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SYNTHESIS OF (2S,4aS,8aR)-(-)-1,1,4a-TRIMETHYL-2-DECALOL, AN INHIBITOR OF STEROID BIOSYNTHESIS

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Abstract -- (2S,4aS,8aR)-(-)-1,1,4a-Trimethyl-2-decalol was synthesized from (S)-(+)-3-hydroxy-2,2-dimethylcyclohexanone in 31 % overall yield in 8 steps.

In 1978, (2S*,4aS*,8aR*)-1,1,4a-trimethyl-2-decalol (±)-**1a** was found to be an inhibitor of cholesterol biosynthesis by Spencer, Chang and their respective co-workers.[1,2] The compound (±)-**1a** specifically inhibits squalene-2,3-epoxide cyclase in Chinese hamster ovary cells.[2] The synthesis of (±)-**1a** was first reported in 1958.[3] Then, in the same year, (2R,4aR,8aS)-(+)-**1a** was also prepared.[4] Nelson et al. resolved (±)-**1a** and found both of the enantiomers to be inhibitors of steroid biosynthesis.[1] We became interested in synthesizing (2S,4aS,8aR)-(-)-**1a**, which is a structural unit widely distributed among sesqui-, di- and triterpenoids.

For our purpose (S)-(+)-3-hydroxy-2,2-dimethylcyclohexanone **2a** seemed to be an ideal starting material with its OH group in correct S-configuration. The ketol (S)-**2a** was

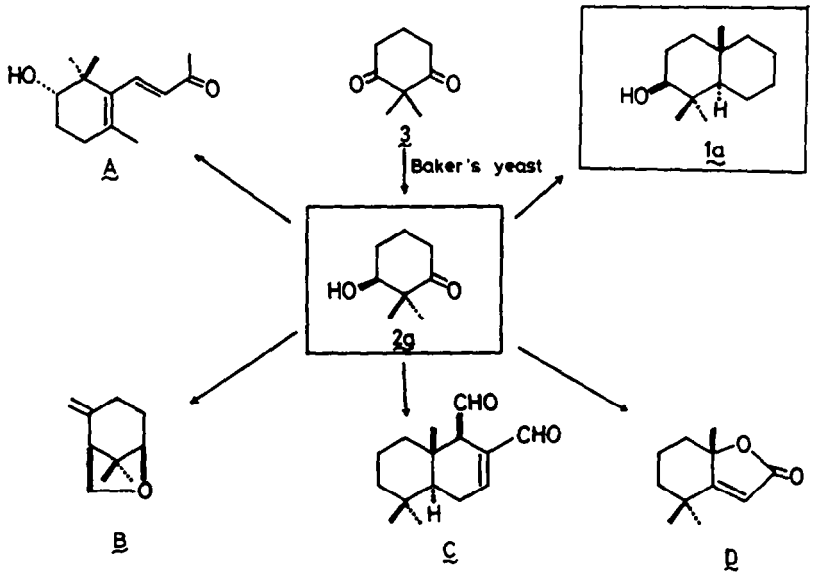

Fig. 1. Conversion of (S)-3-hydoxy-2,2-dimethylcyclohexanone to various optically active compounds.

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readily available by the reduction of 2,2-dimethylcyclohexane-1,3-dione **3** with fermenting baker's yeast.[5,6] Fig. 1 illustrates the versatility of **2a** as a common building block for the syntheses of various optically active natural products **A**~**D**. (S)-2-Hydroxy-β-ionone **A** is a tobacco flavor,[5] karahana ether **B** is a constituent of Japanese hop oil,[6] polygodial **C** is an insect antifeedant,[7] and dihydroactinidiolide **D** is a pheromone component of the red imported fire ant.[8]

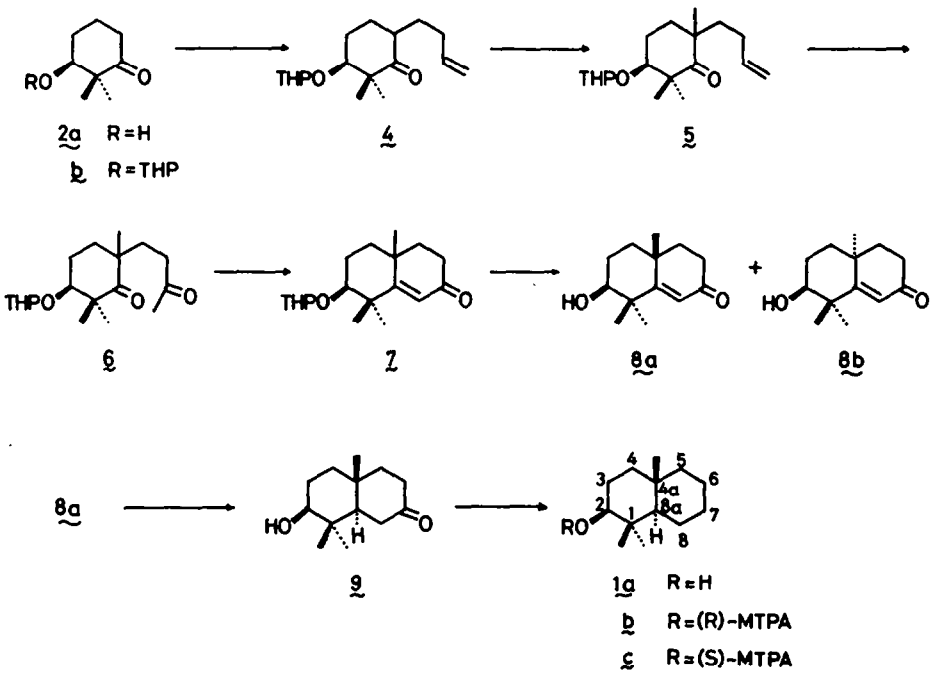

Fig. 2. Synthesis of (2S,4aS,8aR)-(-)-1,1,4a-trimethyl-2-decalol.

Our synthesis of (-)-**1a** from **2a** is shown in Fig. 2. The depicted strategy was adopted after our failure to prepare **7** by the conventional Robinson Annelation methodology. (S)-2,2-Dimethyl-3-tetrahydropyranyloxycyclohexanone **2b** of 98.5 % e.e. was prepared quantitatively from **2a** as reported previously.[5,6] Alkylation of **2b** with 3-butenyl iodide and LiN(i-Pr)$_2$ (LDA) in THF-HMPA gave **4** as a stereoisomeric mixture in 92 % yield. The reactivity of 3-butenyl bromide was insufficient to be employed in this alkylation reaction. Methylation of **4** with MeI and LDA in THF-HMPA furnished **5** as a stereoisomeric mixture in 92.5 % yield. In a preliminary small-scale experiment, the two stereoisomers were found to be separable by SiO_2 chromatography. The less polar and the more polar isomers were obtained in a ratio of 71:29. They were separately converted to a bicyclic intermediate **8a** and its isomer **8b**. The major and less polar product led to **8a**, while the minor and more polar one gave **8b**. In a large-scale run, the product **5** was chromatographed over SiO_2. The desired less polar isomer was eluted in earlier fractions to secure **5** enriched in the desired stereoisomer. This olefinic ketone **5** was submitted to the Pd-catalyzed oxidation with $PdCl_2$-CuCl in aq DMF in the presence of O_2[9] to give **6** in 77.8 % yield.

The crystalline diketone **6** was heated with pyrrolidine in C_6H_6 to effect cyclization. The product **7**, obtained in 89.4 % yield, was treated with p-TsOH in MeOH to give a mixture of **8a** and **8b**. These were separated by SiO_2 chromatography to give **8a**, m.p. 77.5~78.0°, $[\alpha]_D^{22}$ -108° ($CHCl_3$), in 84.3 % yield from **7**. As a minor isomer, **8b**, m.p. 112~113°, $[\alpha]_D^{23}$ +130° ($CHCl_3$), was obtained in 4.3 % yield. In the ^1H NMR spectrum of the major and less

polar isomer **8a**, a 1H signal at δ 3.32 was observed as dd (J=6 and 9 Hz), manifesting the axial nature of the CHOH proton. It should be noted that the isomer **8a** with an eq OH group was the less polar one. In the case of **8b**, the signal due to the eq CHOH proton was observed at δ 3.54~3.74 with $W_{h/2}$ =8 Hz.

Hydrogenation of **8a** over Pd-C in MeOH was completely stereoselective to give **9**, m.p. 91.6~92.0°, $[\alpha]_D^{23}$ -5.2° ($CHCl_3$), in 95.7 % yield with 100 % chemical purity as checked by GLC. Finally the Wolff-Kishner reduction of **9** afforded in 91.4 % yield (2S,4aS,8aR)-(-)-1,1,4a-trimethyl-2-decalol **1a**, m.p. 86.5~87.4° (lit.[4] m.p. 87~89°), $[\alpha]_D^{23}$ -11.3° (MeOH) [lit.[1] $[\alpha]_{589}$ -11.7° (MeOH)]. The enantiomeric purity of (-)-**1a** was found to be 100 % e.e. by the HPLC analysis of the corresponding α-methoxy-α-trifluoromethylphenylacetates (MTPA esters),[10] **1b** and **1c**. The overall yield of (-)-**1a** from (+)-**2a** was 31 % in 8 steps.

In conclusion, we developed a new synthesis of (-)-**1a**, which is a useful tool in studying regulation of steroid metabolism. The intermediates **8a** and **9** will be of use as chiral building blocks for syntheses of polycyclic terpenes.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP 140 polarimeter. Fuji-Davison BW-820 MH gel was used for SiO_2 column chromatography.

(S)-(+)-2,2-Dimethyl-3-tetrahydropyranyloxycyclohexanone **2b**. This was obtained in quantitative yield from **2a** [n_D^{23} 1.4754; $[\alpha]_D^{23}$ +24.2° (c=1.03, $CHCl_3$), 98.5 % e.e. (determined by the HPLC analysis of the corresponding MTPA ester[5,6])]; n_D^{23} 1.4731; $[\alpha]_D^{23}$ +24.8° (c=0.71, $CHCl_3$). Its IR and NMR spectra were identical with those reported previously.[5,6]

(3S,6RS)-(+)-6-(3'-Butenyl)-2,2-dimethyl-3-tetrahydropyranyloxycyclohexanone **4**. A soln of LDA was prepared by the dropwise addition of n-BuLi in n-hexane (1.54 N, 28.21 ml, 42.6 mmol) to a stirred and cooled soln of $(i\text{-Pr})_2NH$ (6.07 ml, 43.4 mmol) in dry THF (59 ml) at −60~−40° under Ar. HMPA (22.25 ml) was added to the mixture at −60° and the mixture was warmed to −20° to make it a homogeneous soln. A soln of **2b** (9.17 g, 40.6 mmol) in dry THF (15 ml) was added dropwise to the LDA soln at −65° with stirring and the mixture was stirred for 1 h at −65° under Ar. 3-Butenyl iodide (14.78 g, 81.2 mmol) was added to the mixture, and the mixture was warmed to −10°. After stirring at −10° for 3 h, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with 5 % $Na_2S_2O_3$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (17.6 g) was chromatographed over SiO_2 (300 g). Elution with n-hexane-ether (10:1) gave crude **4**. Further elution with n-hexane-ether (10:1~5:1) gave recovery of the starting material (4.05 g). The crude **4** was distilled to give 5.60 g (92 %, based on the consumed starting material) of pure **4** as an oil, b.p. 113~116°/0.25 Torr; n_D^{23} 1.4775; $[\alpha]_D^{23}$ +10.6° (c=1.69, $CHCl_3$); vmax 3090 (w), 1715 (s), 1645 (m), 1130 (s), 1030 (s), 1000 (s), 910 (s) cm^{-1}; δ (CCl_4) 0.98, 1.07, 1.10, 1.13, 1.17 (total 6H, each s), 1.28~1.75 (6H, m), 1.75~2.20 (6H, m), 2.20~2.75 (3H, m), 3.05~4.00 (3H, m), 4.40~5.15 (3H, m), 5.30~6.15 (1H, m). (Found: C, 72.96; H, 10.07. Calc for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06 %).

(3S,6RS)-(+)-6-(3'-Butenyl)-2,2,6-trimethyl-3-tetrahydropyranyloxycyclohexanone **5**. To a stirred soln of LDA [prepared from n-BuLi (29.9 mmol) and $(i\text{-Pr})_2NH$ (4.18 ml, 29.9 mmol)] in THF (40 ml) and HMPA (10.9 ml), a soln of **4** (5.37 g, 19.9 mmol) in THF (7.1 ml) was added at −65°. The mixture was stirred for 30 min at −65° under Ar. MeI (2.00 ml, 29.9 mmol) was added to the mixture, and the mixture was warmed to −10°. The stirring was continued for 1 hr at −10°. Then the mixture was poured into ice-water and extracted with ether. The ether soln was washed with 5 % $Na_2S_2O_3$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 5.42 g (92.5 %) of **5** as a diastereomeric mixture (TLC: SiO_2, Merck Art 5715 ; eluent, n-hexane-ether=4:1; Rf 0.50 and 0.43). This was chromatographed over SiO_2 (54 g). Elution with n-hexane-ether (10:1) gave most of the less polar isomer of **5** (3.90 g), n_D^{23} 1.4777; $[\alpha]_D^{23}$ +26.6° (c=0.99, $CHCl_3$); vmax 3100 (w), 1695 (s), 1645 (m), 1135 (s), 1120 (s), 1035 (s), 1000 (s), 910 (m) cm^{-1}; δ (CCl_4) 1.02, 1.05, 1.13 (total 9H, each s), 1.25~1.73 (12H, m), 1.73~2.20 (2H, m), 3.10~4.04 (3H, m), 4.40~5.10 (3H, m), 5.30~6.05 (1H, m). (Found: C, 73.58; H, 10.18. Calc for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27 %). Further elution with n-hexane-ether (5:1) gave fractions rich in the more polar isomer of **5**. Prior to this experiment, a small-scale preliminary experiment was carried out employing 180.5 mg of **4** to give 192.8 mg of **5**. SiO_2 chromatography of 170.9 mg of **5** yielded 116.3 mg (61 %) of the less polar **5** and 47.9 mg (25 %) of the more polar **5** upon elution with n-hexane-ether (10:1).

(3S,6RS)-(+)-6-(3'-Oxobutyl)-2,2,6-trimethyl-3-tetrahydropyranyloxycyclohexanone **6**. CuCl (1.31 g, 13.2 mmol) and $PdCl_2$ (700 mg, purity 60.01 %, 2.37 mmol) was suspended in a mixture of DMF (10 ml) and water (1.2 ml). The mixture was stirred for 22 h at room temp under O_2. Then a soln of **5** (3.90 g, 13.3 mmol) in DMF (4 ml) and water (0.5 ml) was added to the mixture. After stirring for 22 h at room temp under O_2, the mixture was diluted with ether and filtered through Celite. The filter cake was washed with ether. The combined filtrate and washings were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (4.02 g) was chromatographed over SiO_2 (65 g) to give 3.20 g (77.8 %) of **6** as a solid. An analytical sample was recrystallized from n-hexane to give needles, m.p. 50~50.8° ; $[\alpha]_D^{23}$+46.1° (c=1.14, $CHCl_3$); vmax 1720 (s), 1700 (s), 1380 (m), 1360 (m), 1130 (s), 1120 (s), 1035 (s) cm^{-1}; δ (CCl_4) 1.03, 1.08, 1.15 (total 9H, each s), 1.30~1.85 (12H, m), 2.04 (3H, s), 2.15~2.44 (2H, m), 3.20~4.00 (3H, m), 4.40~4.80 (1H, m). (Found: C, 69.69; H, 9.48. Calc for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74 %).

(2R,4aRS)-(-)-1,1,4a-Trimethyl-2-tetrahydropyranyloxy-Δ^{8}-7-octalone 7. A soln of 6 (1.39 g, 4.48 mmol) and freshly distilled pyrrolidine (1.1 ml, 13.3 mmol) in dry C_6H_6 (70 ml) was stirred and heated under reflux for 22 h with azeotropic removal of water. The mixture was cooled to room temp and concentrated in vacuo. The residue (1.80g) was chromatographed over SiO_2 (18 g) to give 1.17 g (89.4 %) of 7 as an oil, n_D^{24} 1.5050; $[\alpha]_D^{24}$-51.1° (c=1.02, $CHCl_3$); νmax 3070 (w), 1670 (s), 1600 (m), 1135 (m), 1120 (m), 1030 (s) cm^{-1}; δ (CCl_4) 1.10, 1.23, 1.31 (total 9H, each s), 1.40~2.10 (12H, m), 2.28 (2H, dd, J= 4 and 7.5Hz), 3.00~3.95 (3H, m), 4.40~4.75 (1H, m), 5.74, 5.78 (total 1H, each s). (Found: C, 73.53; H, 9.74. Calc for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65 %).

(2S,4aR)-(-)-1,1,4a-Trimethyl-2-hydroxy-Δ^{8}-7-octalone 8a and (2S,4aS)-(+)-1,1,4a-trimethyl-2-hydroxy-Δ^{8}-7-octalone 8b. p-TsOH (140 mg) was added to a stirred soln of 7 (1.1 g, 3.76 mmol) in MeOH (30 ml). The mixture was stirred for 90 min at room temp. Solid $NaHCO_3$ was added to neutralize p-TsOH in the mixture. The mixture was concentrated in vacuo, diluted with water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (990 mg) was chromatographed over SiO_2 (25 g). The earlier eluted fraction with n-hexane-ether (10:1~6:1) gave 660.4 mg (84.3 %) of 8a. This was recrystallized from n-hexane-ether (5:1) to give plates, m.p. 77.5~78.0°; $[\alpha]_D^{22}$-108° (c=1.03, $CHCl_3$); νmax 3470 (s), 3080 (w), 1660 (s), 1600 (m), 1060 (s) cm^{-1}; δ (CCl_4) 1.11 (3H, s), 1.22 (3H, s), 1.36 (3H, s), 1.46~2.21 (6H, m), 2.37 (2H, dd, J= 4 and 7Hz), 3.21 (1H, s, OH), 3.32 (1H, dd, J= 6 and 9Hz), 5.93 (1H, s). TLC [SiO_2, Merck Art 5715; eluent, n-hexane-EtOAc (1:1)] Rf 0.32. (Found: C, 74.83; H, 9.58. Calc for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68 %). The later eluted fraction with n-hexane-ether (6:1~3:1) gave 34 mg (4.3 %) of 8b. This was recrystallized from n-hexane-ether (6:1) to give plates, m.p. 112~113° ; $[\alpha]_D^{23}$+130° (c=0.54, $CHCl_3$); νmax 3450 (s), 3080 (w), 1660 (s), 1595 (m), 1075 (m), 1040 (m), 980 (s) cm^{-1}; δ ($CDCl_3$) 1.19 (3H, s), 1.21 (3H, s), 1.33 (3H, s), 1.45~2.30 (7H, m), 2.30~2.60 (2H, m), 3.54~3.74 (1H, m), 5.96 (1H, s). TLC [SiO_2, Merck Art 5715; eluent, n-hexane-EtOAc=1:1)] Rf 0.27. (Found: C, 74.85; H, 9.36. Calc for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68 %).

(2S,4aR,8aR)-(-)-1,1,4a-Trimethyl-2-hydroxy-7-decalone 9. A suspension of 10 % Pd-C (30 mg) in a soln of 8a (560 mg, 2.69 mmol) in MeOH (25 ml) was stirred for 3 h under H_2 at room temp. The mixture was filtered and the filter cake was washed with ether. The combined filtrate and washings were concentrated in vacuo. The residue (620 mg) was chromatographed over SiO_2 (6 g) to give 541 mg (95.7 %) of 9 as a solid. This was recrystallized from n-hexane to give colorless needles, m.p. 91.6~92.0° ; $[\alpha]_D^{23}$-5.20° (c=1.13, $CHCl_3$); νmax 3400 (br.m), 1715 (s), 1085 (m), 1030 (s), 993 (m), 943 (m) cm^{-1}; δ (CCl_4) 0.78 (3H, s), 0.95 (3H, s), 1.14 (3H, s), 1.20~1.90 (7H, m), 1.91 (1H, s, OH), 2.10~2.40 (4H, m), 3.00~3.35 (1H, m). GLC (Column, OV-101, 50 m x 0.28 mm at 240°; Carrier gas, N_2, 1 kg/cm^2): Rt 25.5 min (100 %). (Found: C, 74.17; H, 10.36. Calc for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54 %).

(2S,4aS,8aR)-(-)-1,1,4a-Trimethyl-2-decalol 1a. 100 % Hydrazine hydrate (1.1 ml) was added to a soln of 9 (283 mg, 1.35 mmol) in diethylene glycol (13 ml), and the mixture was stirred and heated at 150° for 1 h. To this was added 50 % KOH soln (3 ml) and the mixture was heated at 150° for 30 min. Then the bath temp was gradually raised to remove a low b.p. distillate and the mixture was heated at 210° for 1.5 h. After cooling, it was poured into ice-water (70 ml) and extracted with ether. The ether soln was washed with dil HCl soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 241.6 mg (91.4 %) of 1a as a solid. This was recrystallized from n-pentane to give colorless needles, m.p. 86.5~87.4°; [lit[4] m.p. 87~89°]; $[\alpha]_D^{23}$-11.3° (c=0.32, MeOH); [lit[1] $[\alpha]_{589}$+12.2°, -11.7° (MeOH)]; $[\alpha]_D^{23}$-7.90° (c=0.30, dioxane); [lit[4] $[\alpha]_D$+78° (c=0.3, dioxane) This value was obtained by the ORD measurement of (+)-1a and might be inaccurate due to the state of the art in 1958.]; νmax 3300 (br.s), 3000 (s), 2960 (s), 2870 (s), 1463 (s), 1450 (s), 1388 (s), 1370 (s), 1355 (m), 1340 (m), 1295 (w), 1248 (w), 1230 (w), 1210 (w), 1193 (m), 1175 (w), 1155 (w), 1130 (m), 1100 (s), 1090 (s), 1073 (w), 1055 (m), 1045 (s), 1030 (s), 1015 (s), 1000 (s), 988 (w), 960 (m), 953 (s), 935 (w), 895 (m), 858 (w), 850 (w), 830 (w), 755 (w) cm^{-1}; δ (TMS, $CDCl_3$, 100 MHz, Jeol JMN FX-100) 0.77 (3H, s), 0.90 (3H, s), 0.98 (3H, s), 1.03~1.80 (13H, m), 1.85 (1H, s, OH), 3.23 (1H, dd, J= 7 and 10Hz). ^{13}C-NMR δ (TMS, $CDCl_3$, 25 MHz, Jeol JMN FX-100) 15.04, 19.18, 21.61, 21.74, 27.54, 27.61, 27.78, 34.14, 38.79, 40.26, 45.25, 52.76, 79.36; GLC (Column, SE-30, 2 m x 2 mm at 80°+10°/min; Carrier gas, N_2, 1.1 kg/cm^2): Rt 11.6 min (100 %). (Found: C, 79.41; H, 12.46. Calc for $C_{13}H_{24}O$: C, 79.53; H, 12.32 %).

Determination of the optical purity of 1a. According to the reported procedure,[10] (R)- and (S)-MTPA esters 1b and 1c were prepared from 1a. HPLC (Column, NUCLEOSIL® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-$ClCH_2CH_2Cl$ (20:1), 1.15 ml/min; Detected at 254 nm) co-injection of (R)- and (S)-MTPA ester 1b and 1c: Rt 28.63 min and 34.12 min; (R)-MTPA ester 1b: Rt 28.03 min (single peak). Therefore the optical purity of 1a was determined to be 100 % e.e.

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