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Straightforward Enantioselective Synthesis of Both Enantiomers of Karahana Lactone Using a Domino Ring-Closure Sequence

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Abstract—A straightforward enantioselective synthesis of both enantiomers of karahana lactone is described starting from enantiopure (*R*) or (*S*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one. The key step of the sequence is an acid-induced domino reaction with three pathways running. Because of the first description of karahana lactone as a solid, the structure was secured by X-ray structural analysis.

Introduction

In the course of our interest in the synthesis of natural products, we reported recently[1] the enantiospecific synthesis of (+)-*cis*-γ-Irone based on a one-pot highly controlled diastereoselective protonation of a preformed enolate (Fig. 1). We wish to present herein a connected methodology based on an epimerization induced ring-closure.

Karahana lactone **1** and karahana ether **2** are monoterpenoïds with a unique 6-oxabicyclo[3.2.1]octane skeleton, which have been isolated from Japonese hop 'Shinshu Wase', *Humulus lupulus* L. (Fig. 2).[2–4]

Compound **2** has already been the subject of a few racemic[5–9] and three enantioselective[10–12] syntheses. As to karahana lactone **1**, only one synthesis has been recorded.[10] However, this approach is not straightforward and proceeds from the $RuCl_3/NaIO_4$ oxidation of the corresponding karahana ether, followed by a Wittig methylenation of the keto moiety.

We describe herein the first straightforward enantioselective synthesis of both enantiomers of karahana lactone **1** starting from (*R*) or (*S*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one, (+)-**3** and (−)-**3**, respectively (Scheme 1). The key-transformations are an acid-induced domino reaction[13] of three consecutive steps. Subsequently, karahana ether **2** is readily obtained by reduction of karahana lactone and formation of the ether bond from the corresponding *cis*-diol like reported.[8]

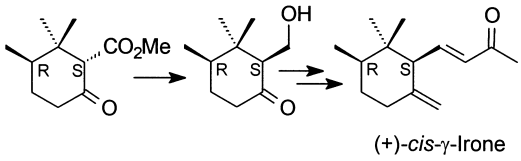


Figure 1.

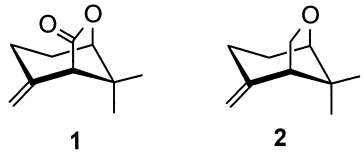
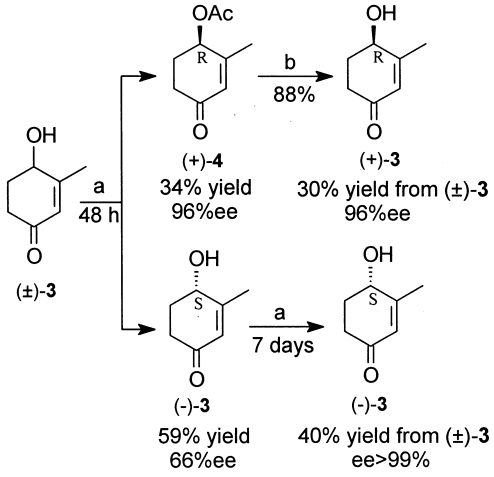


Figure 2.



Scheme 1. (a) 3 equiv. of vinyl acetate, *i*Pr_2O, *Mucor miehei* lipase; (b) Na_2CO_3, MeOH.

Keywords: lipase; domino reaction; (+)/(−)-karahana lactone; (+)/(−)-karahana ether.

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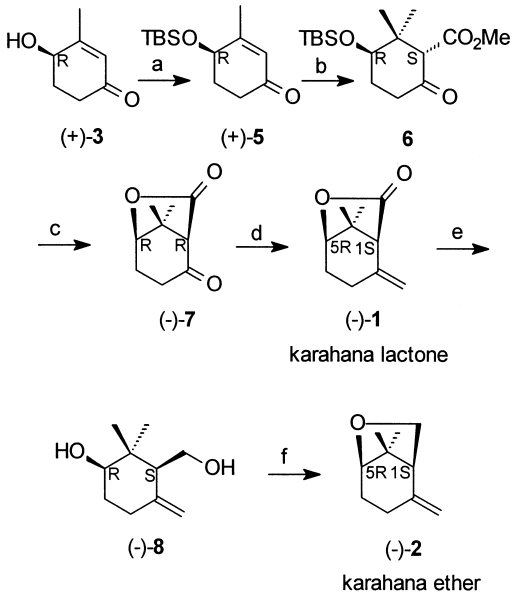


Scheme 2. (a) TBSCl, imidazole, DMF (92%); (b) Me_2CuLi, ether, then HMPA and $CNCO_2Me$ (91%); (c) 1.2 equiv. of *p*-TsOH·H_2O, toluene, reflux (94%); (d) 2.5 equiv. $Ph_3(CH_3)P^+I^-$, *tert*-BuOK, toluene (80%); (e) $LiAlH_4$, ether (95%); (f) 1.1 equiv. of *p*-TsCl, pyridine (81%).

Results and Discussion

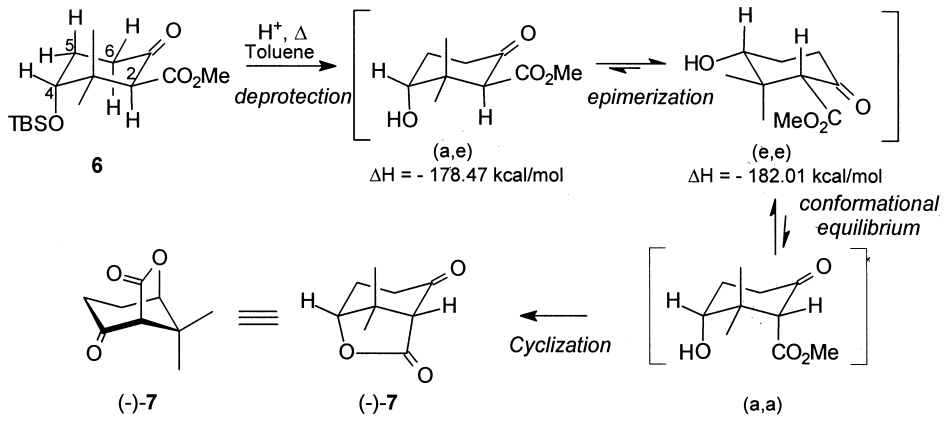
The starting material for the synthesis of (*R*)-**3** and the enantiomer uses (±)-4-hydroxy-3-methyl-cyclohex-2-en-1-one (**3**), which is available in 75% yield following the literature procedure.[14a] Treatment of racemic **3** with 3 equiv. of vinyl acetate in diisopropyl ether in the presence of *Mucor miehei* lipase[15] gave the results outlined in Scheme 1.

The progress of the reaction was monitored by capillary GC. In parallel, enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by GC separation using a chiral phase (see Experimental). The enantiomers of the remaining alcohol and those of the produced acetate were perfectly separated. After 48 h at rt, the active enzyme was recovered for reuse by filtration. Concentration of the filtrate and column chromatography on silica gel afforded 59% yield of the nonreactive alcohol (*S*)-**3** (66% ee) and 34% yield of the (*R*)-acetate **4** (96% ee). This acetate (+)-**4** was not stable and slowly degraded during the course of the reaction (theoretical yield: 41%). The remaining alcohol was resubjected in the same conditions to enzymatic transesterification using the recovered enzyme. The progress of the reaction was monitored by chiral phase analytical GC until one enantiomer of the starting material was completely consumed. After 7 days, (*S*)-alcohol **3** was obtained in 40% overall yield (ee>99%). In the other hand, (*R*)-acetate **4** was hydrolyzed with Na_2CO_3/MeOH to afford (*R*)-alcohol **3** in 88% yield (96% ee; 30% overall yield from racemic **3**). The absolute configuration of the two enantiomeric alcohols was established by comparison with the literature.[14b]

Starting from (+)-**3** as an example (96% ee), our methodology is described in Scheme 2.

Using the standard procedure,[16] TBS (*tert*-butyldimethylsilane) derivative (+)-**5** was obtained in 92% yield. The protected ketol (+)-**5** was converted into the single 2-carbomethoxy-cyclohexanone **6** (91% yield) by the 1,4-addition of lithium dimethylcuprate followed by the quenching with methylcyanoformate[17] in hexamethylphosphoric triamide. Spectra data were performed on crude **6**. The ^1H NMR spectra indicated that **6** was consistent with the *trans* relative configuration of the cyclohexanone substituents on C(2) and C(4) (Scheme 3). The small value of the vicinal coupling constants between H–C-4 and H_{eq}–C-5, H_{ax}–C-5 of **6** (δ_H=3.37 ppm, broad t, $J_{4,5eq}$–$J_{4,5ax}$=3.2 Hz) showed the equatorial position for the proton H–C-4. The absence of long-range W coupling between H–C-2 and H_{eq}–C-6, contrary to precedent,[1] allowed one to attribute the axial position of H–C-2 (δ_H=3.81, s). Treatment of **6** with *p*-TsOH·H_2O (1.2 equiv.) in refluxing toluene for 30 min afforded the crystalline keto-lactone (−)-**7**, in 94% yield, as a single product. The pathway can be regarded as an acid-induced domino reaction[13] in which the subsequent reaction (cyclization by transesterification) results as a consequence of the functionality (*cis*-isomer) formed in the previous steps (deprotection of **6**, epimerization and conformational equilibrium). The sequence is depicted in Scheme 3 with the optimized structure and the final heat of formation of each intermediate alcohol (not isolated) calculated by the PM3 method contained within the HyperChem program.[18]

In the final step, treatment of (−)-**7** with the salt-free Wittig reagent prepared from methyltriphenylphosphonium iodide



Scheme 3. Minimized conformation and heat of formation of the diastereomer alcohols derived from deprotection and acid-induced epimerization of **6**.

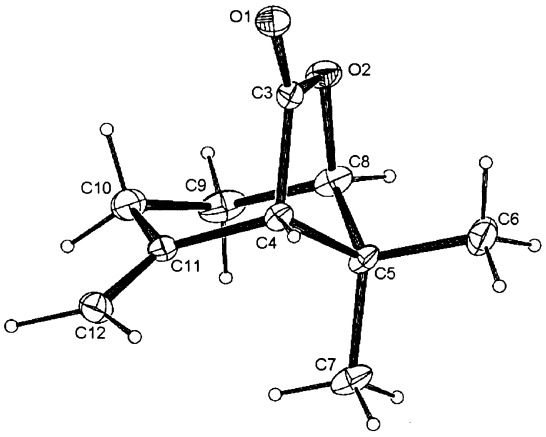


Figure 3. ORTEP of the (1*S*,5*R*)-karahana lactone(−)-**1**.

and *tert*-BuOK gave crystalline karahana lactone (−)-**1** in 80% yield. Purification by recrystallization improved the optical purity of (−)-**1** (ee>99%). $[\alpha]_D^{25}=-295.0$ (*c* 1.0, $CHCl_3$). The crystalline nature of karahana lactone has never been reported,[4,10] consequently the structure was secured by the single crystal X-ray diffraction analysis of (−)-**1** (Fig. 3).

When karahana lactone (−)-**1** was treated with lithium aluminum hydride, the diol (−)-**8** was isolated in 95% yield as a single diastereomer. Reaction of (−)-**8** with 1 equiv. of *p*-toluenesulfonyl chloride in dry pyridine at rt afforded the bicyclic karahana ether (−)-**2** in 81% yield. The spectra data of (−)-**8** and (−)-**2** were identical to those reported in the literature.[5,8]

The same pathway, starting from (−)-**3**, gave (+)-karahana lactone, (+)-**1**, and (+)-karahana ether, (+)-**2**.

In conclusion, the first straightforward enantioselective synthesis of both enantiomers of karahana lactone has been achieved by a short and efficient four-step procedure starting from lipase resolved ketols (**3**). The corresponding karahana ethers have been synthesized subsequently using two steps more.

Experimental

General methods

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker AM-400 or Brucker AM-200 spectrometers. Infrared spectra were obtained as film or KBr pellet using a Perkin–Elmer 1600 FTIR spectrophotometer. Routine monitoring of reactions was performed using Merck 60F 254 silica gel, aluminum supported TLC plates. Column chromatography was performed using Silica gel 60 (230–400 mesh) and gradients pentane/ether as eluent unless otherwise stated. GC analyses were carried out on a Chrompack 9001 using a WCOT fused silica column (25 m×0.32 mm i.d.; CP-Wax-52 CB stationary phase; N_2 carrier gas: 50 kPa). The ee determinations were carried out using a MEGADEX DETTBSβ fused silica column (30 m×0.25 mm i.d.; N_2 carrier gas: 70 kPa). Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Microanalyses were performed on a Technicon CHN analyzer at our University. MO calculations were performed using HYPERCHEM release 5 package (Hypercube, Waterloo, Ontario, Canada) without any modification and running on a 450 MHz PC. Structures were minimized with the following parameters: restricted Hartree–Fock (RHF) level, minimization algorithm, until the root mean square energy gradient was less than 0.001 kcal/mol Å, accelerated convergence. Melting points are uncorrected. Unless otherwise stated, solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduce pressure.

(*R*)-4-Hydroxy-3-methyl-cyclohex-2-en-1-one ((+)-3) and (*S*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one ((−)-3). A mixture of (±)-**3** (1.30 g, 10.3 mmol), vinyl acetate (2.9 ml) and *Mucor miehei* lipase (1.30 g) in 30 ml of diisopropyl ether was magnetically stirred at rt and the reaction progress monitored by GC on a chiral column. After 2 days and 41% conversion, the GC chromatogram showed that the formed acetate (+)-**4** had an enantiomeric excess of 96%. The reaction was stopped by filtration. Removal of the solvent followed by separation on a silica gel column yielded 770 mg (59%) of (−)-**3** (66% ee) and 590 mg (34%) of acetate (+)-**4** (96% ee). The acetate was not stable and was used immediately in the following step.

(−)-3: IR (neat): ν 3300, 3020, 1660, 1631, 1042 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.82 (s, 1H), 4.45–4.35 (m, 1H), 2.61–2.50 (m, 1H), 2.41–2.25 (m, 2H), 2.06–1.95 (m, 1H), 2.02 (s, 3H).^{13}C NMR (50 MHz, $CDCl_3$): δ 199.7, 165.0, 126.2, 68.0, 34.6, 31.5, 20.5. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.84; H 8.02.

(+)-4: $[\alpha]_D^{25}=+43.4$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3031, 1746, 1671, 1634, 1243, 1042 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.92 (m, 1H), 5.57–5.51 (m, 1H), 2.62–2.47 (m, 1H), 2.45–2.20 (m, 2H), 2.11 (s, 3H), 2.10–1.97 (m, 1H), 1.92 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.4, 170.0, 157.9, 128.3, 69.5, 34.0, 28.1, 20.6, 20.1.

The acetate (+)-**4** was treated with Na_2CO_3 (2.2 g, 20.8 mmol) in 15 ml of MeOH for 2 h at rt. The reaction mixture was filtered and concentrated under reduced pressure. Column chromatography gave 390 mg (88%; 30% overall yield from (±)-**3**) of (+)-**3** as an oil. 96% ee, $[\alpha]_D^{25}=+34.1$ (*c* 1.0, $CHCl_3$).

The nonreactive alcohol (−)-**3** was resubjected in the same conditions to lipase-catalyzed acylation using the recovered active enzyme and the progress of the reaction was monitored by chiral phase analytical GC. After 7 days, GC analysis showed that one of both enantiomer was completely consumed. The reaction was stopped by filtration. Removal of the solvent followed by separation on a silica gel column yielded 520 mg (40% overall yield from (±)-**3**) of alcohol (−)-**3**, ee>99%, $[\alpha]_D^{25}=-35.2$ (*c* 1.0, $CHCl_3$).

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-cyclohex-2-en-1-one ((+)-5). The alcohol (+)-**3** (520 mg, 4.13 mmol) was dissolved in DMF (20 ml), imidazole (890 mg,

13.1 mmol) and *tert*-butyldimethylsilyl chloride (844 mg, 5.60 mmol) were added, and the mixture was stirred for 3 h at rt. The solution was poured into water and extracted with ether. The combined organic extracts were washed with water, brine, dried, filtered, and concentrated. Column chromatography gave 912 mg (92%) of (+)-**5**. $[\alpha]_D^{25}=+34.7$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3026, 1687, 1628, 1250, 1103 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ. 5.80 (br. s, 1H), 4.33 (dd, *J*=7.8, 5.0 Hz, 1H), 2.53 (br. dt, *J*=16.2, 5.1 Hz, 1H), 2.37–1.95 (m, 3H), 1.96 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)): δ 198.4, 164.0, 126.4, 69.4, 34.9, 32.4, 25.5, 20.9, 17.8, −4.5, −5.1. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 65.06; H, 10.03.

Methyl (1*S*,3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethyl-6-oxo-cyclohexanecarboxylate 6. To a stirred suspension of copper(I) iodide (1.38 g, 7.25 mmol) in dry ether (15 ml) at −5°C, was added dropwise MeLi (1.5 M in ether, 9.7 ml, 14.5 mmol) under an argon atmosphere. The mixture was stirred for 1 h at −5°C and a solution of (+)-**5** (870 mg, 3.63 mmol) in ether (6 ml) was added dropwise. The reaction mixture was stirred for a further 1 h at 0°C, HMPA (6 ml, 34.5 mmol) was added dropwise under vigorous stirring, the mixture was slowly cooled to −70°C and methyl cyanoformate (1.23 g, 14.5 mmol) in ether (4 ml) was added dropwise. The solution was allowed to rise to rt, then poured into a saturated aqueous NH_4Cl/NH_4OH solution and extracted with ether. The organic layers were combined, washed with brine, dried, and evaporated to furnish 1.04 g (91%) of **6** as an oil. This compound was used in the next step without further purification. IR (neat): ν 1766, 1722, 1262, 1130, 1086, 834 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 3.81 (s, 1H), 3.43 (s, 3H), 3.37 (br. t, *J*=3.2 Hz, 1H), 2.39 (ddd, *J*=14.1, 12.1, 6.9 Hz, 1H), 2.18 (ddd, *J*=14.1, 5.5, 3.6 Hz, 1H), 1.72 (dddd, *J*=14.2, 12.1, 5.5, 2.7 Hz, 1H), 1.51 (dddd, *J*=14.2, 6.9, 3.6, 3.0 Hz, 1H), 1.04 (s, 3H), 1.00 (s, 3H), 0.88 (s, 9H) (min), 0.06 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.3, 169.3, 74.6, 61.9, 51.5, 43.6, 35.7, 29.3, 25.8 (3C), 24.7, 22.56, 18.0, −4.5, −5.0.

(1*S*,5*R*)-8,8-Dimethyl-6-oxabicyclo[3.2.1]octane-2,7-dione ((−)-7). A suspension of ester **6** (850 mg, 2.70 mmol) and *p*-toluenesulfonic acid monohydrate (617 mg, 3.24 mmol) in toluene (20 ml) was placed in an oil bath equilibrated at 110°C. After 30 min, the solution was cooled to rt and filtered through a pad of Celite. The filter-cake was washed with CH_2Cl_2 and the solvent evaporated. Column chromatography gave 427 mg (94%) of (−)-**7** as a solid. An analytical sample was recrystallized from *n*-hexane–ether (4:1). (−)-**7**. Mp=112–113°C. $[\alpha]_D^{25}=-302.0$ (*c* 1.0, $CHCl_3$), [lit. $[\alpha]_D^{22}=-236.0$ (*c* 0.83, $CHCl_3$)[10]]. IR (neat): δ 1785, 1730, 1130, 960 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.46 (br. s, 1H), 2.98 (s, 1H), 2.65–2.30 (m, 3H), 2.13–1.95 (m, 1H), 1.24 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.0, 171.7, 84.1, 66.5, 45.5, 33.4, 25.0, 24.9, 19.6. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.17.

(1*S*,5*R*)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one ((−)-1). *(−)-Karahana lactone*. A solution of $Ph_3P^+MeI^-$ (2.40 g, 5.95 mmol) and potassium *tert*-butoxide (748 mg, 6.67 mmol) in toluene (60 ml) was heated under reflux for 3 h. After the suspension had settled for 3 h at room temperature, the supernatant solution was added to a solution of (−)-**7** (400 mg, 2.38 mmol) in toluene (15 ml). The reaction mixture was stirred at rt for 2 h and the mixture was poured into water and extracted with Et_2O. The organic phase was successively washed with H_2O, aq. NH_4Cl and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography gave 316 mg (80%) of (−)-**1** as a solid. Recrystallisation in *n*-hexane (240 mg, needles) gave the product with an improved optical purity (ee>99%). Mp=57.5–58.5°C; $[\alpha]_D^{25}=-295.0$ (*c* 1.0, $CHCl_3$), [lit. $[\alpha]_D=-236.0$ (*c* 0.83, $CHCl_3$)[10]]. IR (KBr): ν 3080, 1783, 1652, 1245, 1140, 1045, 900 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.89 (br. s, 1H), 4.82 (br. s, 1H), 4.33 (br. d, *J*=4.0 Hz, 1H), 2.74 (s, 1H), 2.41–2.26 (m, 2H), 2.07–1.69 (m, 2H), 1.16 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.6, 139.6, 112.5, 85.1, 59.1, 42.3, 25.3, 25.0, 24.3, 19.8 Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.37; H, 8.51.

(1*S*,5*R*)-*cis*-3-Hydroxy-2,2-dimethyl-6-methylenecyclohexanemethanol ((−)-8). A solution of (−)-**1** (150 mg, 0.88 mmol) in dry ether (3 ml) was slowly added to a stirred slurry of $LiAlH_4$ (86 mg, 2.26 mmol) in dry ether (5 ml) at 0°C. The solution was allowed to rise to rt. After 1 h 30 min, Celite (10 g) and $Na_2SO_4{\cdot}10H_2O$ (5 g) were added and the solution was stirred for a further 30 min. The mixture was filtered through a pad of $MgSO_4$ and concentrated. A column chromatography of the oil afforded 146 mg (95%) of pure (−)-**8**. $[\alpha]_D^{25}=-54.0$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3500, 1641, 1086, 1005, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.92 (s, 1H), 4.73 (s, 1H), 3.91 and 3.67 (ABX, *J*=10.8, 7.5, 2.3 Hz, 2H), 3.45 (dd, *J*=5.1, 3.5 Hz, 1H), 2.61 (br. s, 2×OH), 2.55–2.41 (m, 1H), 2.13–1.79 (m, 3H), 1.62 (dq, *J*=13.4, 5.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.1, 110.2, 73.9, 62.8, 54.6, 38.6, 30.5, 21.4, 27.7, 29.2 Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.31; H, 10.69.

(1*S*,5*R*)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]-octane ((−)-2). *(−)-Karahana ether*. *p*-Toluenesulphonyl chloride (133 mg, 0.70 mmol) was added to a stirred solution of diol (−)-**8** (100 mg, 0.65 mmol) in dry pyridine (4 ml) at 0°C and the mixture was allowed to rise to rt. After stirring for 3 h, the mixture was poured into water and extracted with Et_2O. The organic phase was washed with 1 M HCl, saturated $NaHCO_3$, brine and dried over $MgSO_4$. After filtration, concentration in vacuo (bath temp 3–4°C) furnished an oil. Column chromatography afforded the bicyclic ether (−)-**2** as a colorless liquid with a pleasant camphor-like odor (81 mg, 81% yield). $[\alpha]_D^{25}=-68.0$ (*c* 1.0, pentane), [lit. $[\alpha]_D=-70.3$ (*c* 1.02, pentane),[10] −47.5 (*c* 0.30, pentane),[11] −65.5 (*c* 0.44, pentane)[12]]. IR (neat): ν 3066, 1645, 1240, 1042, 890 cm^{-1}. (200 MHz, $CDCl_3$): δ 4.62 (t, *J*=2.2 Hz, 1H), 4.53 (t, *J*=2.2 Hz, 1H), 4.01 (dd, *J*=8.2, 4.3 Hz, 1H), 3.78 (d, *J*=8.2 Hz, 1H), 3.73 (d, *J*=3.5 Hz, 1H), 2.50–2.33 (m, 1H), 2.29 (d, *J*=4.3 Hz, 1H), 2.10 (dd, *J*=15.6, 6.4 Hz, 1H), 1.80–1.50 (m, 2H), 1.05 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.0, 107.5, 82.4, 71.1, 53.9, 42.2, 28.5, 25.8, 25.4, 20.8 Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.67; H, 10.61.

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