Application of the Stereoselective Diels−Alder Reaction of Enantiopure 2-Sulfinyl Dienes: Synthesis of (−)-(1*S*,5*R*)-Karahana Ether†

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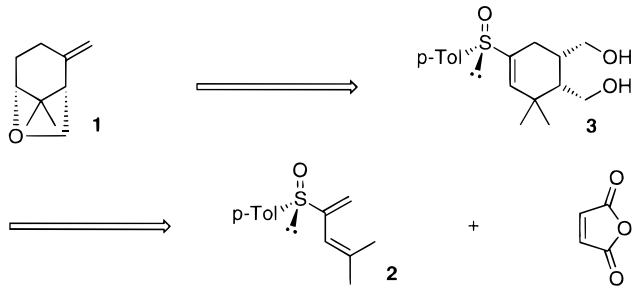
Although a number of methods for the preparation of enantiopure sulfinyl dienes have been reported to date,[1] investigation of their reactivity has received little attention, even with racemic systems.[2] Nevertheless, preliminary results showed a promising synthetic potential for these novel chiral dienes, regarding their ability to promote high endo and facial diastereoselectivities in [4 + 2] cycloadditions.[3] For instance, we obtained a single diastereomer (among four) by reacting (+)-(*E*)-(*R*)-2-(*p*-tolylsulfinyl)-1,3-pentadiene with *N*-methylmaleimide at ambient temperature and without a catalyst.[3e]

We wish to describe herein the first application of our methodology in the field of natural product chemistry. Karahana ether (**1**) is a volatile monoterpenoid with a pleasant camphor-like odor, which has been isolated from Japanese hop "Shinshu Wase".[4] It contains a 6-oxabicyclo-[3.2.1]octane skeleton, which is also encountered in some recently isolated sesqui- and diterpenoids.[5−7] Compound **1** has already been the subject of a few racemic[8] and two enantioselective[9] syntheses, which generally involve an intramolecular displacement of a sulfonate by an alkoxide ion for the construction of the ethereal cycle.

Starting from (+)-(*R*)-4-methyl-2-(*p*-tolylsulfinyl)-1,3-pentadiene (**2**), we devised a different approach outlined in the retrosynthetic Scheme 1, which highlights some features of the sulfoxide group chemistry, namely, chiral auxiliary in asymmetric Diels−Alder reaction[3] and activating group in heteroatom addition.[10,11]

Scheme 1



Stereoselective Diels−Alder reaction of enantiopure sulfinyl diene **2**[1i,k] with maleic anhydride was performed in refluxing THF for 3 days. After basic hydrolysis and acidification, both crystalline dicarboxylic acids **4** and **5** were easily isolated in a 90% yield by a simple filtration (Scheme 2). The stereoisomer ratio was shown to be 4:1 by ^{1}H NMR. According to our previous results in a similar case,[3e] the major cycloadduct is probably the diacid **4** resulting from hydrolysis of the corresponding anhydride whose preferred conformation is of the "*folded*" boat type.[12] All attempts to reduce directly the mixture of diacids **4** and **5** into diols **3** and **10** failed.[13] Using the procedure of Soaï slightly modified by Martinez,[14] reduction of diacids **4** and **5** gave "*folded*" **6**, **7** and "*extended*" **8**, **9** lactones in 76% and 20% yields, respectively, after chromatographic separation. In both cases, the regioisomeric ratio **6**:**7** and **8**:**9** were shown to be 7:3 by ^{1}H NMR in accordance with the integration and multiplicities of H-3a and H-7a. Further reduction with in situ-generated calcium borohydride[15] afforded diols **3** and **10** in nearly quantitative yields.

A key step of our synthesis was the construction of the tetrahydrofuran moiety, which corresponds to a favorable 5-*exo*-*trig* cyclization[16] by taking advantage of the sulfoxide activating influence (Scheme 3). One intramolecular conjugate addition of an alkoxide ion onto an α,β-ethylenic sulfoxide has already been achieved in spiroketal

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(13) $LiAlH_4$ reduction afforded only degradation products. $NaBH_4$/MeOH reduction of an in situ generated bis(mixed carbonic anhydride) resulted in the formation of either stereo- and regioisomeric lactones **6**−**9** or epimeric diols.

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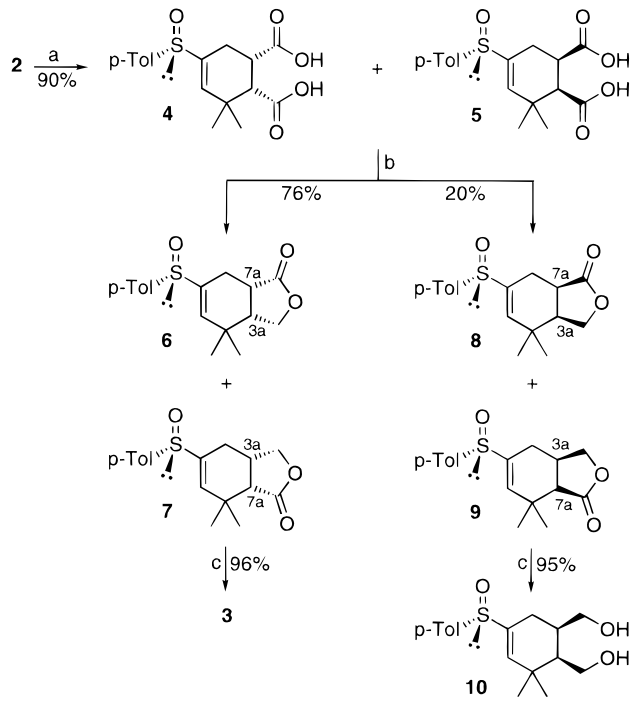
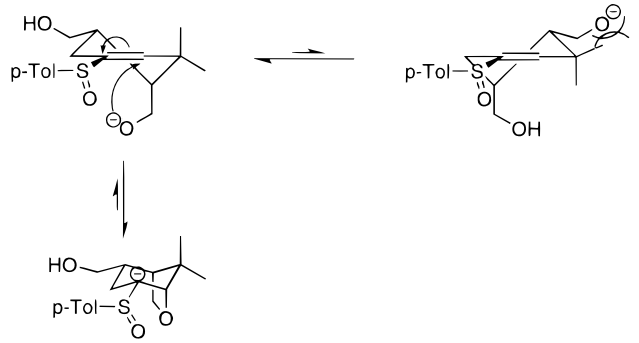
Scheme 2[a]



[a] Reagents and conditions: (a) (1) maleic anhydride, THF, reflux, 3 d, (2) aqueous Na_2CO_3, rt, 2 h, (3) aqueous HCl; (b) (1) $ClCO_2Et$, Et_3N, DME, −7 °C, 0.5 h, (2) $NaBH_4$, H_2O, rt, 0.5 h, (3) chromatographic separation; (c) $NaBH_4$, $CaCl_2$, EtOH, 45 °C, 30 min.

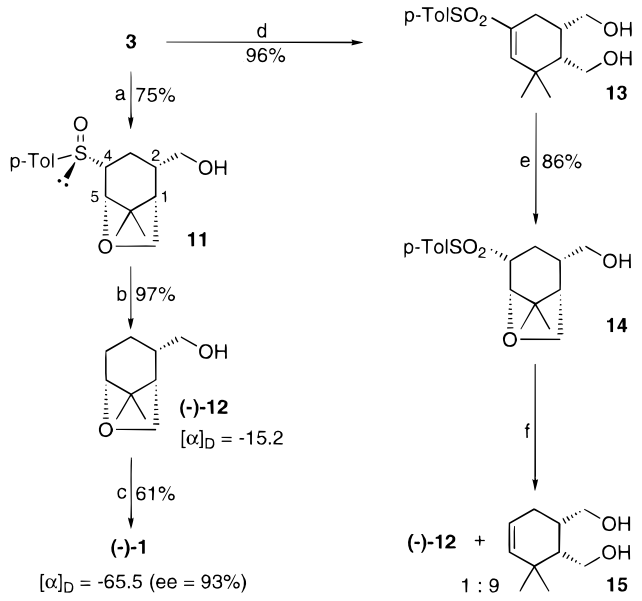
Scheme 3



synthesis by using alkali hydrides in tetrahydrofuran.[10] But, this procedure proved to be unsuccessful when applied to the diol **3**, even upon heating. We then turned to the use of some protic media, among which 2-propanol furnished the best result. Thus, treatment of **3** with sodium isopropoxide at 65−70 °C for 15 h led to a mixture of desired ether **11** and starting material in a 82:18 ratio (Scheme 4). That the same ratio was observed after a longer reaction time (36 h) suggested a thermodynamic equilibrium between both anionic intermediates (Scheme 3).

The *all-syn* geometry of bicyclic alcohol **11** was deduced from its 400 MHz ^{1}H NMR spectrum, which exhibits no coupling constant between H-1, H-2 and H-4, H-5. In order to eventually improve the efficiency of this cyclization, sulfoxide **3** was converted into the corresponding sulfone **13** in a nearly quantitative yield by treatment with metachloroperbenzoic acid. Although such a strategy has already been applied to substituted tetrahydrofuran synthesis using a catalytic amount of potassium hydride in THF,[17] this led to a mixture of desired product **14** and starting material in a 1:2 ratio, even with excess

Scheme 4[a]



[a] Reagents and conditions: (a) *i*-PrONa, *i*-PrOH, 70 °C, 15 h; (b) Raney Ni, MeOH, rt, 14 h; (c) (1) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF, rt, 2 h, (2) aqueous 30% H_2O_2, 0 °C to rt, 1.5 h; (d) 70% *m*-CPBA, CH_2Cl_2, rt, 12 h; (e) EtONa, rt, 44 h; (f) Mg, cat. $HgCl_2$, EtOH, rt, 2 h.

KH and prolonged reaction times. Cyclization of **13** was achieved by exposure to sodium ethoxide in ethanol for 12 h at ambient temperature. A 92:8 mixture was thus obtained, from which *all-syn* bicyclic product **14** was isolated in 86% yield.

Next, the sulfoxide group of **11** was cleanly removed using Raney nickel in methanol to give **12** (97% yield). Unfortunately, all attempts to obtain **12** from the sulfone **14** using electron transfer agents, such as classical 6% sodium amalgam (with or without NaH_2PO_4 buffer) or magnesium with catalytic mercuric chloride,[18] gave unsatisfactory results. In each case, desired **12** was formed together with a significant amount of cyclohexenediol **15** (up to 90%), which resulted from a Julia-type elimination. Consequently, although less effective in the cyclization step, the sulfoxide route was preferred.

Final one-pot dehydration of primary alcohol **12** *via* its *o*-nitrophenyl selenide[19] followed by *in situ* oxidation into the corresponding unstable selenoxide[20] afforded (−)-karahana ether (**1**) in 61% yield after purification.[21]

This constitutes the first utilization of enantiopure 2-sulfinyl dienes in natural product stereoselective synthesis. We are currently investigating further applications of these promising chiral intermediates.

Experimental Section

General Methods. THF was distilled from Na/benzophenone, *i*-PrOH from CaO, and triethylamine from KOH. Melting points are uncorrected. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded in KBr dispersion for solids and thin films on NaCl

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(21) (+)-Karahana ether (+)-**1** was also prepared from **10** by using the same reaction sequence as for (−)-**1** (see Experimental Section).

plates for liquids. High-resolution mass measurements were obtained by electron impact at 70 eV. Flash chromatography was run on silica gel 60 (230−400 mesh).

(1*S*,2*S*,*R*$_S$)- and (1*R*,2*R*,*R*$_S$)-3,3-Dimethyl-5-(*p*-tolylsulfinyl)cyclohex-4-ene-1,2-dicarboxylic Acids (4) and (5). A solution of **2**[1i,k] (3.30 g, 15 mmol) and maleic anhydride (3.00 g, 30 mmol) in dry THF (15 mL) was heated under reflux for 3 d. The resulting dark brown mixture was poured into a 5% Na_2CO_3 aqueous solution (200 mL) and stirred for 2 h at rt. After removal of the THF under reduced pressure, the aqueous layer was washed with Et_2O and saturated with NaCl and acidified with concentrated HCl until pH = 1. The resulting precipitate was isolated by filtration and washed with cold water. Drying under vacuum gave **4** and **5** (4.50 g, 4:1, 90%) as a beige solid, which was used directly in the next step: mp 180−190 °C (THF/H_2O); IR (KBr) 3407, 1743, 1710, 1594, 1263, 1209, 1022, 987, 815 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.16 (s, 3H), 1.19 (s, 3H), 2.10 (ddd, J = 17.2, 11.2, 1.9 Hz, 1H), 2.22 (dd, J = 17.2, 5.8 Hz, 1H), 2.38 (s, 3H), 2.73 (d, J = 3.8 Hz, 1H), 2.94 (m, 1H), 6.27 and 6.40 (2s, 1H), 7.36−7.42 and 7.38−7.50 (2 AA′BB′ systems, J = 8.2 Hz, 4H). Anal. Calcd for $C_{17}H_{20}O_5S$: C, 60.68; H, 6.01; S, 9.52. Found: C, 60.51; H, 6.19; S, 9.51.

(3a*S*,7a*S*,*R*$_S$)-4,4-Dimethyl-6-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydro-3*H*-isobenzofuran-1-one (6), (3a*S*,7a*S*,*R*$_S$)-7,7-Dimethyl-5-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydro-3*H*-isobenzofuran-1-one (7), (3a*R*,7a*R*,*R*$_S$)-4,4-Dimethyl-6-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydro-3*H*-isobenzofuran-1-one (8), and (3a*R*,7a*R*,*R*$_S$)-7,7-Dimethyl-5-(*p*-tolylsulfinyl)-3a,4,7,7a-tetrahydro-3*H*-isobenzofuran-1-one (9). To a solution of **4** and **5** (4.30 g, 12.8 mmol) and Et_3N (4.0 mL, 28.7 mmol) in dry DME (100 mL) at −7 °C was added $ClCO_2Et$ (4.2 mL, 43.9 mmol) dropwise. After being stirred for 30 min, the resulting mixture was filtered and placed in a 1 L Erlenmeyer flask. $NaBH_4$ (1.50 g) in H_2O (15 mL) was slowly added before the mixture was stirred for an additional 30 min. After quenching with a 20% HCl aqueous solution and extraction with CH_2Cl_2, the organic phase was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. Chromatographic separation (Et_2O) of the residue gave a first fraction (R_f 0.29, ether) which contained **8** and **9** (0.80 g, 20%, 7:3) as a white solid: IR (neat) 1772, 1596, 1153, 1043, 811 cm^{-1}. **8**: ^{1}H NMR δ 1.05 (s, 3H), 1.18 (s, 3H), 2.06 (ddd, J = 18.4, 6.2, 2.3 Hz, 1H), 2.27 (ddd, J = 18.4, 10.3, 1.3 Hz, 1H), 2.41 (s, 3H), 2.48 (q, J = 7.4 Hz, 1H), 2.82 (ddd, J = 10.3, 7.9, 6.2 Hz, 1H), 4.30 (dd, J = 9.2, 7.0 Hz, 1H), 6.55 (s), 7.30−7.46 (AA′BB′ system, J = 8.1 Hz, 4H); ^{13}C NMR δ 18.3 (t), 21.4 (q), 23.9 (q), 29.4 (q), 33.5 (s), 35.7 (d), 44.8 (d), 68.9 (t), 125.1 (d), 130.2 (d), 137.9 (d), 138.8 (s), 140.2 (s), 142.2 (s), 178.5 (s). **9**: ^{1}H NMR δ 1.28 (s), 1.38 (s), 1.91 (ddd, J = 18.4, 6.4, 2.1 Hz, 1H), 2.13 (ddd, J = 18.4, 9.0, 1 Hz, 1H), 2.41 (s, 3H), 2.44 (d), 2.85 (m), 3.83 (dd, J = 9.0, 5.4 Hz, 1H), 4.04 (dd, J = 9.2, 7.4 Hz, 1H), 4.25 (dd, J = 9.0, 6.5 Hz, 1H), 6.55 (s), 7.30−7.45 (AA′BB′ system, J = 8.3 Hz, 4H); ^{13}C NMR δ 20.4 (t), 21.4 (q), 25.1 (q), 31.1 (q), 33.2 (d), 34.0 (s), 47.9 (d), 71.7 (t), 125.0 (d), 130.0 (d), 139.8 (d), 141.9 (s), 175.5 (s); HRMS calcd for $C_{17}H_{20}O_3S$ 304.1133, found 304.1127. The second fraction (R_f 0.21, ether) contained **6** and **7** (2.96 g, 76%, 7:3) as a white solid: IR (neat) 1772, 1596, 1153, 1045, 970, 811 cm^{-1}. **6**: ^{1}H NMR δ 1.01 (s, 3H), 1.20 (s, 3H), 1.95 (ddd, J = 18.5, 5.4, 2.3 Hz, 1H), 2.41 (s, 3H), 2.49 (q, J = 7 Hz, 1H), 2.58 (ddd, J = 18.5, 10.5, 1.3 Hz, 1H), 2.87 (ddd, J = 10.5, 8.0, 5.4 Hz, 1H), 4.30 (dd, J = 9.4, 6.9 Hz, 1H), 6.56 (m, 1H), 7.30−7.43 (AA′BB′ system, J = 8.2 Hz, 4H); ^{13}C NMR δ 16.7 (t), 21.4 (q), 23.6 (q), 29.1 (q), 33.6 (s), 35.7 (d), 44.5 (d), 68.9 (t), 124.6 (d), 130.1 (d), 138.5 (s), 140.0 (d), 140.9 (s), 141.8 (s), 178.7 (s). **7**: ^{1}H NMR δ 1.31 (s), 1.40 (s) 1.54 (ddd, J = 18.0, 7.2, 2.2 Hz, 1H), 2.41 (s, 3H), 2.47 (d, J = 7.7 Hz, 1H), 2.89 (m, 1H), 3.77 (dd, J = 9.0, 3.9 Hz, 1H), 4.04 (dd, J = 9.4, 6.3 Hz, 1H), 4.22 (dd, J = 9.0, 5.8 Hz, 1H), 6.56 (m, 1H), 7.30−7.41 (AA′BB′ system, J = 8.4 Hz, 4H); ^{13}C NMR δ 19.3 (t), 21.4 (q), 24.7 (q), 31.1 (q), 32.9 (d), 34.2 (s), 48.0 (d), 71.8 (t), 124.4 (d), 130.0 (d), 138.5 (s), 140.4 (s), 141.4 (s), 141.9 (d), 175.2 (s)

(−)-(1*S*,2*S*,*R*$_S$)-[[6-(Hydroxymethyl)-5,5-dimethyl-3-*p*-tolylsulfinyl]cyclohex-3-enyl]methanol (3). To a solution of **6** and **7** (2.76 g, 9.0 mmol) in EtOH (125 mL) were successively added $CaCl_2$ (1.35 g, 12.0 mmol) and $NaBH_4$ (0.80 g, 21.0 mmol). The mixture was stirred at 45 °C for 30 min and quenched with a 10% HCl aqueous solution. After removal of the EtOH under reduced pressure and extraction with AcOEt, the organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed with acetone−cyclohexane 1:1 to give **3** (2.76 g, 96%) as a white solid: mp 131−134 °C (toluene); $[\alpha]_D$ −1.2 (*c* 1.26, Me_2CO); IR (neat) 3396, 1365, 1035, 809 cm^{-1}; ^{1}H NMR δ 1.14 (s, 3H), 1.19 (s, 3H), 1.64 (ddd, J = 17.6, 10.9, 2.0 Hz, 1H), 1.76 (m, 1H), 2.14 (dd, J = 17.6, 4.9 Hz, 1H), 2.26 (m, 1H), 2.40 (s, 3H), 3.33 (dd, J = 11.1, 8.6 Hz, 1H), 3.64 (m, 3H), 6.32 (s, 1H), 7.28−7.41 (AA′BB′ system, J = 8.1 Hz, 4H); ^{13}C NMR δ 18.5 (t), 21.3 (q), 26.5 (q), 30.3 (q), 35.7 (d), 36.6 (s), 47.4 (d), 58.8 (t), 64.3 (t), 124.4 (d), 129.9 (d), 138.6 (s), 140.6 (s), 141.2 (s), 142.4 (d). Anal. Calcd for $C_{17}H_{20}O_5S$: C, 66.18; H, 7.86; S, 10.38. Found: C, 65.95; H, 7.75; S, 10.25.

(−)-(1*R*,2*R*,*R*$_S$)-[[6-(Hydroxymethyl)-5,5-dimethyl-3-*p*-tolylsulfinyl]cyclohex-3-enyl]methanol (10). Following the same procedure as described above, **10** was obtained in 95% yield as a white solid: $[\alpha]_D$ −0.7 (*c* 0.7, Me_2CO); ^{1}H NMR δ 1.16 (s), 1.72 (ddd, J = 17.5, 4.5, <1 Hz, 1H), 1.77 (m, 1H), 2.01 (ddd, J = 17.5, 10.0, 1.7 Hz, 1H), 2.25 (m, 1H), 2.41 (s, 3H), 2.85 (m, 1H), 3.25 (m, 1H), 3.51 (dd, J = 11.0, 8.8 Hz, 1H), 3.63 (m, 2H), 3.74 (dd, J = 11.0, 4.0 Hz, 1H), 6.33 (s, 1H), 7.29−7.43 (AA′BB′ system, J = 8.2 Hz, 4H).

(+)-(1*S*,2*S*,4*R*,5*S*,*S*$_S$)-[8,8-Dimethyl-4-(*p*-tolylsulfinyl)-6-oxabicyclo[3.2.1]oct-2-yl]methanol (11). Na (230 mg, 10 mmol) was dissolved in dry *i*-PrOH (50 mL) at 50 °C under Ar. A solution of **3** (2.60 g, 8.4 mmol) in *i*-PrOH (50 mL) was then added and the resulting mixture heated at 65−70 °C for 15 h. After cooling and quenching with H_2O, *i*-PrOH was evaporated under reduced pressure and the residue extracted with AcOEt. The organic phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude solid was purified by chromatography (CH_2Cl_2−THF−EtOH 90:9:1) to afford starting material **3** (0.40 g, 15%) and **11** (1.95 g, 75%) as a white solid: R_f 0.58 (CH_2Cl_2−THF 1:1); $[\alpha]_D$ +123 (*c* 1.05, EtOH); ^{1}H NMR δ 1.02 (t, J = 9.0 Hz, 2H), 1.10 (s, 3H), 1.19 (s, 3H), 1.91 (dd, J = 4.4, 2.1 Hz, 1H), 2.07 (m, 1H), 2.41 (s, 3H), 2.83 (t, J = 9.0 Hz, 1H), 3.41 (m, 2H), 3.84 (d, J = 8.8 Hz, 1H), 3.97 (dd, J = 8.8, 4.4 Hz, 1H), 4.39 (s, 1H), 7.31−7.54 (AA′BB′ system, J = 8.0 Hz, 4H); ^{13}C NMR δ 19.4 (q), 20.2 (t), 21.4 (q), 26.2 (q), 36.5 (d), 42.3 (s), 44.0 (d), 65.0 (t), 67.1 (t), 66.5 (d), 78.6 (d), 125.4 (d), 129.9 (d), 139.0 (s), 142.2 (s). Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.18; H, 7.86. Found: C, 66.24; H, 7.87.

(−)-(1*S*,2*S*,5*R*)-(8,8-Dimethyl-6-oxabicyclo[3.2.1]oct-2-yl)-methanol ((−)-12). A mixture of **11** (1.75 g, 5.67 mmol) and Raney Ni (8 g, from Acros) in dry MeOH (175 mL) was stirred at rt for 14 h. After filtration on Celite and removal of the MeOH under reduced pressure, the residual oil was dissolved in Et_2O, washed with H_2O and brine, dried ($MgSO_4$), and filtered. Concentration in vacuo yielded (−)-**12** (0.93 g, 97%) as a colorless oil, which was used directly in the next step (purity >98% according to GC): R_f 0.40 (ethyl acetate); $[\alpha]_D$ −15.2 (*c* 1.15, EtOH); IR (thin film) 3392, 1058 cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H), 1.11 (s, 3H), 1.18 (m, 1H), 1.52 (m, 1H), 1.65 (m, 2H), 1.86 (d, J = 4.4 Hz, 1H), 2.14 (m, 1H), 3.39 (dd, J = 10.4, 8.2 Hz, 1H), 3.47 (dd, J = 10.4, 5.9 Hz, 1H), 3.69 (d, J = 3.7 Hz, 1H), 3.81 (d, J = 8.6 Hz, 1H), 3.85 (dd, J = 8.6, 4.7 Hz, 1H); ^{13}C NMR δ 19.8 (t), 19.9 (q), 26.5 (q), 27.1 (t), 36.7 (d), 41.5 (s), 44.5 (d), 66.0 (t), 66.6 (t), 82.1 (d); EIMS m/z (relative intensity) 170 (14, $M^{\bullet+}$), 152 (13, $M - H_2O^{\bullet+}$), 96 (61), 95 (65), 81 (100), 69 (94), 55 (84), 43 (73), 41 (73), 28 (67); HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1311.

(+)-(1*R*,2*R*,5*S*)-(8,8-Dimethyl-6-oxabicyclo[3.2.1]oct-2-yl)-methanol ((+)-12). According to the procedure described for **11**, **10** (1.10 g, 3.56 mmol) gave an unseparable 1:4 mixture of starting material and desired bicyclic alcohol, which was used directly in the next step: ^{1}H NMR δ 0.98 (s, 3H), 1.03 (s, 3H), 1.60 (q, J = 12.5 Hz, 1H), 1.95 (m, 1H), 2.06 (dt, J = 13.7, 6.0 Hz, 1H), 2.23 (m, 1H), 2.43 (s, 3H), 2.86 (dd J = 11.4, 6.3 Hz, 1H), 3.44 (s, 1H), 3.50 (dd, J = 10.6, 8.2 Hz, 1H), 3.60 (dd, J = 10.6, 5.8 Hz, 1H), 3.91 (m, 2H), 7.33−7.55 (AA′BB′ system, J = 8.1 Hz, 4H). According to the procedure described for (−)-**12**, hydrogenolysis of the crude product (1.05 g, 3.4 mmol) with Raney Ni (4 g) in dry MeOH (100 mL) yielded (+)-**12** (0.37 g, 60%) after chromatography (CH_2Cl_2 containing 5−10% THF) as a colorless oil: $[\alpha]_D$ +15.0 (*c* 0.3, ethanol).

(+)-(1*S*,2*S*)-[[6-(Hydroxymethyl)-5,5-dimethyl-3-*p*-tolylsulfonyl]cyclohex-3-enyl]methanol (13). To a solution of **3** (523 mg, 1.69 mmol) in CH_2Cl_2 (15 mL) was added solid 70% *m*-CPBA (550 mg, 1.7 mmol) in portions. After being stirred

for 12 h at rt, the reaction mixture was diluted with CH_2Cl_2, washed twice with a solution made up of equal volumes of a 10% Na_2SO_3 solution and a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (cyclohexane−acetone 7:3 to 6:4) to yield **13** (530 mg, 96%) as a white solid: $[\alpha]_D$ +24.5 (*c* 0.53, Me_2CO); IR (KBr) 3232, 1596, 1311, 1297, 1147, 1043 cm^{-1}; ^1H NMR δ 1.16 (s, 3H), 1.17 (s, 3H), 1.76 (ddd, *J* = 8.8, 4.4, 4.4 Hz, 1H), 2.15 (m, 2H), 2.27 (m, 1H), 2.44 (s, 3H), 3.42 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.68 (m, 3H), 6.72 (s, 1H), 7.32−7.71 (AA′BB′ system, *J* = 8.1 Hz, 4H).

(+)-(1*S*,2*S*,4*R*,5*S*)-[8,8-Dimethyl-4-(*p*-tolylsulfonyl)-6-oxabicyclo[3.2.1]oct-2-yl]methanol (14). To dry EtOH (4 mL) was added Na (92 mg, 4 mmol) under a N_2 atmosphere. After dissolution was complete, **13** (584 mg, 1.8 mmol) in dry EtOH (3 mL) was added. The reaction mixture was stirred for 44 h at rt and quenched with H_2O. After solvent removal under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (ethyl acetate−cyclohexane 7:3) of the crude product yielded **14** (505 mg, 86%) as a white solid: $[\alpha]_D$ +51 (*c* 1.09, Me_2CO); ^1H NMR δ 1.09 (s, 3H), 1.11 (s, 3H), 1.38 (ddd, *J* = 13.3, 12.5, 12.2 Hz, 1H), 1.87 (d, *J* = 4.0 Hz, 1H), 1.92 (ddd, *J* = 13.3, 6.0, 5.6 Hz, 1H), 2.17 (m, 1H), 2.45 (s, 3H), 3.26 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.41 (m, 1H), 3.49 (m, 1H), 3.62 (d, *J* = 8.9 Hz, 1H), 3.81 (dd, *J* = 8.9, 4.5 Hz, 1H), 4.22 (s, 1H), 7.34−7.75 (AA′BB′ system, *J* = 8.2 Hz, 4H); ^{13}C NMR δ 19.3 (q), 21.1 (t), 21.6 (q), 26.0 (q), 36.2 (d), 43.1 (s), 43.9 (d), 64.2 (d), 65.0 (t), 67.2 (t), 79.4 (d), 129.3 (d), 129.6 (d), 134.8 (s), 144.5 (s).

(−)-(1*S*,5*R*)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]-octane ((−)-Karahana Ether ((−)-1)). To a solution of (−)-**12** (445 mg, 2.64 mmol) and *o*-$NO_2PhSeCN$ (805 mg, 3.55 mmol) in dry THF (8.5 mL) was slowly added *n*-Bu_3P (0.90 mL) under an Ar atmosphere. After being stirred for 2 h at rt, the reaction mixture was cooled at 0 °C, and a 30% H_2O_2 aqueous solution (3.1 mL, 26.4 mmol) was added. After 1.5 h at rt, the mixture was diluted with Et_2O, washed with H_2O, dried ($MgSO_4$), filtered, and gently concentrated under atmospheric pressure. The residue was chromatographed (pentane containing 0−1% ether) and distilled under 100 mm Hg to give (−)-**1** (243 mg, 61%, purity >96%) as a colorless oil: R_f 0.60 (pentane−ether 9:1); $[\alpha]_D$ −65.5 (*c* 0.44, pentane) [lit. $[\alpha]_D$ −70.3 (*c* 1.02, pentane),[9a] −47.5 (*c* 0.3, pentane)[9b]];[22] ^1H NMR δ 0.96 (s, 3H), 1.08 (s, 3H), 1.65 (m, 1H), 1.74 (ddd, J = 13.7, 8.3, 4.0 Hz, 1H), 2.12 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.32 (d, *J* = 4.6 Hz, 1H), 2.41 (m, 1H), 3.76 (d, *J* = 4.0 Hz, 1H), 3.81 (d, J = 8.1 Hz, 1H), 4.03 (dd, J = 8.1, 4.6 Hz, 1H), 4.55 (dd, *J* = 2.4, 2.3 Hz, 1H), 4.64 (dd, *J* = 2.4, 2.3 Hz, 1H); ^{13}C NMR δ 20.9 (q), 25.5 (q), 25.8 (t), 28.6 (t), 42.2 (s), 54.0 (d), 71.2 (t), 82.4 (d), 107.5 (t), 149.0 (s).

(+)-(1*R*,5*S*)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]-octane ((+)-Karahana Ether (+)-1)). According to the above procedure, dehydration of (+)-**12** (320 mg, 1.88 mmol) gave (+)-**1** (175 mg, 62%) after purification as a colorless oil: $[\alpha]_D$ +64.0 (*c* 0.27, pentane).

(+)-(1*S*,2*S*)-[6-(Hydroxymethyl)-5,5-dimethyl-cyclohex-3-enyl]methanol (15). A mixture of **14** (65 mg, 0.2 mmol), powdered Mg (15 mg, 0.60 mmol), and a few crystals of $HgCl_2$ in dry EtOH was stirred for 2 h at rt. The reaction mixture was poured into a cold 5% HCl aqueous solution and extracted with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a 9/1 mixture of **15** and (−)-**12** (crude yield: 99%) as a colorless oil. **15**: ^1H NMR δ 1.03 (s, 3H), 1.10 (s, 3H), 1.73 (ddd, *J* = 8.4, 4.2, 4.2 Hz, 1H), 1.93 (ddd, *J* = 18.0, 4.5, 4.5 Hz, 1H), 2.03 (dddd, *J* = 18.0, 10.5, 2.7, 2.5 Hz, 1H), 2.31 (m, 1H), 3.63 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.72 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.77 (dd, *J* = 11.1, 6.7 Hz, 1H), 3.79 (dd, *J* = 11.1, 3.8 Hz, 1H), 5.35 (d, *J* = 10.0Hz, 1H), 5.56 (ddd, *J* = 10.0, 4.5, 2.7 Hz, 1H); ^{13}C NMR δ 24.6 (t), 27.4 (q), 31.4 (q), 35.0 (s), 35.5 (d), 47.5 (d), 59.7 (t), 65.4 (t) 123.7 (d), 136.7 (d).

Supporting Information Available: Copies of ^1H NMR spectra (400 MHz) of compounds **1**, **6** + **7**, **8** + **9**, and **12**−**14** (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; ordering information is given on any current masthead page.

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(22) The optical purity of 93%[9a] was found to be identical to the enantiomeric excess that was determined by chiral GC on Chiraldex G-TA.