room temperature before it was quenched with saturated aqueous ammonium chloride solution (0.5 mL). The mixture was concentrated to approximately 0.5 mL followed by neutralization with solid sodium carbonate and then extracted with ethyl acetate. Concentration of the organic extract at reduced pressure gave a crude product which was dissolved in ethyl acetate. The resulting solution was filtered through a pad of silica gel to give (+)-**19** (19 mg, 95%) after removal of the solvent as a white solid: mp 358 °C; $[\alpha]_D^{20}$ +23 (*c* 0.96, MeOH); IR (KBr) 3100−3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (m, 1H), 4.01 (ddd, J = 9.5, 4.4, 3.4 Hz, 1H), 2.10 (m, 1H), 1.98 (m, 2H), 1.77 (quintet, J = 3.0 Hz, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 1.23−1.42 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 69.75, 64.62, 40.49, 37.89, 36.92, 27.31, 25.39, 17.82; MS *m*/*z* 124 (28), 95 (100), 80 (71); HRMS (−H_2O) calcd for $C_8H_{12}O$ 124.0888, obsd 124.0885; HRCIMS (CH_4) (−1H) calcd for $C_8H_{13}O_2$ 141.0916, obsd 141.0908.

(1*S*,4*S*,5*S*)-5-((Di-*tert*-butylsilyl)oxy)bicyclo[2.2.2]octan-2-one ((+)-21). Using the same procedure as for the synthesis of (+)-**3**, (+)-**21** was prepared from (+)-**10** (33 mg, 0.24 mmol), di-*tert*-butylchlorosilane (90 mg, 0.50 mmol), and imidazole (80 mg, 1.2 mmol) in DMF (1.5 mL). Chromatography (neutral alumina, heptane−ethyl acetate 95:5, R_f 0.39) gave (+)-**21** as an oil (61 mg, 90%): $[\alpha]_D^{20}$ +16 (*c* 0.61, $CHCl_3$); IR (KBr) 2080 (Si−H), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.07 (m, 1H), 4.00 (s, 1H, Si−H), 2.72 (doublet of multiplets, J = 18.8 Hz, 1H), 2.27 (m, 1H), 2.18−2.25 (m, 2H), 2.05 (ddd, J = 18.9, 2.9, 1.1 Hz, 1H), 1.55−1.81 (m, 5H), 0.96 (s, broad, 18H); ^{13}C NMR ($CDCl_3$) δ 216.72, 71.16, 43.03, 38.13, 36.06, 35.22, 27.28, 27.21, 22.27, 21.96, 19.94, 19.77; HRMS (−tBu) calcd for $C_{12}H_{21}O_2Si$ 225.1311, obsd 225.1312.

(1*S*,4*S*)-Bicyclo[2.2.2]octane-2,5-dione ((+)-14). Dry DMSO (0.56 g, 7.2 mmol) diluted with CH_2Cl_2 (0.9 mL) was added dropwise to a solution of freshly distilled oxalyl chloride (0.18 mL, 2.1 mmol) in CH_2Cl_2 (1.8 mL) at −60 °C. The temperature was raised to −15 °C, and then (+)-**10** (100 mg,

0.71 mmol) in CH_2Cl_2 (0.8 mL) was added. The mixture was kept for 10 min at −15 °C and then cooled to −20 °C followed by addition of freshly distilled triethylamine (1.2 mL, 8.6 mmol). The mixture was kept for 10 min at −20 °C and then 30 min at room temperature followed by addition of water and separation of the phases. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed sequentially with brine, 0.1 M HCl, aqueous saturated sodium hydrogen carbonate, and brine and dried. Concentration of the organic extract at reduced pressure gave a crude product which was dissolved in ethyl acetate. The resulting solution was filtered through a pad of silica gel to give (+)-**14** (96 mg, 98%) after removal of the solvent; mp 202−204 °C (lit.[9] mp 205 °C); $[\alpha]_D^{20}$ +50 (*c* 0.55, $CHCl_3$); IR and NMR data were consistent with those reported;[9] HRMS calcd for $C_8H_{10}O_2$ 138.0681, obsd 138.0682.

Racemic Bicyclo[2.2.2]octane-2,5-dione ((±)-14). A mixture of 1-((trimethylsilyl)oxy-1,3-cyclohexadiene (0.90 g, 5.4 mmol), 2-chloroacrylonitrile (0.60 g, 6.9 mmol), 2,6-di-*tert*-butyl-4-methylphenol (approximately 20 mg) as a radical scavenger, and sodium carbonate (approximately 20 mg) in benzene (3 mL) was degassed with argon and kept at 70 °C for 36 h in a thick-walled screw-capped test tube. The mixture was cooled to room temperature, water and ethyl acetate were added, and the organic phase was separated. The aqueous phase was extracted twice with ethyl acetate, and the combined organic phase was washed twice with 0.2 M HCl and dried. Concentration at reduced pressure gave a 1:1 mixture of the 2-cyano-2-chloro diastereomers (0.73 g, 74%) as an oil. Hydrolysis to give racemic bicyclo[2.2.2]octane-2,5-dione was perfomed as follows (KOH/DMSO[33] resulted in a very low yield): a solution of the crude diastereomeric mixture (0.10 g, 0.54 mmol), CH_2Cl_2 (10 mL), 2 M NaOH (10 mL), and tetrabutylammonium hydrogen sulfate (0.20 g, 0.59 mmol) was kept at room temperature with vigorous stirring for 3 days. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed in sequence with 0.1 M HCl, saturated aqueous sodium bicarbonate, and brine and dried. Concentration at reduced pressure followed by chromatography (SiO_2, heptane−ethyl acetate 1:1, R_f 0.28) gave (±)-**14** (43 mg, 58%), mp 202−204 °C (benzene), (lit.[3] mp 205−206 °C). IR and NMR data were consistent with those reported.[9]

Racemic Bicyclo[2.2.2]octane-2,5-diols (±)-12, (±)-15, and (±)-22. Sodium borohydride (20 mg, 53 mmol) was added to a solution of (±)-**14** (50 mg, 0.36 mmol) in methanol−water (80:20, 5 mL) at 0 °C. The solution was kept at this temperature for 30 min and then concentrated at reduced pressure to approximately 1 mL. Saturated sodium chloride was added, and the mixture was extracted several times with CH_2Cl_2. The combined organic phase was dried and then concentrated at reduced pressure to give a mixture of (±)-**12,** (±)-**15**, and (±)-**22** (41 mg, 80%).

Determination of the Enantiomeric Purities. GC Analyses. The samples were analyzed by GC using a *β*-DEX 120 column (Supelco) at 120 °C isothermic and were found to be 98% ee for (+)-**12** and (+)-**14**. A mixture of (±)-**14** and the optically active sample gave only two peaks. The retention times were 45.57 and 46.07 min for (−)- and (+)-**14**, respectively. Retention times for the trifluoroacetate derivatives of the optically active sample (+)-**12** and the racemic mixture of *endo,exo*, *exo,exo*, and *endo,endo* ((±)-**12**) diols were 14.08 min ((±)-*endo,exo*, double intensity), 17.54 and 17.80 min ((±)-*exo,exo*), 24.16 min ((+)-**12**), and 26.34 min ((−)-**12**), respectively. It is worth noting the extraordinary separation of the diastereomers (e.g. 10.08 min between (±)-*endo,exo* and (+)-**12**).

HPLC Analyses. The enantiomeric purity of **14** could also be determined using HPLC with a Chiralcel OJ (J. T. Baker) column (hexane−2-propanol 1:1, flow rate 1 mL/min). Under these conditions (−)-**14** eluted at 8.60 min and (+)-**14** at 11.33 min. Columns such as α-DEX 120 (Supelco) for GC or DNBPG (covalent) (J. T. Baker) for HPLC gave no separation of the enantiomers.

Diastereomeric separations efficient enough to increase or decrease the enantiomeric purities were not involved in the synthetic operations presented. All optically active compounds in this article should therefore have enantiomeric purities as determined for (+)-**12** and (+)-**14**.

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Supporting Information Available: ^{13}C NMR spectra for those compounds whose elemental analysis data are given as HRMS data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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