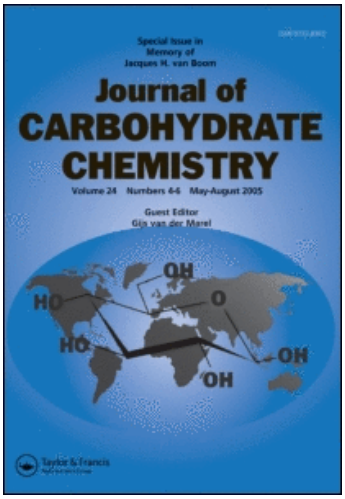

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

A Facile Synthesis of (*S*)-2-Benzyloxybutanal and (*S*)-3-Benzyloxy-2-Pentanone From 2-Deoxy-D-Ribose

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To cite this Article Suami, Tetsuo , Tadano, Kin-Ichi , Iimura, Youichi and Yokoo, Hiroshi(1986) 'A Facile Synthesis of (*S*)-2-Benzyloxybutanal and (*S*)-3-Benzyloxy-2-Pentanone From 2-Deoxy-D-Ribose', Journal of Carbohydrate Chemistry, 5: 1, 1 — 10
To link to this Article: DOI: 10.1080/07328308608082637
URL: http://dx.doi.org/10.1080/07328308608082637

J. CARBOHYDRATE CHEMISTRY, 5(1), 1-10 (1986)

A FACILE SYNTHESIS OF (*S*)-2-BENZYLOXYBUTANAL AND (*S*)-3-BENZYLOXY-2-PENTANONE FROM 2-DEOXY-D-RIBOSE

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Received May 12, 1985 - Final Form October 31, 1985

ABSTRACT

The versatile chiral synthons, (*S*)-2-benzyloxybutanal and (*S*)-3-benzyloxy-2-pentanone, were synthesized from 2-deoxy-D-ribose in acceptable overall yields. 2-Deoxy-D-ribose was converted into (2*R*,3*S*)-3-O-benzyl-pentane-1,2,3-triol in a straightforward manner. From this compound, both desired chiral aldehyde and ketone were obtained by periodate oxidation and by deoxygenation of the primary hydroxyl group followed by oxidation of the secondary hydroxyl group.

INTRODUCTION

Recently, much interest has been focused on synthesis of natural products employing a carbohydrate as a starting material.[1] The intrinsic enantiomeric purity existing in a

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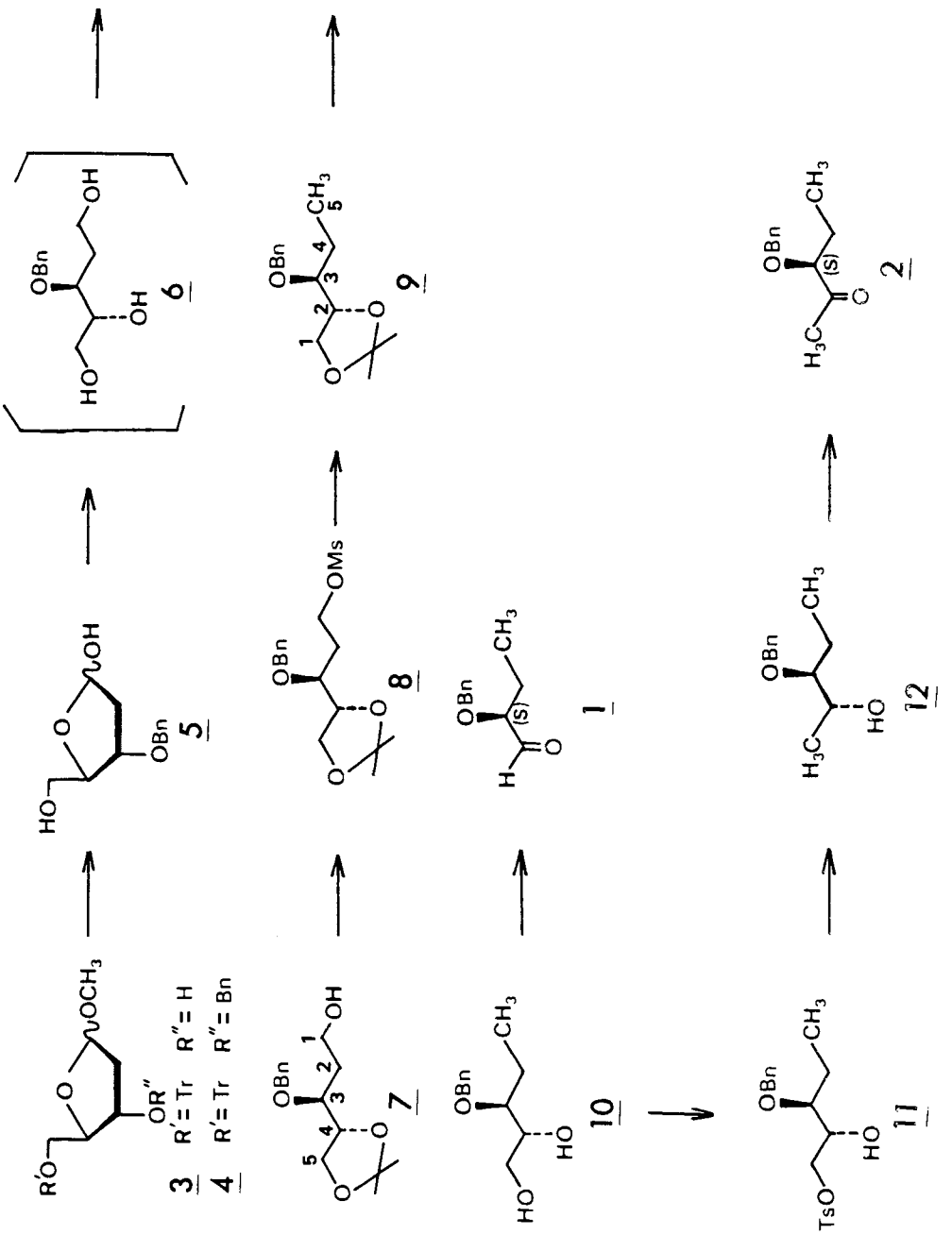
natural carbohydrate allows the synthesis to be carried out in an enantiospecific or an enantioselective fashion. Chiral aldehydes and ketones derived from carbohydrate can be versatile synthons for a variety of synthetic reactions, such as an aldol type carbon-carbon bond formation, a Grignard reaction, and so on. (*S*)-2-Benzyloxybutanal (1), a chiral aldehyde possessing a protected hydroxyl group at the α-position, is a typical example of this kind of synthon. Compound 1 has been prepared by another synthetic route,[2] and the synthetic utility of 1 was demonstrated in the total synthesis of (1*S*,7*S*)-*exo*-brevicomin[2] (an enantiomer of the principal aggregation pheromone of the female western pine beetle (*Dendroctonus brevicomins*). The synthesis of natural (1*R*,7*R*)-(+)-*exo*-brevicomin was also achieved starting from an enantiomer of 1.[3] In this article, we wish to report a facile synthesis of 1 and also an enantiospecific synthesis of (*S*)-3-benzyloxy-2-pentanone (2) which is a versatile chiral ketone possessing a protected hydroxyl group at the α-position, starting from known methyl 2-deoxy-5-O-trityl-α,β-D-*erythro*-pentofuranoside (3).[4]

RESULTS AND DISCUSSION

O-Benzylation of 3 with benzyl bromide and sodium hydride gave the 3-O-benzyl derivative (4) as an anomeric mixture of 95% yield. Hydrolysis of 4 in 1 M HCl gave 3-O-benzyl-2-deoxy-α,β-D-*erythro*-pentose (5) in 69% yield. Treatment of 5 with sodium borohydride followed by O-isopropylidenation of the resulting D-*erythro*-pentitol derivative (6) with 2,2-dimethoxypropane afforded 3-O-benzyl-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentitol (7) in 84% yield. Mesylation of 7 in the usual manner yielded the 1-O-mesyl derivative (8) in 94% yield. Deoxygenation of 8 with lithium aluminum hydride afforded the 5-O-deoxy derivative



[(2*R*,3*S*)-3-O-benzyl-1,2-O-isopropylidene-pentane-1,2,3-triol] (9) in 80% yield. De-O-isopropylidenation of 9 with 80% aqueous trifluoroacetic acid gave the 1,2-diol (10) in 94% yield. Cleavage of the glycol by sodium periodate resulted in the formation of 1 in a quantitative yield. The specific rotation of 1 ($[\alpha]_D^{21}$-96.6°) coincided with the reported value.[2]

Another synthon 2 was prepared from 10. Regioselective tosylation of the primary hydroxyl group of 10 gave the compound (11) in 75% yield. The corresponding ditosyl derivative also formed in 7% yield and compound 10 was recovered in 10% yield. Deoxygenation of 11 with lithium aluminum hydride afforded (2*R*,3*S*)-3-O-benzyl-pentane-2,3-diol (12) in a yield of 83%. Pyridinium chlorochromate oxidation of 12 afforded 2 in 82% yield.

EXPERIMENTAL

General Procedures. Melting points were determined with a Mitamura Riken micro apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a JEOL DIP-4 polarimeter. Column chromatography was performed with Wakogel C-300 (Wako Pure Chemicals), and TLC was carried out on glass plates coated with Wakogel B-5 F, compounds being detected with UV light and by spraying with sulfuric acid followed by heating. Preparative TLC (PTLC) was performed on glass plates (20x20 cm) coated with Merck Kieselgel 60 PF_{254}. IR spectra were recorded on a Hitachi Model-225 spectrometer (KBr) and JEOL Model A-202 spectrometer ($CHCl_3$). ^1H NMR spectra were recorded on a Varian EM-390 spectrometer, and chemical shifts for a $CDCl_3$ solution are recorded in δ values from internal tetramethylsilane. High resolution mass spectra were taken on a Hitachi M-80 mass spectrometer. Elemental analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

Methyl 3-O-benzyl-2-deoxy-5-O-trityl-α,β-D-*erythro*-pentofuranoside (4). Sodium hydride (50% emulsion in mineral oil, 0.49 g, 20.4 mmol) was washed with petroleum ether (30 mL) and suspended in DMF (10 mL). To the suspension was added a solution of methyl 2-deoxy-5-O-trityl-α,β-D-*erythro*-pentofuranoside[4] (3) (5.31 g, 13.6 mmol) in DMF (40 mL). The mixture was stirred for 30 min, and benzyl bromide (2.43 mL, 20.4 mmol) was added to the mixture. The mixture was stirred for 22 h, and excess base was quenched with EtOH (20 mL). The mixture was diluted with water (250 mL) and extracted with ethyl acetate containing 1% triethylamine (250 mL x 3). The combined organic extracts were washed with water (150 mL x 3), dried (Na_2SO_4), and concentrated. The residue was purified on SiO_2 (200 g, ethyl acetate:toluene=1:10 containing 1% triethylamine), and fractions with R_f 0.61 on TLC (ethyl acetate:toluene=1:10) were concentrated to afford 4 (6.17 g, 95%) as a colorless syrup. $[\alpha]_D^{15}$+21.8° (*c* 1.00, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3000 and 2920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94-2.00 (2H, m, H-2,2'), 3.01-3.27 (2H, m, H-5,5'), 3.30 (3H, s, OCH_3), 3.73-4.25 (2H, m, H-3,4), 4.31, 4.35 (total 2H, each s, $OCH_2C_6H_5$), 4.84-5.06 (1H, m, H-1), 7.00-7.60 (15H, m, $C(C_6H_5)_3$), 7.12 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71. Found: C, 79.56; H, 6.95.

3-O-Benzyl-2-deoxy-α,β-*erythro*-pentose (5). A solution of 4 (36.9 mg, 0.08 mmol) in a mixture of dioxane (2 mL) and 1 M HCl (1 mL) was stirred for 24 h, and the solution was neutralized with saturated aqueous $NaHCO_3$. The solution was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified on SiO_2 (5 g, ethanol:toluene=1:7), and fractions with R_f 0.21 (ethanol:toluene=1:10) were concentrated to afford 5 (11.8 mg, 69%), mp 90-92 °C; $[\alpha]_D^{17}$+30.0° (3 min) - +7.4° (5 h) (*c* 0.5, $CHCl_3$); IR ν_{max}^{KBr} 3390, 3300, 2895, 2860 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.64-2.42 (2H, m, H-2,2'), 2.30-2.51 (1H, m, OH), 2.92-3.41 (1H, m, OH), 3.28-4.57 (6H, m, H-3,4,5,5',$OCH_2C_6H_5$), 5.03-5.56 (1H, m, H-1), 7.23 (5H, s, $OCH_2C_6H_5$).

Anal. calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.54; H, 7.11.

3-O-Benzyl-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentitol (7). To a solution of 5 (1.79 g, 7.97 mmol) in ethanol (30 mL) was added sodium borohydride (0.604 g, 16.0 mmol) in ethanol (45 mL). After stirring for 1 h, the solution was neutralized with 1 M HCl. The solution was concentrated and the residue was triturated with ethyl acetate:ethanol=5:1 (50 mL x 3). An insoluble material was removed by filtration and the filtrate was dried (Na_2SO_4) and concentrated. The residue consisted mainly of 3-O-benzyl-2-deoxy-D-*erythro*-pentitol (6) and was used in a successive reaction without any purification. To a stirred solution of the residue in acetone (18 mL), 2,2-dimethoxypropane (4.9 mL, 39.9 mmol) and D-camphorsulfonic acid (0.185 g, 0.80 mmol) were added. After stirring for 4 h, the solution was neutralized with saturated aqueous $NaHCO_3$, diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified on SiO_2 (200 g, ethanol:toluene=1:7). Fractions with R_f 0.50 on TLC (ethanol:toluene=1:7) were concentrated to give 7 (1.79 g, 84%) as a colorless syrup. $[\alpha]_D^{20}$ -2.7° (*c* 0.91, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3480, 2990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36, 1.41 (each 3H, each s, $C(CH_3)_2$), 1.60-1.92 (2H, m, H-2, 2'), 2.08-2.42 (1H, m, OH), 3.50-4.19 (6H, m, H-1,1',3,4,5,5'), 4.57 (2H, s, $OCH_2C_6H_5$), 7.35 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.37; H, 8.24.

3-O-Benzyl-2-deoxy-4,5-O-isopropylidene-1-O-mesyl-D-*erythro*-pentitol (8). To a stirred solution of 7 (52.1 mg, 0.20 mmol) in pyridine (1 mL) was added mesyl chloride (0.023 mL, 0.29 mmol).

After stirring for 1 h, the reaction mixture was concentrated. The residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on PTLC (ethyl acetate:hexane=3:4), and the UV positive band was extracted with $CHCl_3$ to give 8 (63.0 mg, 94%) as a syrup: $[\alpha]_D^{19}$ -12.2° (*c* 0.86, MeOH); IR $\nu_{max}^{CHCl_3}$ 2990, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35, 1.41 (each 3H, each s, $C(CH_3)_2$), 1.80-2.19 (2H, m, H-2, 2'), 2.86 (3H, s, OSO_2CH_3), 3.44-4.75 (8H, m, H-1,1',3,4,5,5', $OCH_2C_6H_5$), 7.35 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02; S, 9.31. Found: C, 55.80; H, 7.01; S, 9.27.

(2*R*,3*S*)-3-O-Benzyl-1,2-O-isopropylidene-pentane-1,2,3-triol (9). To a solution of 8 (37.2 mg, 0.11 mmol) in ether (1 mL) was added lithium aluminum hydride (8.2 mg, 0.22 mmol). The mixture was refluxed for 2 h and the excess hydride was destroyed with water (0.04 mL) and a 15% NaOH solution (0.01 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic extract was dried (Na_2SO_4) and concentrated. The residue was purified on PTLC (ethyl acetate:hexane=1:8), and the UV positive band was extracted with $CHCl_3$ to give 9 (21.5 mg, 80%) as a syrup. R_f 0.76 on TLC (ethyl acetate:hexane=1:4); $[\alpha]_D^{19}$ +23.4° (*c* 1.07, MeOH); IR $\nu_{max}^{CHCl_3}$ 2290 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=7 Hz, H-5,5',5"), 1.31, 1.37 (each 3H, each s, $C(CH_3)_2$), 1.48-1.86 (2H, m, H-4,4'), 3.42 (1H, q, J=6 Hz, H-3), 3.78-4.11 (3H, m, H-1,1',2), 4.52 (2H, s, $OCH_2C_6H_5$), 7.37 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.26; H, 8.75.

(2*R*,3*S*)-3-O-Benzyl-pentane-1,2,3-triol (10). A solution of 9 (103 mg, 0.41 mmol) in 80% aqueous trifluoroacetic acid (1 mL) was stirred for 1.5 h, and the solution was neutralized with 1 M NaOH. The solution was diluted with water (5 mL) and extracted with chloroform (10 mL x 3). The organic extract was dried

(Na_2SO_4) and concentrated. The residue was purified on PTLC (ethanol:toluene=1:6), and the UV positive band was extracted with chloroform to afford 10 (82 mg, 94%) as a syrup. R_f 0.16 on TLC (ethanol:toluene=1:10); $[\alpha]_D^{20}$+12.7° (*c* 0.73, MeOH); IR $\nu_{max}^{CHCl_3}$ 3440, 2930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3H, t, J=7 Hz, H-5,5', 5"), 1.40-1.78 (2H, m, H-4,4'), 2.74-3.19 (2H, m, OH x 2), 3.25-3.87 (4H, m, H-1,1',2,3), 4.47 (2H, s, $OCH_2C_6H_5$), 7.30 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{12}H_{18}O_3$: *m/z* 210.1255. Found: M, 210.1288.

(*S*)-2-Benzyloxybutanal (1). To a stirred solution of 10 (42.4 mg, 0.20 mmol) in methanol (1 mL) was added an aqueous solution (1 mL) of sodium periodate (51.8 mg, 0.24 mmol). After 45 min, the solution was diluted with water (4 mL), and extracted with chloroform (6 mL x 3). The organic extracts were dried (Na_2SO_4) and concentrated to give 1 (35.9 mg, quantitatively) as a syrup, R_f 0.64 on TLC (ethyl acetate:hexane=1:3); $[\alpha]_D^{21}$-96.6° (*c* 0.47, $CHCl_3$), lit.[2] $[\alpha]_D$ -95°; IR $\nu_{max}^{CHCl_3}$ 2960, 2940, 2870, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=9 Hz, H-4, 4', 4"), 1.71 (2H, quintet, J=9 Hz, H-3,3'), 3.69 (1H, dt, J=2 Hz, J=9 Hz, H-2), 4.42-4.79 (2H, m, $OCH_2C_6H_5$), 7.35 (5H, s, $OCH_2C_6H_5$), 9.64 (1H, d, J=2 Hz, CHO).

Anal. calcd for $C_{11}H_{14}O_2$: *m/z* 178.0993. Found: M, 178.0964.

(2*R*,3*S*)-3-O-Benzyl-1-O-tosyl-pentane-1,2,3-triol (11). To a stirred solution of 10 (80.2 mg, 0.38 mmol) in pyridine (2 mL) was added tosyl chloride (109 mg, 0.57 mmol). After stirring at 0 °C for 3 h then at room temperature for 3 h, the reaction mixture was concentrated. The residue was partitioned between dichloromethane (10 mL) and water (10 mL), and the aqueous layer was extracted with dichloromethane (10 mL x 2). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified on PTLC (ethanol:toluene=1:20). From a band with R_f 0.84 on TLC (ethanol:toluene=1:10), (2*R*,3*S*)-3-O-benzyl-1,2-di-O-tosyl-pentane-1,2,3-triol (9.2 mg, 7%) was obtained; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J=

7 Hz, H-5,5',5"), 1.21-1.54 (2H, m, H-4,4'), 2.43 (6H, s, 2x $OSO_2C_6H_4\underline{CH_3}$), 3.56-3.80 (1H, m, H-3), 4.18 (2H, d, J=5 Hz, H-1,1'), 4.50 (2H, s, $O\underline{CH_2}C_6H_5$), 4.64 (1H, q, J=5 Hz, H-2), 7.20-7.83 (8H, m, $2xOSO_2C_6\underline{H_4}CH_3$), 7.28 (5H, s, $OCH_2C_6\underline{H_5}$). From a band with R_f 0.53, 11 (104 mg, 75%) was obtained as colorless crystals, and from a band with R_f 0.22, 10 (8.1 mg, 10%) was recovered.

11: mp 66.5-68 °C; $[\alpha]_D^{20}$+24.2° (*c* 0.50, MeOH); IR ν_{max}^{KBr} 3540, 2960, 1595, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J=8 Hz, H-5,5',5"), 1.42-1.74 (2H, m, H-4,4'), 2.12-2.42 (1H, m, OH), 2.38 (3H, s, $OSO_2C_6H_4\underline{CH_3}$), 3.36 (1H, q, J=6 Hz, H-3), 3.68-4.20 (3H, m, H-1,1', 2), 4.24-4.60 (2H, m, $O\underline{CH_2}C_6H_5$), 7.23-7.88 (4H, m, $OSO_2C_6\underline{H_4}CH_3$), 7.29 (5H, s, $OCH_2C_6\underline{H_5}$).

Anal. calcd for $C_{19}H_{24}O_5S$: C, 62.62; H, 6.64; S, 8.80. Found: C, 62.78; H, 6.66; S, 8.54.

(2*R*,3*S*)-3-O-Benzyl-pentane-2,3-diol (12). A solution of 11 (34.1 mg, 0.09 mmol) in ether (1 mL) with lithium aluminum hydride (7.1 mg, 0.19 mmol) was refluxed for 100 min. Excess hydride was destroyed with ethyl acetate (1 mL), and an insoluble material was removed by filtration. The filtrate was concentrated and the residue was purified on PTLC (ethanol:toluene=1:12). A UV positive band was extracted with chloroform, and the extract was concentrated to afford 12 (15.1 mg, 83%) as a syrup, R_f 0.49 on TLC (ethanol:toluene=1:12); $[\alpha]_D^{21}$-9.0° (*c* 1.23, MeOH); IR $\nu_{max}^{CHCl_3}$ 3420, 2970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=8 Hz, H-5, 5',5"), 1.16 (3H, d, J=8 Hz, H-1,1',1"), 1.39-1.77 (2H, m, H-4, 4'), 1.77-2.13 (1H, m, OH), 3.14-3.33 (1H, m, H-3), 3.71-4.00 (1H, m, H-2), 4.52 (2H, s, $O\underline{CH_2}C_6H_5$), 7.37 (5H, s, $OCH_2C_6\underline{H_5}$).

Anal. calcd for $C_{12}H_{18}O_2$: *m/z* 194.1305. Found: M, 194.1295.

(*S*)-3-Benzyloxy-2-pentanone (2). To a stirred solution of 12 (12.6 mg, 0.065 mmol) in dry dichloromethane (1 mL) was added pyridinium chlorochromate[5] (30.8 mg, 0.143 mmol). After stirring for 1.5 h, ether (3 mL) was added to the mixture. An insoluble material was removed, and the filtrate was concentrated.

The residue was purified on PTLC (ethyl acetate:toluene=1:10), and a UV positive band was extracted with chloroform. The extract was concentrated to afford 2 (10.2 mg, 82%) as a syrup, R_f 0.54 on TLC (ethyl acetate:toluene=1:10); $[\alpha]_D^{21}$ -52.8° (*c* 0.80, MeOH); IR $\nu_{max}^{CHCl_3}$ 2970, 2950, 2880, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J=8 Hz, H-5,5',5"), 1.51-1.88 (2H, m, H-4,4'), 2.14 (3H, s, H-1,1',1"), 3.64 (1H, t, J=6 Hz, H-3), 4.27-4.63 (2H, m, $OCH_2C_6H_5$), 7.34 (5H, s, $OCH_2C_6H_5$).

Anal. calcd for $C_{12}H_{15}O_2$: *m/z* 191.1071. Found: M-H, 191.1089.

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