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SYNTHESIS OF (1S,5R)-KARAHANA ETHER AND (1S,5R)-KARAHANA LACTONE. THE OPTICALLY ACTIVE FORMS OF UNIQUE MONOTERPENES WITH A 6-OXABICYCLO[3.2.1]OCTANE RING SYSTEM

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Abstract -- (1S,5R)-(-)-Karahana ether (8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octane) and (1S,5R)-(-)-karahana lactone (8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one) were synthesized from (S)-3-hydroxy-2,2-dimethylcyclohexanone. The natural karahana lactone was shown to be almost racemic (ca. 1.3 % e.e.).

In 1968 Naya and Kotake isolated karahana ether **1** as a new constituent of Japanese hop "Shinshu-wase", Humulus lupulus L.[1,2] A closely related monoterpene, karahana lactone **2**, was also isolated by them from the same source.[3] These two monoterpenes contain the same bicyclic skeleton: 6-oxabicyclo[3.2.1]octane. This unique structure aroused an interest among chemists to synthesize karahana ether **1**. Coates and Melvin were the first to synthesize (±)-**1** in 1970.[4] Then two syntheses of (±)-**1** were reported in 1979 by Mukaiyama, et al.[5] and by Yamada, et al.[6] However, no synthesis of optically active **1** has been reported. As to karahana lactone **2**, not even a synthesis of its racemate has been recorded. We therefore became interested in synthesizing both **1** and **2** in optically active forms. Such a synthesis would also clarify the absolute configuration of the natural products by chiroptical comparisons. Herein we describe the first synthesis of (1S,5R)-(-)-karahana ether **1** and (1S,5R)-(-)-karahana lactone **2**.

The key-step of our synthesis was the cyclization of the diol monotosylate **A** by an intramolecular S_N2-type displacement to give (1S,5R)-**1**. The intermediate **A** could be derived from (S)-3-hydroxy-2,2-dimethylcyclohexanone **B** (=**4a**). Microbial reduction of a prochiral diketone **3** to (S)-**4a** was first reported by Kieslich, Djerassi and their co-workers.[7] They reduced **3** with Kloeckera magna ATCC 20109 and obtained (S)-**4a** of >95 % e.e.[7] We found that the reduction of **3** can also be effected with conventional baker's yeast, and secured (S)-**4a** of ca. 99 % e.e. as determined by the HPLC analysis of the corresponding (S)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[8] **4c**. Our distilled (S)-**4a** showed a larger specific rotation value, $[\alpha]_D^{21}$ +24.1° ($CHCl_3$), than that reported previously by Djerassi, $[\alpha]_D^{20}$ +11.5° ($CHCl_3$).[7]

With a sufficient amount of **4a** in hand, we proceeded to the next stage, and attem-

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pted the conversion of **4a** to the pivotal intermediate with a C_{10} skeleton like **A**. After protecting the OH group of **4a** as a THP ether, the resulting **4b** was treated with HCO_2Et and NaOMe to give **5**. The method of Ireland and Marshall[9] was employed to prepare **8** from **5**. Thus, treatment of **5** with n-BuSH and p-TsOH yielded **6b** contaminated with a considerable amount of **6a** (**6a**:**6b**=1:2). Etherification of **6a** with dihydropyran and p-TsOH smoothly gave **6b**. The overall yield of **6b** from **4a** was 87.1 %. When **4a** was directly converted to **6a** without protecting the OH group, complete racemization at C-3 took place to give (±)-**6a**. This racemization was ascribed to the retroaldol-aldol equilibration at the C-3 position. Reduction of **6b** with $NaBH_4$ gave **7**. Removal of n-BuSH from **7** by treatment with $HgCl_2$ and $CdCO_3$ was followed by dehydration to give the α,β-unsaturated aldehyde **8** in 85.7 % yield from **6b**. Reduction of **8** with $NaBH_4$ gave **9a** in 66.0 % yield. For the determination of the optical purity of **9a**, the corresponding diol **9b** was converted to its bis-(R)-MTPA ester **9c**. The HPLC analysis of **9c** revealed the optical purity of **9b** to be 98.4 % e.e. To attach the remaining C at the C-1 position, we employed Still's modification of the Wittig rearrangement.[10] Treatment of **9a** with NaH was followed by alkylation of the resulting alkoxide with $(n\text{-Bu})_3SnCH_2I$[11] to give **10**. After purification by SiO_2 chromatography, **10** was treated with n-BuLi to effect [2.3]sigmatropic rearrangement furnishing **11a** in 83 % yield from **9a**. Thus, the required C_{10}-intermediate was secured.

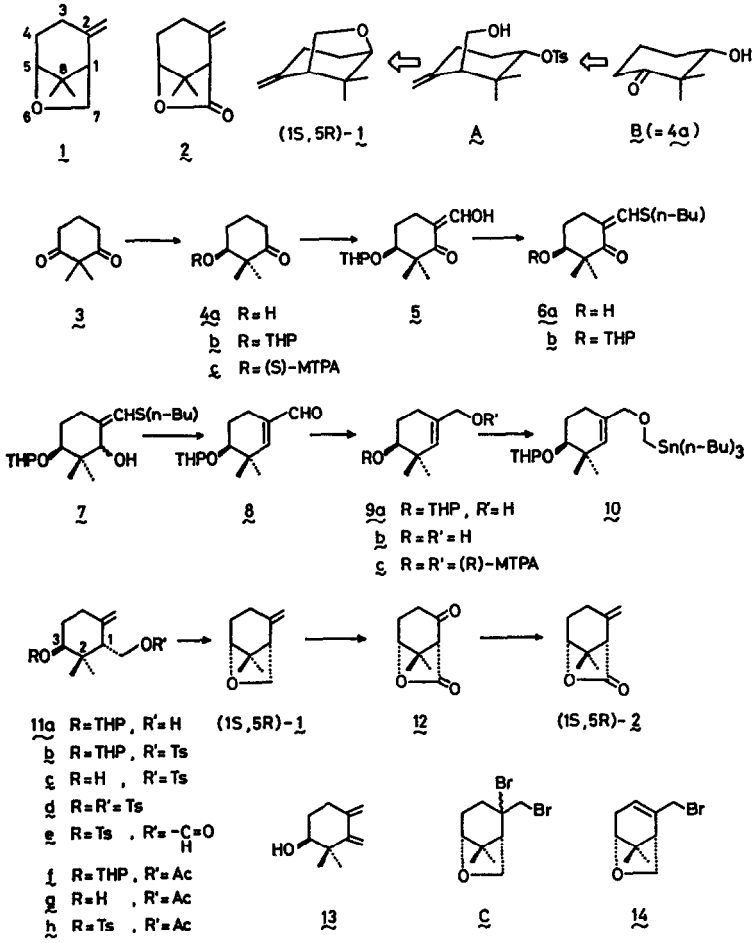

Fig.1. Synthesis of (1S,5R)-Karahana ether and (1S,5R)-Karahana lactone

The next task was the key-cyclization. At this stage the absolute configuration was unknown at the newly-formed chiral center at the C-1 position. We therefore first attempted the cyclization of a diol monotosylate **11c** derivable from **11a**. The diol mono THP ether **11a** was tosylated to **11b** and its THP protective group was removed with p-TsOH in MeOH to give **11c**. No reaction took place when **11c** was treated with C_5H_5N. Under more drastic conditions such as NaH in DMF, **11c** yielded a diene **13**. This clearly indicated that the OH group at C-3 and the CH_2OTs group at C-1 of **11c** were in trans-relationship. We therefore assigned an (S)-configuration to the C-1 position of **11c** as shown in the formula. The HPLC analysis of **11c** revealed it to be contaminated with 7.3 % of the cis-isomer. After several fruitless attempts to invert the configuration at C-3, we found that only the CH_2OTs group of **11d**, m.p. 118.0~118.3 °, could be displaced when **11d** was treated with HCO_2Cs in toluene in the presence of 18-crown-6[cf.12] to give **11e** in 66.6 % yield. This finding enabled a new approach to cyclization of **11e** by an intramolecular S_N2 displacement of the TsO group at C-3 by the CH_2O^- group at C-1. Cyclization of **11e** to (1S,5R)-karahana ether **1**, $[\alpha]_D^{21}$ -70.3 ° (n-pentane), was effected in 91 % yield by treatment of **11e** with NaOMe in MeOH. The overall yield of (1S,5R)-**1** from **11a** was 25.6 % in 5 steps. To find a more efficient synthesis, we surveyed another route. Acetylation of **11a** with Ac_2O and C_5H_5N gave **11f**, which was treated with p-TsOH in MeOH to yield **11g**. Tosylation of **11g** with p-TsCl and C_5H_5N furnished **11h**. Treatment of **11h** with NaOMe in MeOH afforded (1S,5R)-karahana ether **1**, $[\alpha]_D^{21}$ -70.0 ° (n-pentane), in 75.3 % overall yield in 4 steps from **11a**. The overall yield of (1S,5R)-**1** by the latter improved process was 30.6 % from (S)-**4a** in 12 steps. The IR, ^{1}H-NMR and mass spectra of our synthetic (1S,5R)-**1** were identical with the authentic spectra of karahana ether kindly sent to us by Dr. Y. Naya.

Unfortunately, neither the $[\alpha]_D$ value nor an authentic sample of karahana ether **1** was available to us. However, Dr. Naya was so generous as to provide us with an authentic sample of karahana lactone **2** isolated in 1968. With the assumption that karahana ether **1** and karahana lactone **2** share the same absolute stereochemistry as congeners isolated from the same source, we initiated the conversion of (1S,5R)-**1** to (1S,5R)-**2** so as to compare the chiroptical properties of natural **2** with those of synthetic (1S,5R)-**2**. This comparison would certainly clarify the stereochemistry of the natural product. At first we wanted to protect the methylene group at the C-2 position of **1** by addition of Br_2 to give **C**. But treatment of (1S,5R)-**1** with $C_5H_5NHBr_3$ gave not **C** but **14** as a single product. Direct oxidation of (1S,5R)-**1** was therefore carried out with $RuCl_3$ and $NaIO_4$ as described by Sharpless, et al.[13] The product was 2-ketokarahana lactone **12**, m.p. 48.3~50.0 °, resulting from the oxidation of $-CH_2O-$ to -COO- with concomitant cleavage of $C{=}CH_2$ to C=O. In order to reconstruct the methylene group, **12** was submitted to the Wittig reaction with $Ph_3P{=}CH_2$ in DME to give (1S,5R)-karahana lactone **2**, $[\alpha]_D^{22}$ -236 ° ($CHCl_3$), in 29.8 % overall yield from (1S,5R)-**1**. The IR, ^{1}H-NMR and mass spectra of our synthetic (1S,5R)-**2** were in complete accord with those of Dr. Naya's authentic sample. The identity of our synthetic **2** with the natural lactone was also proved by a GLC co-injection experiment. The optical purity of (1S,5R)-**2** must be >98.4 % e.e., considering the high optical purity of (S)-**4a** (ca. 99 % e.e.) and of (S)-**9a** (98.4 % e.e.). In addition, the crystalline nature of the immediate precursor **12** enabled its purification by recrystallization, which must have further improved its optical purity. The large specific rotation value of our synthetic **2** encouraged us to measure the specific rotation of Dr. Naya's authentic **2**. Even after 17 years' storage, her sample was proved to be 100 % pure by GLC analysis. Its specific rotation, however, was surprisingly small: $[\alpha]_D^{23}$ -3.06 ° ($CHCl_3$). This implies that the optical purity of natural (-)-karahana lactone **2** is only 1.3 % e.e. In other words, it is nearly racemic. It therefore seems natural to regard karahana ether **1**, the congener of **2**, as racemic, too.

In conclusion, we synthesized for the first time (1S,5R)-karahana ether 1 and (1S,5R)-karahana lactone 2. The natural monoterpene 2 was found to be almost racemic. This implies either of the following two possibilities: 1) The Japanese hop "Shinshu-wase" actually produces almost racemic 2, or 2) Karahana lactone 2 was formed as an artifact by a non-enantioselective oxidative process during the storage of the hop. Indeed a radical cyclization of an acyclic monoterpene like geraniol was achieved non-enantioselectively by Coates and Melvin as the key-step of their synthesis of (±)-karahana ether.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco A-102 spectrometer. ^{1}H-NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter. Mass spectra were recorded on a Hitachi RMU-6M spectrometer or a Jeol DX-300 spectrometer.

2,2-Dimethylcyclohexane-1,3-dione **3**. According to the reported procedure[7], **3** was obtained from 2-methylcyclohexane-1,3-dione in 66 % yield. Its IR and ^{1}H-NMR spectra were identical with those reported previously.[7]

(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone **4a**. Dry baker's yeast (200 g, Oriental Yeast Co.) was added to a soln of sucrose (450 g) in tap water (3 l) at 30°. The mixture was stirred for 10 min at 30° with aeration (16 l/min), when brisk fermentation took place. A soln of **3** (15.0 g, 0.107 mol) in 95 % EtOH (30 ml) and 0.2 % Triton X-100 (120 ml) was added to the mixture, and the fermentation was continued with stirring at 30° for 48 h after the addition of **3**. Then ether (ca. 200 ml) was added to the mixture, which was left to stand overnight at room temp. After the precipitaion of the yeast cells, the mixture was filtered through Celite. The filtrate was saturated with NaCl and extracted with EtOAc. The filter-cake was washed with EtOAc. The combined EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residual oil (27 g) was chromatographed over Merck Kieselgel 60 (220 g). Elution with n-hexane-EtOAc (10:1~5:1) gave recovered **3** (4.74g). Elution with n-hexane-EtOAc (1:2) gave 8.8 g (79 % based on the consumed **3**) of **4a**. A small portion of it was distilled to give an analytical sample, b.p. 85~87°/3.7 Torr; n_D^{21} 1.4747; $[\alpha]_D^{21}$ +24.1° (c=1.12, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ +11.5° (c=0.9, $CHCl_3$)], $[\alpha]_D^{23}$ +23.6° (c=1.03, MeOH); ν max 3470 (s), 1705 (s), 1120 (m), 1055 (s), 985 (s), 965 (m) cm^{-1}; δ(CCl_4) 1.04 (3H, s), 1.08 (3H, s), 1.30~2.00 (4H, m), 2.00~2.50 (3H, m), 3.52 (1H, m). According to the reported procedure,[9] (S)-MTPA ester **4c** was prepared from **4a**. HPLC analysis of **4c** (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Eluent, n-hexane:THF=30:1, 1.03 ml/min; Detected at 254 nm): Rt 25.6 min (99.4 %), 29.5 min (0.6 %). The optical purity of (S)-**4a** was therefore 98.8 % e.e.

(S)-(+)-2,2-Dimethyl-3-tetrahydropyranyloxycyclohexanone **4b**. p-TsOH (100 mg) was added to a soln of (S)-**4a** (16.01 g, 112.6 mmol) and 2,3-dihydropyran (14.0 g, 166.7 mmol) in dry CH_2Cl_2 (180 ml). The mixture was stirred for 30 min at room temp. It was then washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$ + K_2CO_3) and concentrated in vacuo to give 26 g of crude **4b**. This was distilled to give 25.5 g (quantitative) of pure **4b**, b.p. 90~102°/0.35 Torr; n_D^{22} 1.4740; $[\alpha]_D^{22}$ +35.7° (c=1.09, $CHCl_3$); ν max 1710 (s), 1120 (s), 1035 (s), 995 (s) cm^{-1}; δ(CCl_4) 1.00~1.20 (6H, signals at 1.04, 1.08, 1.10, 1.15), 1.32~1.74 (6H, m), 1.74~2.17 (4H, m), 2.17~2.47 (2H, m), 3.17~4.13 (3H, m), 4.42~4.75 (1H, m). (Found: C, 69.03; H, 9.73. Calc for $C_{13}H_{22}O_3$: C, 69.04; H, 9.76 %).

(3S)-6-Formyl-2,2-dimethyl-3-tetrahydropyranyloxycyclohexanone **5**. To a stirred and ice-cooled suspension of NaOMe (4.76 g, 88.2 mmol) in dry C_6H_6 (200 ml) was added a soln of **4b** (18.1 g, 79.8 mmol) in dry THF (100 ml) at 0~6°. After stirring for 10 min at 6°, freshly distilled HCO_2Et (45 ml, great excess) was added dropwise with stirring and ice-cooling. The ice-bath was then removed and the mixture was left to stand overnight at room temp. Water (100 ml) was added to the mixture with stirring and the aq layer was separated. The org layer was extracted with 5 % NaOH soln. The combined aq soln was carefully acidified with dil HCl to pH 3 at 2~5°, and rapidly extracted with EtOAc. The extract was dried ($MgSO_4$), and concentrated in vacuo to give 19 g of crude **5** as an oil. This was employed in the next step without further purification.

(S)-(-)-6-n-Butylthiomethylene-2,2-dimethyl-3-tetrahydropyranyloxycyclohexanone **6b**. The above described crude **5** (19 g) was dissolved in dry C_6H_6 (250 ml), and n-BuSH (10 ml, 8.4 g, 93.1 mmol) and p-TsOH (100 mg) were added. The mixture was stirred and heated under reflux for 3.5 h with azeotropic removal of water. It was then cooled to room temp and poured into ice-water (200 ml). The C_6H_6 layer was separated and the aq layer was extracted with ether. The combined extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 24.6 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 130 g). Elution with n-hexane-ether (8:1) gave **6b** (11.6 g). Further elution with n-hexane-ether (4:1) gave **6a** (6.9 g). The OH group of **6a** was protected again as THP ether to give **6b**. The total amount of **6b** was 22.7 g (87.1 % from **4b**), $n_D^{21.5}$ 1.5194; $[\alpha]_D^{21.5}$ -36.2° (c=1.087, $CHCl_3$); ν max 1665 (s), 1545 (s), 1155 (s), 1125 (s), 1115 (s), 1075 (s), 1055 (s), 1030 (s), 985 (s) cm^{-1}; δ(CCl_4) 0.94 (3H, deformed t, J= 6Hz), 1.05 (3H, s), 1.12 (3H, s), 1.20~2.17 (12H,br.m), 2.33 (2H, dt, J= 2 and 8Hz), 2.82 (2H, t, J= 7Hz), 3.20~4.05 (3H, m), 4.45~4.90 (1H, m), 7.34 (1H, br.s). (Found: C, 65.99; H, 9.35. Calc for $C_{18}H_{30}O_3S$: C, 66.22; H, 9.26 %).

(S)-(-)-3,3-Dimethyl-4-tetrahydropyranyloxy-1-cyclohexenecarbaldehyde **8**. A soln of $NaBH_4$ (6 g, 158.4 mmol) in 95 % EtOH (200 ml) was added dropwise to a stirred and ice-cooled soln of **6b** (22.5 g, 68.9 mmol) in THF (150 ml). After stirring for 1.5 h at 0~4°, the mixture was concentrated in vacuo. The residue was diluted with water (250 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 19.5 g of crude **7**. This was dissolved in 95 % EtOH (180 ml) and added to a suspension of $CdCO_3$ (12.0 g, 69.5 mmol) and $HgCl_2$ (18.9 g, 69.5 mmol) in 95 % EtOH (200 ml). The mixture was stirred and heated under reflux for 1.5 min. It was then cooled to room temp and concentrated in vacuo. The residue was diluted with C_6H_6 and water, and filtered through Celite. The org layer was separated and the aq layer was extracted with C_6H_6. The combined C_6H_6 soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residual oil (19.2 g) was chromatographed over SiO_2 (Merck Kieselgel 60, 190 g) to give 14.1 g (85.7 % from **6b**) of **8**, n_D^{22} 1.4902; $[\alpha]_D^{21}$ -21.6° (c=1.074, $CHCl_3$); ν max 2710 (w), 1680 (s), 1640 (m), 1130 (s), 1115 (s),

1075 (s), 1060 (s), 1030 (s) cm^{-1}; δ(CCl_4) 1.00~1.30 (6H, signals at 1.06, 1.10, 1.16), 1.30~2.00 (8H, br.m), 2.00~2.40 (2H, m), 3.19~4.05 (3H, m), 4.50~4.80 (1H, m), 6.28 (1H, br.s), 9.41 (1H, s). (Found: C, 70.16; H, 9.28. Calc for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31 %).

(S)-(-)-3,3-Dimethyl-4-tetrahydropyranyloxy-1-cyclohexenemethanol **9a**. A soln of $NaBH_4$ (5.0 g, 132 mmol) in 95 % EtOH (160 ml) was added dropwise to a stirred and ice-cooled soln of **8** (14.1 g, 59 mmol) in THF (120 ml). The mixture was stirred for 1 h at 0~5°, and then concentrated in vacuo. The residue was diluted with water (200 ml) and extracted with ether. The extract was washed with brine, dried ($MgSO_4$ + K_2CO_3) and concentrated in vacuo to give 12.0 g of an oil. This was distilled to give 9.4 g (66.0 %) of **9a**, b.p. 113~115 °/0.1 Torr; n_D^{22}1.4897; $[\alpha]_D^{22}$-6.67°(c=1.05, $CHCl_3$); ν max 3420 (br.s), 1135 (s), 1115 (s), 1060 (s), 1020 (s) cm^{-1}; δ (CCl_4) 0.85~1.10 (6H, signals at 0.93, 0.97, 1.05), 1.15~2.20 (10H, m), 3.15~3.70 (3H, m), 3.83 (3H, br.s), 4.51~4.78 (1H, m), 5.25 (1H, br.s). (Found: C, 69.61; H, 10.21. Calc for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07 %).

Determination of the optical purity of **9a**. AcOH (15 ml) was added to a soln of **9a** (740 mg, 3.08 mmol) in THF (7.5 ml) and water (7.5 ml) with stirring. The mixture was stirred for 24 h at room temp. Then K_2CO_3 was added with stirring to neutralize the mixture. It was diluted with water (100 ml) and extracted with ether. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give an oil (670 mg). This was purified by SiO_2 chromatography (Merck Kieselgel 60, 5 g) to give 420 mg (87.4 %) of **9b**. Employing (R)-MTPA, **9c** was prepared by the standard procedure.[9] HPLC analysis of **9c** (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane:THF=100:1, 1.3 ml/min; Detected at 254 nm): Rt 63.7 min (99.2 %) and 69.4 min (0.8 %). The optical purity of **6b** (and hence **6a**) was therefore 98.4 % e.e.

(S)-3,3-Dimethyl-4-tetrahydropyranyloxy-1-cyclohexanemethyl tri-n-butylstannylmethyl ether **10**. NaH (60 % dispersion in mineral oil, 2.00 g, 50 mmol) was placed in a 300 ml three-necked flask fitted with a thermometer, an Ar-baloon and a rubber septum. NaH was washed three times with dry n-pentane and dried in vacuo. Dry THF (130 ml) and dry DMF (34 ml) was added to the flask and a soln of **9a** (9.37 g, 39.0 mmol) in dry THF (40 ml) was added dropwise to a stirred suspension of NaH under Ar. The mixture was stirred for 1.25 h at room temp. Subsequently $(n\text{-}Bu)_3SnCH_2I$ (21.6 g, 50.1 mmol) was added portionwise. After the addition, the mixture was stirred for 44 h at room temp under Ar. It was then poured into ice-water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$ + K_2CO_3) and concentrated in vacuo to give 29.6 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 190 g). Elution with n-hexane gave recovered $(n\text{-}Bu)_3SnCH_2I$ (6.7 g). Subsequent elution with n-hexane-ether (10:1~5:1) gave 16.4 g of **10**, ν max 1060 (s), 1035 (s) cm^{-1}. Further elution with ether gave unchanged **9a** (740 mg). The yield of **10** was therefore 84.1 % based on consumed **9a**. This was employed in the next step without further purification.

(1S,3S)-(+)-2,2-Dimethyl-6-methylene-3-tetrahydropyranyloxycyclohexanemethanol **11a**. A soln of **10** (16.4 g, 30.2 mmol) in dry THF (180 ml) was cooled to -68° under Ar. To this was added dropwise a soln of n-BuLi in n-hexane (1.60 M, 25 ml) with stirring at < -60° under Ar. The mixture was stirred for 1 h at -65°. It was then allowed to warm to -20° during 1 h. The mixture was poured into sat NH_4Cl soln (300 ml) and extracted with ether. The ether extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$ + K_2CO_3) and concentrated in vacuo to give 18.3 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 91 g). Elution with n-hexane-ether (10:1) gave $(n\text{-}Bu)_4Sn$. Further elution with ether gave 7.54 g (98.2 %) of **11a**, n_D^{22}1.4906; $[\alpha]_D^{22}$+28.1°(c=1.07, $CHCl_3$); ν max 3470 (br.m), 3080 (w), 1645 (w), 1030 (s) cm^{-1}; δ($CDCl_3$) 0.80~1.10 (6H, signals at 0.90, 0.94, 0.99), 1.10~2.03 (8H, br.m), 2.03~2.45 (3H, m), 3.21~4.19 (6H, m), 4.50~4.80 (1H, m), 4.76 (1H, s), 4.90 (1H, s). (Found: C, 70.45; H, 10.44. Calc for $C_{15}H_{26}O_3$: C, 70.87; H, 10.30 %).

(1S,3S)-(+)-3-Hydroxy-2,2-dimethyl-6-methylenecyclohexanemethyl tosylate **11c**. p-TsCl (7.80 g, 40.9 mmol) was added to a stirred and ice-cooled soln of **11a** (7.05 g, 27.7 mmol) in dry C_5H_5N (35 ml). The mixture was stirred for 6 h at 0~5°. It was then poured into ice-water (120 ml) and extracted with ether. The extract was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$ + K_2CO_3), and concentrated in vacuo to give 10.8 g of crude **11b** as an oil. This was dissolved in MeOH (200 ml), and p-TsOH (1 g) was added with stirring. The soln was stirred for 70 min at room temp. It was then neutralized with solid $NaHCO_3$, and concentrated in vacuo. The residue was diluted with water (150 ml) and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 8.8 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 81 g) to give 6.86 g (76.0 % from **11a**) of **11c**, n_D^{19}1.5347; $[\alpha]_D^{21}$ +6.0° (c=0.982, $CHCl_3$); νmax 3470 (br.m), 3080 (w), 1650 (w), 1600 (m), 1360 (s), 1180 (s) cm^{-1}; δ (CCl_4) 0.85 (3H, s), 0.92 (3H, s), 1.40~1.90 (2H, m), 1.70 (1H, s, OH), 1.90~2.34 (3H, m), 2.44 (3H, s), 3.35~3.66 (1H, m), 4.11 (2H, d, J= 7Hz), 4.56 (1H, s), 4.80 (1H, s), 7.35 (2H, d, J= 8Hz), 7.79 (2H, d, J= 8Hz); HPLC (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane:THF=3:1, 0.85 ml/min; Detected at 254 nm): Rt 12.4 min (7.3 %) and 14.9 min (92.7 %). (Found: C, 63.08; H, 7.35. Calc for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46 %).

(1S,3S)-(+)-2,2-Dimethyl-6-methylene-3-tosyloxycyclohexanemethyl tosylate **11d**. p-TsCl (10.57 g, 55.4 mmol) was added to a stirred soln of **11c** (2.00 g, 6.2 mmol) and 4-(N,N-dimethylamino)pyridine (40 mg) in dry C_5H_5N (20 ml). The mixture was stirred for 2.5 days at room temp. It was then poured into ice-water and extracted with $CHCl_3$. The extract was washed with 2 N-HCl, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 2.88 g (97.6 %) of a solid. This was recrystallized from n-hexane-C_6H_6 (1:2) to give 2.28 g (77.3 %) of pure **11d**, m.p. 118.0~118.3° ; $[\alpha]_D^{21}$+15.9°(c=1.735, $CHCl_3$); ν max 1655 (w), 1600 (w), 1500 (w), 1360 (s), 1345 (s), 1175 (s) cm^{-1}; δ ($CDCl_3$) 0.74 (3H, s), 0.87 (3H, s), 1.50~1.90 (2H, m), 1.97~2.40 (3H, m), 2.44 (6H, s), 4.15 (2H, d, J= 6Hz), 4.43 (1H, deformed t, J= 6Hz), 4.63 (1H, s), 4.87 (1H, s), 7.40 (4H, d, J= 8Hz), 7.85 (4H, d, J= 8Hz); HPLC (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane:THF=6:1, 0.8 ml/min; Detected at 254 nm): Rt 26.8 min (single peak). (Found: C, 60.33; H, 6.25. Calc for $C_{24}H_{30}O_6S_2$: C, 60.23; H, 6.32 %).

(1S,3S)-(+)-2,2-Dimethyl-6-methylene-3-tosyloxycyclohexanemethyl formate **11e**. HCO_2H (3.47 g, 74.5 mmol) was added dropwise to a stirred soln of Cs_2CO_3 (8.1 g, 24.9 mmol) in dry MeOH (120 ml). The mixture was stirrred for 1 h at room temp. MeOH was then revomed in vacuo. The excess HCO_2H was removed by distillation with dry toluene (three times), and the residual moist solid was dried in vacuo overnight. A soln of dicyclohexyl-18-crown-6 (1.15 g, 3.09 mmol) in dry toluene (10 ml) was added to the flask in which HCO_2Cs was prepared and dried. To this mixture was added a soln of **11d** (1.49 g, 3.11 mmol) in dry toluene (50 ml). The mixture was stirred and heated at 110° for 35 h. It was then cooled to room temp and mixed with water (80 ml). The org layer was separated and the aq layer was extracted with C_6H_6. The combined org soln was washed with water, sat $NaHCO_3$ soln and brine, dried (Na_2SO_4) and concentrated in vacuo to give 2.66 g of an oil. This was

chromatographed over SiO_2 (Merck Kieselgel 60, 26 g) to give 730 mg (66.6 %) of **11e**, n_D^{21}1.5200; $[\alpha]_D^{21}$+29.8°(c=1.270, $CHCl_3$); νmax 3080 (w), 1730 (s), 1650 (w), 1600 (m), 1500 (w), 1190 (s), 1180 (s) cm^{-1}; δ(CCl_4) 0.84 (3H, s), 0.95 (3H, s), 1.61~2.08 (2H, m), 2.08~2.38 (3H, m), 2.46 (3H, s), 4.34 (2H, d, J= 7Hz), 4.63 (1H, t, J= 5Hz), 4.70 (1H, s), 4.94 (1H, s), 7.44 (2H, d, J= 8Hz), 7.81 (2H, d, J= 8Hz), 8.14 (1H, s). (Found: C, 61.12; H, 6.84. Calc for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86 %).

(1S,3S)-2,2-Dimethyl-6-methylene-3-tetrahydropyranyloxycyclohexanemethyl acetate **11f**. Ac_2O (1 ml, 9.1 mmol) was added to a stirred soln of **11a** (310 mg, 1.22 mmol) in dry C_5H_5N (3 ml). The mixture was stirred overnight at room temp. It was then poured into ice-water (20 ml) and extracted with ether. The extract was washed with sat $CuSO_4$ soln, water and brine, dried (K_2CO_3) and concentrated in vacuo to give 360 mg (quantitative) of **11f**, νmax 3080 (w), 1745 (s), 1650 (w), 1035 (s) cm^{-1}. This was employed in the next step without further purification.

(1S,3S)-(+)-3-Hydroxy-2,2-dimethyl-6-methylenecyclohexanemethyl acetate **11g**. p-TsOH (6 mg) was added to a stirred soln of **11f** (310 mg, 1.05 mmol) in MeOH (6 ml). The mixture was stirred for 80 min at room temp. It was then poured into 5 % $NaHCO_3$ soln (50 ml), and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated in vacuo to give 300 mg of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 3 g) to give 240 mg (95.7 %) of **11g** as an oil, n_D^{23}1.4828; $[\alpha]_D^{23}$+5.76°(c=1.18, $CHCl_3$); ν max 3480 (br.s), 3090 (w), 1745 (s), 1650 (m), 1240 (s), 1060 (s), 1040 (s), 900 (m) cm^{-1}; δ($CDCl_3$) 0.97 (6H, s), 1.55~1.90 (3H, m), 2.01 (3H, s), 1.90~2.58 (3H, m), 3.20~3.80 (1H, br.m), 4.36 (2H, d, J= 7Hz), 4.65 (1H, s), 4.86 (1H, s). (Found: C, 68.15; H, 9.48. Calc for $C_{12}H_{20}O_3$: C, 67.89; H, 9.56 %).

(1S,3S)-2,2-Dimethyl-6-methylene-3-tosyloxycyclohexanemethyl acetate **11h**. p-TsCl (2.0 g, 10.5 mmol) was added to a stirred soln of **11g** (230 mg, 1.08 mmol) and 4-(N,N-dimethylamino)pyridine (ca. 5 mg) in dry C_5H_5N (3.5 ml). The mixture was stirred for 2.5 days at room temp. It was then poured into ice-water (30 ml) and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 360 mg (90.7 %) of **11h** as an oil, νmax 3080 (w), 1745 (s), 1650 (m), 1600 (m), 1500 (w), 1365 (s), 1240 (s), 1190 (s), 1180 (s) cm^{-1}. This was employed in the next step without further purification.

(1S,5R)-(-)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]octane [(1S,5R)-karahana ether] **1**. (a) From **11e**. A soln of NaOMe in MeOH (2.8 g of 28 % NaOMe in MeOH was diluted with MeOH to 10 ml, and its 2 ml was used; 2.90 mmol as NaOMe) was added to a stirred soln of **11e** (730 mg, 2.07 mmol) in MeOH (10 ml). The mixture was stirred for 20 h at room temp. It was then diluted with water (35 ml) and extracted with n-pentane. The extract was washed with water, sat $NaHCO_3$ soln and brine, dried (K_2CO_3) and concentrated in vacuo (bath temp 1~2°). The residual oil (311 mg) had a camphor-like smell. The oil was purified by SiO_2 chromatography (Merck Kieselgel 60, 1 g). Elution with n-pentane gave 293 mg of an oil. This was distilled to give 283.2 mg (91.0 %) of **1**, b.p. 100~110°(bath temp)/85 Torr; n_D^{21}1.4781; $[\alpha]_D^{21}$-70.3°(c=1.020, n-pentane); ν max 3080 (w), 2980 (s), 2960 (s), 2900 (s), 1650 (m), 1500 (w), 1480 (w,sh), 1465 (m,sh), 1450 (m), 1438 (m), 1390 (m), 1370 (m), 1350 (w), 1290 (w), 1240 (w), 1225 (w), 1205 (w), 1175 (w), 1150 (w), 1065 (s), 1038 (s), 1020 (m), 1000 (w), 980 (m), 965 (w), 935 (m), 925 (m), 910 (m), 880 (s), 850 (w), 800 (w), 775 (w), 740 (w), 705 (w) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, s), 1.07 (3H, s), 1.50~1.90 (2H, m), 2.09~2.40 (3H, m), 3.80 (2H, deformed d, J= 8Hz), 4.03 (1H, dd, J= 4.5 and 8Hz), 4.50~4.80 (2H, m); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 20.88, 25.49, 25.83, 28.61, 42.25, 54.05, 71.18, 82.44, 107.46, 148.99; MS: m/z 152 (M^+, 4 %), 137 (M^+-15, 1.5 %), 122 (33 %), 107 (100 %, base peak), 79 (51 %); GLC (Column, OV-1, 1 m x 4 mm at 60°+8°/min; Carrier gas, N_2, 1 kg/cm^2) Rt 6.4 min (100 %). (Found: m/z 152.1171. Calc for $C_{10}H_{16}O$: 152.1202). The IR, ^{1}H-NMR and mass spectra of (1S,5R)-1 were identical with the authentic spectra kindly sent to us by Dr. Y. Naya.
(b) From **11h**. A soln of NaOMe in MeOH (2.6 g of 28 % NaOMe in MeOH was diluted with MeOH to 10 ml, and its 1 ml was used; 1.35 mmol as NaOMe) was added to a stirred soln of **11h** (353.3 mg, 0.96 mmol) in MeOH (5 ml). The mixture was stirred for 24 h at room temp. It was then diluted with water and extracted with n-pentane. The extract was washed with water, sat $NaHCO_3$ soln and brine, dried (K_2CO_3) and concentrated in vacuo in an ice-bath at 1~2°. The residual oil was chromatographed over SiO_2 (Merck Kieselgel 60, 1.7 g). Elution with n-pentane-ether (10:1) gave an oil. This was distilled to give 125.7 mg (86.8 %) of (1S,5R)-1, $[\alpha]_D^{22}$-70.0° (c=1.035, n-pentane). The spectral data were identical with those of **1** prepared from **11e**.

(1R,5R)-(-)-8,8-Dimethyl-6-oxabicyclo[3.2.1]octane-2,7-dione **12**. $RuCl_3 \cdot H_2O$ (6 mg) was added to a biphasic mixture consisting of CCl_4 (3 ml), MeCN (3 ml), water (4.5 ml), (1S,5R)-1 (118 mg, 0.785 mmol) and $NaIO_4$ (2.86 g, 13.4 mmol). The mixture was stirred vigorously for 24 h at room temp. It was then warmed to 40° and stirred vigorously for 48 h. CH_2Cl_2 (15 ml) was added to the mixture and it was filtered through Florisil. The filter-cake was washed with CH_2Cl_2. The combined filtrate and washings were diluted with water, and the org layer was separated. The aq layer was extracted with CH_2Cl_2. The combined org soln was dried ($MgSO_4$) and filtered through Celite. The filtrate was concentrated in vacuo to give 70.7 mg (53.4 %) of **12** as a solid. An analytical sample was recrystallized from n-hexane-ether (6:1) to give needles, m.p. 48.3~50.0°; $[\alpha]_D^{21}$-206°(c=0.715, $CHCl_3$); νmax (KBr) 1785 (s), 1735 (s), 1125 (s), 950 (s) cm^{-1}; δ($CDCl_3$) 1.08 (3H, s), 1.25 (3H, s), 2.02~2.70 (4H, m), 2.97 (1H, s), 4.40~4.54 (1H, m). (Found: m/z 168.0768. Calc for $C_9H_{12}O_3$: 168.0786).

(1S,5R)-(-)-8,8-Dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one [(1S,5R)-karahana lactone] **2**. A suspension of $Ph_3P^+MeBr^-$ (1.07 g, 3 mmol; dried at 80°/3 Torr for 24 h) in dry DME (28 ml) under Ar was cooled to -10°, and a soln of n-BuLi in n-hexane (1.55 M, 1.8 ml, 2.79 mmol) was added dropwise with stirring. The orange mixture was stirred at -10° for 1 h and allowed to settle before use. To a soln of **12** (30.1 mg, 0.179 mmol) in dry DME (1 ml) was added the "salt free" Wittig reagent (2.2 ml) prepared as described above via syringe at -5° under Ar. The mixture was stirred at -5° for 1 h and 1.8 ml of the Wittig reagent was added again. An ice-salt bath was removed and the mixture was stirred for 3.5 h at room temp. To the mixture was added 5 % NH_4Cl soln (1 ml), and the mixture was concentrated in vacuo. The residue was diluted with 5 % NH_4Cl soln (20 ml) and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 140 mg of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 2.8 g) to give 16.6 mg (55.8 %) of (1S,5R)-2, n_D^{23}1.4850; $[\alpha]_D^{23}$-236°(c=0.83, $CHCl_3$); νmax 3090 (w), 2980 (s), 2900 (m), 1785 (s), 1655 (m), 1480 (m), 1460 (m), 1400 (w), 1380 (w), 1345 (m), 1300 (m), 1275 (w), 1255 (m), 1230 (w), 1205 (w), 1185 (w), 1140 (s), 1062 (m), 1040 (s), 1005 (w), 990 (w), 975 (w), 950 (s), 900 (m), 880 (m), 865 (m), 715 (w), 700 (w) cm^{-1}; δ(CCl_4) 0.97 (3H, s), 1.15 (3H, s), 1.62~2.01 (2H, m), 2.03~2.50 (2H, m), 2.60 (1H, s), 4.10~4.28 (1H, m), 4.70~4.90 (2H,br.m); MS: m/z 166 (M^+), 137 (M^+-29, 2 %), 122 (M^+-44, 31 %), 107 (100 % base peak), 91 (33.5 %), 79 (46 %); GLC (Column, OV-1, 1 m x 4 mm at 80°+6°/min; Carrier gas, N_2, 1 kg/cm^2) Rt 6.4 min (100 %). The Rt was identical with that of the natural **2** by a

co-injection experiment. (Found: m/z 166.0989. Calc for $C_{10}H_{14}O_2$: 166.0994). The IR, ^{1}H-NMR and mass spectra of (1S,5R)-2 were identical with the authentic spectra kindly provided by Dr. Y. Naya. Her authentic 2 showed the following specific rotation: $[\alpha]_D^{23}$ -3.06° (c=0.49, $CHCl_3$).

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