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FACILE SYNTHESIS OF (4S)-(-)-[9-^{3}H]LIMONENE

Yoshikazu Hiraga, Hiroshi Danjo, Takatoshi Ito and *Takayuki Suga

Department of Chemistry, Faculty of Science,
Hiroshima University, Kagamiyama,
Higashi-Hiroshima 724, Japan

SUMMARY

(4*S*)-[9-^{3}H]-1-Methyl-4-(1'-methylethenyl)cyclohexene ((4*S*)-(-)-[9-^{3}H]limonene) was synthesized from (1'*S*,2*RS*)-2-(4'-methylcyclohex-3'-enyl)propanal ((4*S*,8*RS*)-(-)-1-*p*-menthen-9-al) *via* a convenient route in a high yield with improved enantiomeric purity.

Key words: (4*S*)-(-)-[9-^{3}H]limonene, tosylation, iodination, high yield, enantiomeric purity

INTRODUCTION

In the course of studies on the biosynthesis of carvone in *Mentha spicata* (spearmint), we needed radioactive (4*S*)-(-)-limonene (**1**) as substrate. It is reported that [9-^{3}H]limonene is synthesized from 1-*p*-menthen-9-al (**3**) in 15% yield [1]. Re-examination of this synthesis using a non-radioactive (4*S*)-(-)-limonene (**1**) resulted in a low yield and poor enantiomeric purity. This inconvenient result is probably due to the inefficient conversion of (1'*S*,2*RS*)-2-(4'-methylcyclohex-3'-enyl)propanol ((4*S*,8*RS*)-(-)-1-*p*-menthen-9-ol) (**2**) to **1** by introduction of an unsaturation at the 8-position *via* bromination and debromination. In the present work, we could synthesize (4*S*)-(-)-[9-^{3}H]limonene ([9-^{3}H]-**1**) in a high yield by completing the conversion of [9-^{3}H]-**2** to [9-^{3}H]-**1** *via* a tosylation-iodination-deiodination procedure. In addition, the non-radioactive preliminary experiments indicated that this modified method improved greatly the enantiomeric purity.

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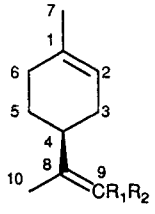
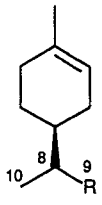


1: $R_1 = R_2 = H$
[9-^{3}H] - 1: $R_1 = {}^3H$, $R_2 = H$



2 : R = CH_2OH
3 : R = CHO
[9-^{3}H] - 2 : R = CH^3HOH
4 : R = CH^3HOTs
5 : R = CH^3HI
Ts = *p* - toluenesulfonyl

RESULTS AND DISCUSSION

The 8(9)-double bond of non-radioactive (4*S*)-(-)-limonene (**1**) was hydroborated with 9-borabicyclo[3.3.1]nonane (9-BBN), followed by oxidation with alkaline hydrogen peroxide to afford (4*S*,8*RS*)-(-)-1-*p*-menthen-9-ol (**2**) in 77% yield. The menthen-9-ol (**2**) was oxidized with pyridinium dichromate (PDC) to give (4*S*,8*RS*)-(-)-1-*p*-menthen-9-al (**3**) in 72% yield. The menthen-9-al (**3**) was reduced with NaB^3H_4 in isopropyl alcohol to give tritiated menthen-9-ol ([9-^{3}H]-**2**). This tritiated menthen-9-ol ([9-^{3}H]-**2**) was then converted to its tosylate (**4**) by treatment with *p*-toluenesulfonyl chloride (TsCl) and dimethylaminopyridine (DMAP) in dichloromethane. After iodination of the tosylate (**4**) with sodium iodide in acetone, a tritiated iodide (**5**) thus obtained was deiodinated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give (4*S*)-(-)-[9-^{3}H]limonene ([9-^{3}H]-**1**). The overall yield of [9-^{3}H]-**1** from the menthen-9-al (**3**) was 55%. The enantiomeric purity of limonene ((-) : 72% ee) synthesized by our method using the cold sample was higher than that of the limonene ((-) : 38% ee) by the literature method [1].

Thus, we established a facile synthesis of (4*S*)-(-)-[9-^{3}H]limonene ([9-^{3}H]-**1**) from non-radioactive (4*S*)-(-)-limonene (**1**). Although this modified method involves one more step for the introduction of an unsaturation at the 8-position, it is more facile and efficient rather than the literature method [1], because not only the last two steps could be performed as one pot reaction without purification of the product, but also the enantiomeric purity of the tritiated limonene was greatly improved. This method has also the possible extension to the synthesis of the deuteriated limonene.

EXPERIMENTAL

Material. (4*S*)-(-)-Limonene {$[\alpha]^{25}_D$ -119.0° (neat) lit. -122.6° (neat) [2]} and other chemicals were commercial products. NaB^3H_4 was purchased from Amersham Japan. Radiochemical purity was checked by means of a HPLC radioanalyzer (ALOKA, RLC-700). The radioactivity of the ^{3}H-labelled compounds was measured on an ALOKA liquid scintillation counter, model LSC-3100. IR and NMR spectra were obtained on a JASCO

A-102 and a JEOL GSX 500 (^{1}H, 500.16 MHz ; ^{13}C, 125.78 MHz) instruments, respectively. Optical rotation was measured on a JASCO DIP-360 polarimeter. Enantiomeric purities were determined on a GLC (Shimadzu GC-15A) attached with a chiral column (CP-cyclodextrin-B-236-M-19, CHROMPACK), using on-column injection and flame ionization detection with H_2 as carrier.

(4*S*,8*RS*)-(-)-1-*p*-Menthen-9-ol (**2**) To (4*S*)-(-)-limonene (**1**) (5.0 g, 33 mmol) dissolved in dry tetrahydrofuran (THF, 5 ml), 9-BBN(dimer) (6.0 g, 25 mmol) dissolved in dry THF (40 ml) was added dropwise with stirring at 0 °C. After stirring for 2 h at 0 °C and for another hour at r.t., an excess of the 9-BBN was quenched with water (10 ml). Then the reaction mixture was oxidized with a mixture of 30% hydrogen peroxide (15 ml) and 3 M sodium hydroxide solution (15 ml) at 45 °C. After saturating with potassium carbonate, the organic layer was separated and the aqueous phase was extracted with ether. The ether soln was combined with the THF solution. The combined soln was dried over $MgSO_4$. The extract obtained after removal of the solvents was subjected to silica gel column chromatography (hexane:ether ; 5:5 v/v) to afford **2** (3.9 g, 77%) : $[\alpha]^{25}_D$ -79.3° (*c* 0.58, hexane) ; IR (neat) 3325 (O-H) and 1040 cm^{-1} (C-O) ; ^{1}H NMR ($CDCl_3$) δ = 5.37 (br. *s*, H-C(2)), 3.65 (*dd*, *J* = 10, 6.0 Hz, 1H, CH_2(9)), 3.50 (*d*, *J* = 10 Hz, 1H, CH_2(9)), 1.64 (*s*, CH_3 (7)), 0.94 (*d*, *J* = 6.5 Hz,CH_3 (10)), 0.91 (*d*, *J* = 6.5 Hz, CH_3 (10)), 1.20-2.00 (*m*, 9H, CH_2 (3), H-C(4), CH_2(5), CH_2 (6), H-C(8), O-H) ; ^{13}C NMR ($CDCl_3$) δ = 134.0, 133.9 (C(1)), 120.8, 120.7 (C(2)), 66.3, 66.2 (C(9)), 40.2, 40.0 (C(8)), 35.3, 35.2 (C(4)), 30.8, 30.6 (CH_2), 29.8, 27.8 (CH_2), 27.3, 25.5 (C(5)), 23.5 (C(7)), 13.7, 13.3 (C(10)). The 1:1 area ratio of the signals at δ = 0.91 and 0.94 ppm (CH_3) in the ^{1}H NMR and pairing of the respective ^{13}C-signals of C(1), C(2) and C(9) indicated the presence of two diastereomers.

(4*S*,8*RS*)-(-)-1-*p*-Menthen-9-al (**3**) To freshly prepared PDC [3] (2.5 g, 6.6 mmol) suspended in dry dichloromethane (5 ml), the menthen-9-ol (**2**) (500 mg, 3.25 mmol) was added dropwise at room temperature. After stirring for 20 h at r.t., the reaction mixture was filtered and the tarry residue was washed with ether. The combined filtrate was worked up by washing successively with 1 M HCl, sat. $NaHCO_3$ and sat. NaCl solution. After removal of the solvent, the crude menthen-9-al (**3**) obtained was purified by silica gel column chromatography (hexane:ether ; 8:2 v/v) to give **3** (354 mg, 72%) : $[\alpha]^{25}_D$ -85.2° (*c* 0.54, hexane) ; IR (neat) 2700 (C-H

of -CHO) and 1725 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$) δ = 9.68 (*d*, *J* = 2.0 Hz, H-C(9)), 9.66 (*d*, *J* = 2.0 Hz, H-C(9)), 5.36 (br. *s*, H-C(2)), 2.28 (*m*, H-C(8)), 1.65 (*s*, CH_3 (7)), 1.38 (*m*, H-C(5)), 1.08 (*d*, *J* = 6.5 Hz, CH_3 (10)), 1.06 (*d*, *J* = 6.5 Hz, CH_3 (10)), 1.66-2.10 (*m*, 6H, CH_2 (3), H-C(4), H-C(5), CH_2 (6)) ; ^{13}C NMR ($CDCl_3$) δ = 205.5, 205.4 (C(9)), 134.1, 134.0 (C(1)), 120.0, 119.9 (C(2)), 51.0, 50.7 (C(8)), 34.4, 34.3 (C(4)), 30.1, 30.0 (CH_2), 29.7, 28.1 (CH_2), 27.3, 25.5 (CH(5)), 23.4 (C(7)), 10.4, 10.3 (C(10)). The 1:1 area ratio of the signals at δ = 1.08 and 1.06 ppm (CH_3) in the ^1H NMR and pairing of the respective ^{13}C-signals of C(1), C(2) and C(9) indicated the presence of two diastereomers.

[9-^{3}H]-(4*S*,8*RS*)-(-)-1-*p*-Menthen-9-ol ([9-^{3}H]-**2**) A soln of **3** (112 mg, 0.74 mmol) in 1.5 ml of *i*-PrOH was treated with NaB^3H_4 (2.3 mg, 0.05 mmol ; 925 MBq, 18.5 GBq/mmol) for 2 h at 0 °C and then 1 h at room temperature. In order to omit the separation step of the tritiated menthen-9-ol from the unchanged **3** and to complete the reduction, $NaBH_4$ (27.2 mg, 0.71 mmol) was added and the mixture was stirred for another hour at room temperature. After removal of the solvent, the residue was hydrolyzed with H_2O (3 ml) and the aq. soln was extracted with ether (4 × 3 ml). Removal of the solvent from the combined ether soln, after drying over Na_2SO_4, afforded [9-^{3}H]-**2**. It was used for the next reaction without purification.

[9-^{3}H]-(4*S*,8*RS*)-1-*p*-Menthen-9-yl tosyl ester ((1'*S*,2*RS*)-[1-^{3}H]-2-(4'-Methylcyclohex-3'-enyl)propyl tosyl ester) (**4**) [9-^{3}H]-**2** obtained above was treated with TsCl (265 mg, 1.5 mmol) and DMAP (217 mg, 1.8 mmol) in dichloromethane (6 ml) for 18 h at room temperature. The reaction mixture, after washing successively with H_2O, 10% HCl, sat. $NaHCO_3$ and sat. NaCl soln, was extracted with ether. Removal of the solvent from the ether soln, after drying over Na_2SO_4, afforded **4**. It was used for the next reaction without purification.

(4*S*)-(-)-[9-^{3}H]Limonene ([9-^{3}H]-**1**) **4** and sodium iodide (55 mg, 3.7 mmol) were refluxed in acetone (4 ml) for 17 h at 70 °C to afford **5** [4]. This reaction was monitored by TLC (hexane:ether ; 9:1 v/v). After the iodination was completed, DBU (1 ml) was added to the reaction mixture. Then, the mixture was refluxed for 3 h at 70 °C [5]. A product was extracted with pentane to give the pentane soln, which was dried over Na_2SO_4. The product obtained from the pentane soln was purified by silica gel column chromatography (pentane) to give [9-^{3}H]-**1** (56 mg, 0.41 mmol ; 259 MBq, 629 MBq/mmol). The overall yield of [9-^{3}H]-**1** from **3** was 55%.

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