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A Synthesis of (+)-Nonactic Acid by Means of the Sulfur-Ylide rearrangement

Toshio Honda,* Hirohide Ishige, Junko Araki, Saeko Akimoto, Kazuo Hirayama, and Masayoshi Tsubuki

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

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Abstract: (+)-Nonactic acid (**1**) has been synthesized by employing a condensation of the tetrahydro-2-furanthione (**9**) with dimethyl α-diazomalonate in the presence of rhodium acetate as a key reaction.

Recently we have been involved[1] in the development of a new carbon-carbon bond forming reaction *via* the rearrangement of sulfur-ylide intermediates, easily derived by preferential participation of a carbene or carbenoid with divalent sulfur. By applying this strategy to the thioglycosides, we have established[2] a novel C-glycosylation reaction, involving the synthesis of a C-nucleoside, (+)-showdomycin. This reaction was successfully expanded to the use of the chiral tetrahydro-2-furanthione derivatives as divalent sulfur equivalents providing the 2-(acylmethylene)tetrahydrofuran derivatives in good yields by Takano.[3] As part of our continuing work on the utilization of the above strategy in natural product synthesis, we investigated a synthesis of (+)-nonactic acid (**1**),[4] a subunit of macrotetrolide antibiotic, nonactin (Figure 1).

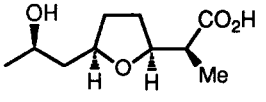

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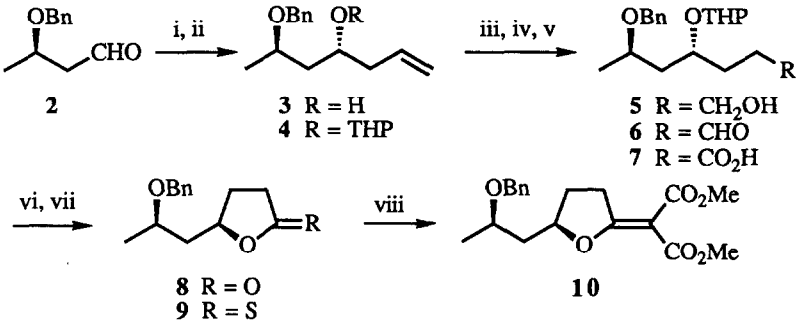
Figure 1.

Although Barrett has published[5] the synthesis of racemic *tert*-butyl nonactate starting from a 5-substituted γ-butyrolactone, the utilization of an optically active γ-butyrolactone derivative as a starting material has received relatively little attention in the chiral synthesis of nonactic acid.

Our synthesis began with the preparation of the chiral tetrahydro-2-furanthione (**9**) as follows.

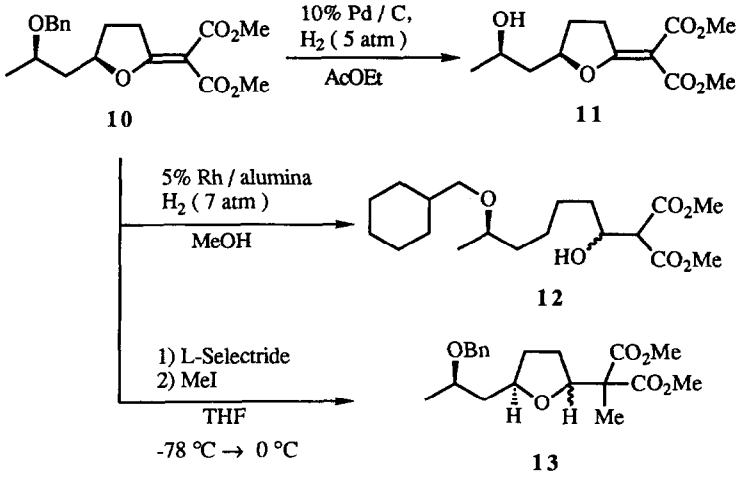
(3*R*)-Benzyloxybutyraldehyde (**2**) was treated with allyltrimethylsilane in the presence of titanium tetrachloride according to Reetz's procedure[6] to give the alcohol (**3**) stereoselectively, which was then converted into its tetrahydropyranyl ether (**4**) in an usual manner. Hydroboration of **4**, followed by oxidative work up



Reagents and conditions: i, allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78°C; ii, DHP, PPTS, CH_2Cl_2, rt, iii, BH_3, THF, rt; then H_2O_2, NaOH, rt; iv, Swern ox.; v, $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, tert-BuOH-THF-H_2O, rt; vi, aq.HCl, rt; vii, Lawesson's reagent, toluene, reflux; viii, dimethyl α-diazomalonate, $Rh_2(OAc)_4$, toluene, reflux.

Scheme 1.

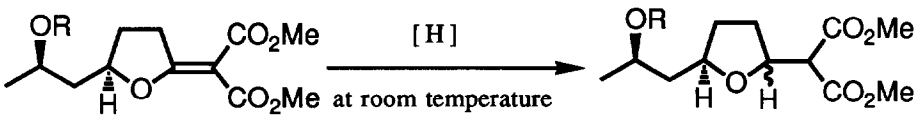
afforded the primary alcohol (**5**). Swern oxidation of **5**, followed by further oxidation of the resulting aldehyde (**6**) with sodium chlorite in the presence of 2-methyl-2-butene gave the acid (**7**) in 81% yield from **5**. Deprotection of the tetrahydropyranyl group of **7** afforded the lactone (**8**), which on treatment with Lawesson's



Scheme 2.

reagent[7] in refluxing toluene afforded the desired γ-thiolactone (**9**) in 83% yield from **7**. Condensation of the thiolactone (**9**) with dimethyl α-diazomalonate in refluxing toluene in the presence of a catalytic amount of rhodium acetate provided the α,β-unsaturated ester (**10**) in 98% yield (Scheme 1). The crucial step in this synthesis involved a stereoselective reduction of the α,β-unsaturated ester (**10**) or its derivatives to construct a 2,5-*cis*-substituted tetrahydrofuran ring system. Catalytic reduction of **10** over palladium-carbon under 5 atm of hydrogen in ethyl acetate at room temperature gave only the debenzylated product (**11**), whereas the reduction of **10** over rhodium on alumina under 7 atm of hydrogen provided the over-reduction product (**12**) (Scheme 2). Thus the protecting group of the hydroxyl function and reduction conditions were carefully investigated, and the results obtained by the hydrogenation of α,β-unsaturated esters were summarized in Table 1. The highest

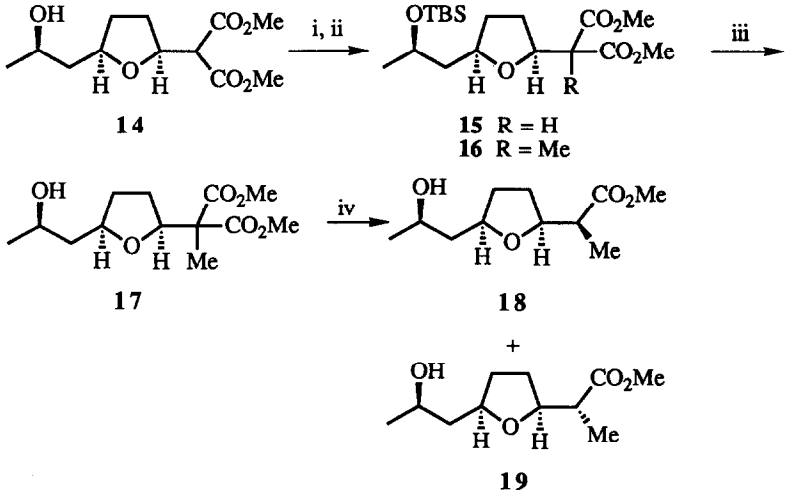
Table 1. Reduction of the α,β-Unsaturated Ester



Starting Material	Catalyst	Solvent	Time	Yield (%)	Product (*cis* : *trans*)
R = H	5% Rh / alumina, H_2 (1 atm)	MeOH	10 min	60	R = H (1.7 : 1)
R = H	Mg	MeOH	3 h	75	R = H (1.4 : 1)
R = H	5% Rh / alumina, H_2 (1 atm)	MeOH : 5%HCl (10 : 1 v/v)	0.5 h	40	R = H (7 : 1)
R = H	PtO_2, H_2 (1 atm)	MeOH	3 h	80	R = H (1 : 1)
R = TBS	5% Rh / alumina, H_2 (1 atm)	MeOH	10 min	80	R = TBS (1.2 : 1)
R = Ac	5% Rh / alumina, H_2 (1 atm)	MeOH	10 min	94	R = Ac (1.2 : 1)
R = Ac	Mg	MeOH	3 h	70	R = H (1 : 1)
R = Bn	10% Pd / C, H_2 (7 atm)	MeOH	48 h	80	R = H (3 : 1)
R = Bn	10% Pd / C, H_2 (7 atm)	MeOH : 5%HCl (10 : 1 v/v)	48 h	80	R = H (4 : 1)

stereoselectivity in the reduction of **10** to **14** was obtained by using rhodium on a alumina as a catalyst under a hydrogen atmosphere, however, the conversion yield was decreased to 40% owing to the formation of the over-reduction product (**12**). The best result in terms of the conversion yield and stereoselectivity was obtained by reduction of **10** over palladium-carbon in methanol-5% hydrochloric acid (10:1 v/v) under 7 atm of hydrogen at room temperature to afford the *cis* and *trans* compounds in 80% yield in a ratio of 4:1 as a separable mixture. The similar improvement of the stereoselectivity in the catalytic reduction of a α,β-unsaturated carbonyl system in the presence of hydrochloric acid was already reported by Augustine.[8] In this conversion, the debenzylation of **10** occurred prior to the reduction of the α,β-unsaturated ester system. These results clearly indicated that the α,β-unsaturated diester was strongly resistant to the catalytic reduction, although Barrett,[5] Bartlett,[4e] and Batmangherlich[4f] have independently reported the similar catalytic reduction of α,β-unsaturated monoesters in good yields with high stereoselectivities. Interestingly the conjugate reduction of **10** with L-Selectride[9] followed by trapping of the resulting enolate with methyl iodide furnished the methylated product (**13**) in one step, although the desired stereoselectivity at the 3-position could not be observed in this reaction providing a mixture of the *cis* and *trans* isomers in a ratio of 1 : 3.

Protection of **14** with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide gave the silyl ether (**15**), which on alkylation with methyl iodide and potassium *tert*-butoxide in tetrahydrofuran at 0 °C afforded the methylated compound (**16**) in quantitative yield. After deprotection of the silyl group of **16** with tetrabutylammonium fluoride, the hydroxyl compound (**17**) was subjected to a decarbomethoxylation reaction on treatment with sodium chloride in aqueous dimethyl sulfoxide[10] to furnish (+)-methyl nonactate (**18**) and its 2-epimer (**19**) in 78% yield in a ratio of 1:1 (Scheme 3). The spectroscopic data including the specific optical rotation of **18** were identical with those reported.[4e]



Reagents and conditions: i, TBSCl, imidazole, DMF, rt; ii, tert-BuOK, MeI, THF, 0°C; iii, Bu_4NF, THF, rt; iv, NaCl, DMSO-H_2O, reflux.

Scheme 3.

Since the conversion of (+)-methyl nonactate (**18**) into (+)-nonactic acid (**1**) by hydrolysis has already been achieved,[4e] this synthesis constitutes its formal total synthesis.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported in ppm on the δ scale from internal tetramethylsilane. J values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. TLC was carried out on precoated 0.25 mm silica gel 70 F_{254} (Wako) plates.

(4*R*, 6*R*)-6-Benzyloxy-4-[(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxy]hept-1-ene (4) --- A solution of the alcohol (**3**) (18.8g, 85.5 mmol) and 3,4-dihydropyran (23.2 ml, 0.26 mol) in CH_2Cl_2 (200 ml) in the presence of pyridinium *p*-toluenesulfonate (2.15 g, 8.6 mmol) was stirred at ambient temperature for 18 h. The solution was basified with saturated $NaHCO_3$ solution and washed with water. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-ethyl acetate (95 : 5 v/v) as eluent to afford the tetrahydropyranyl ether (**4**) (25.5 g, 98%) as a colorless oil. IR($CHCl_3$) 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ 1.22 (3H, d, J=6.1 Hz, C7-Me), 1.43-1.82 (8H, m), 2.18-2.42 (2H, m, C3-H_2), 3.41-4.67 (5H, m), 4.34 and 4.47 (each 1H, each d, J=11.6 Hz, OCH_2Ph), 5.03-5.09 (2H, m, C1-H), 5.73-5.92 (1H, m, C2-H), 7.21-7.39 (5H, m, Ph). Anal. Calcd for $C_{19}H_{28}O_3$: C 74.96; H 9.27. Found: C 75.52; H 9.38.

(4*R*, 6*R*)-6-Benzyloxy-4-[(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxy]heptan-1-ol (5) --- To a stirred solution of the olefin (**4**) (25.5 g, 84 mmol) in THF (250 ml) was added a 1M solution of BH_3 in THF (252 ml, 0.25 mol) at 0 °C under an atmosphere of argon and the mixture was further stirred for 1 h at ambient temperature. After addition of water (250 ml) and 3M NaOH solution (250 ml), 30% H_2O_2 (250 ml) was added dropwise to the solution at 30-50 °C and the resulting mixture was stirred at room temperature for 1h. The solution was diluted with ether and the ethereal layer was washed with brine, dried over Na_2SO_4, and evaporated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1 : 1 v/v) gave the alcohol (**5**) (25.2g, 93%) as a colorless oil. IR($CHCl_3$) 3550 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.22 (3H, d, J=6.1 Hz, C7-Me), 1.48-1.87 (13H, m), 3.42-4.06 (6H, m), 4.46 and 4.60 (each 1H, each d, J=11.0 Hz, OCH_2Ph), 4.60-4.63 (1H, m), 7.22-7.39 (5H, m, Ph).

(4*R*, 6*R*)-6-Benzyloxy-4-[(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxy]heptanal (6) --- To a stirred solution of oxalyl chloride (10.25 ml, 117 mmol) in dry CH_2Cl_2 (500 ml) was added dimethyl sulfoxide (12.08 ml, 156 mmol) at -50 °C and the mixture was stirred for 20 min. After addition of the alcohol (**5**) (25.21 g, 78 mmol) at -50 °C, the solution was further stirred for 50 min, then Et_3N (54.46 ml, 0.39 mol) was added dropwise at the same temperature. The resulting mixture was gradually warmed up to room temperature and treated with brine. The mixture was extracted with benzene and the organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-ethyl acetate (4 : 1 v/v) to provide the aldehyde (**6**) (22.64 g, 90%) as a colorless oil. IR($CHCl_3$) 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.22 (3H, d, J=6.1 Hz, C7-Me), 1.38-2.60 (12H, m), 3.33-4.03

(4H, m), 4.34 and 4.61 (each 1H, each d, J=11.6 Hz, OC*H*$_2$Ph), 4.37-4.60 (1H, m, OCHO), 7.08-7.37 (5H, m, Ph), 9.73 (1H, br s, CHO). Anal. Calcd for $C_{19}H_{28}O_4$: C 71.22; H 8.81. Found: C 71.53; H 8.97.

(4*R*, 6*R*)-6-Benzyloxy-4-[(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxy]heptanoic Acid (7) --- To a stirred solution of the aldehyde (**6**) (21.12 g, 66 mmol) in *tert*-butanol (120 ml) and 2-methyl-2-butene (59.4 ml, 495 mmol) was added a solution of sodium chlorite (50.74 g, 495 mmol) and KH_2PO_4 (67.37 g, 436 mmol) in water (1.4 l) at ambient temperature and the mixture was further stirred for 3 h. After removal of the organic solvents, the residue was extracted with ethyl acetate and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (85 : 15 v/v) afforded the acid (**7**) (19.87 g, 90%) as a colorless oil. IR($CHCl_3$) 3100, 1720 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.23 (3H, d, J=6.1 Hz, C7-Me), 1.43-2.54 (12H, m), 3.92-4.64 (5H, m), 4.35 and 4.62 (each 1H, each d, J=11.6 Hz, OC*H*$_2$Ph), 7.04-7.38 (5H, m, Ph), 9.0-11.0 (1H, br s, CO_2H).

(5*R*)-[(2*R*)-Benzyloxypropyl]tetrahydro-2-furanone (8) --- A solution of the acid (**7**) (19.31 g, 57 mmol) in THF (1 l) and 10% hydrochloric acid (60 ml) was stirred for 3 h at room temperature. After treatment with saturated $NaHCO_3$ solution, the solution was concentrated to leave a residue, which was extracted with ethyl acetate. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (9 : 1 v/v) afforded the lactone (**8**) (13.4 g, 100%) as a colorless oil. IR($CHCl_3$) 1735 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.24 (3H, d, J=6.1 Hz, C3'-Me), 1.70-2.40(4H, m), 2.53 (2H, dt, J=2.4 and 9.2 Hz, C3-H), 3.79-3.88 (1H, m, C2'-H), 4.63 and 4.93 (each 1H, each d, J=11.0 Hz, OC*H*$_2$Ph), 4.72-4.82 (1H, m, C5-H), 7.31-7.34 (5H, m, Ph). MS *m/z* 234(M^+) (Found: 234.1258. Calcd for $C_{13}H_{18}O_3$: 234.1257). $[\alpha]_D$ -77° (c=0.3, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_3$: C 71.77; H 7.74. Found: C 72.02; H 7.83.

(5*R*)-[(2*R*)-Benzyloxypropyl]tetrahydro-2-furanthione (9) --- A solution of the lactone (**8**) (140 mg, 0.6 mmol) and Lawesson's reagent (0.18 g, 0.45 mmol) in toluene (1.4 ml) was refluxed for 30 min. After cooling to room temperature, the solution was diluted with ether and filtered through a Celite pad to remove the insoluble material. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4 : 1 v/v) gave the thiolactone (**9**) (123.8 mg, 83%) as a yellow oil. ^{1}H-NMR($CDCl_3$)δ 1.26 (3H, d, J=6.1 Hz, C3'-H), 1.56-1.98 (3H, m), 2.31-2.43 (1H, m), 3.02 (1H, ddd, J=8.5, 9.8, and 18.9 Hz, C3-H), 3.17 (1H, ddd, J=3.7, 9.2, and 18.9 Hz, C3-H), 3.91 (1H, dq, J=6.1 and 12.2 Hz, C2'-H), 4.45 and 4.65 (each 1H, each d, J=11.0 Hz, OC*H*$_2$Ph), 5.13 (1H, ddd, J=6.7, 8.6, and 12.8 Hz, C5-H), 7.25-7.39 (5H, m, Ph). MS *m/z* 250(M^+) (Found: 250.1021. Calcd for $C_{14}H_{18}O_2S$: 250.1026). $[\alpha]_D$ -152° (c=1.5, $CHCl_3$).

(5*R*)-[(2*R*)-Benzyloxypropyl]-2-[di(methoxycarbonyl)methylene]tetrahydrofuran (10) --- A solution of the thiolactone (**9**) (110 mg, 0.44 mmol) and dimethyl α-diazomalonate (110 mg, 0.66 mmol) in toluene (2 ml) in the presence of rhodium acetate (20 mg, 0.044 mmol) was refluxed for 3 h. After the solution was diluted with ether, the mixture was filtered through a Celite pad, and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4 : 1 v/v) gave the diester (**10**) (144.6 mg, 98%) as a yellow oil. IR($CHCl_3$) 1735, 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.23 (3H, d, J=6.1 Hz, C3'-Me), 1.67-1.84 (3H,m), 2.19-2.30 (1H, m), 3.06 (1H, dt, J=9.2 and 18.9 Hz, C3-H), 3.31 (1H, ddd, J=4.9, 9.2, and 18.9 Hz, C3-H), 3.72 (3H, s, OMe), 3.77 (3H, s, OMe), 3.71-3.80 (1H, m, C2'-H), 4.43 and 4.61 (each 1H, each d, J=11.0 Hz, OCH_2Ph), 4.74-4.84 (1H, m, C5-H), 7.15-7.38 (5H, m, Ph). MS *m/z* 348 (M^+) (Found: 348.1568. Calcd for $C_{19}H_{24}O_6$: 348.1571). $[\alpha]_D$ -106° (c=1.1, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}O_6$: C 65.50; H 6.94. Found: C 65.69; H 7.08.

(5*R*)-[(2*R*)-Hydroxypropyl]-2-[di(methoxycarbonyl)methylene]tetrahydrofuran (11) --- A solution of the benzyl ether (**10**)(0.6 g, 1.7 mmol) in ethyl acetate (6 ml) in the presence of 10% Pd-C (0.3 g) under 5 atm of hydrogen was stirred overnight at room temperature. After removal of the insoluble material by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4 : 6 v/v) gave the hydroxyl compound (**11**)(0.4 g, 90%) as a colorless oil. IR($CHCl_3$) 3500, 1720, 1635 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.25 (3H, d, J=6.7 Hz, C3'-Me), 1.72-1.86 (3H, m), 2.22-2.32 (1H, m), 2.46 (1H, br s, OH), 3.06 (1H, dt, J=9.2 and 18.3 Hz, C3-H), 3.33 (1H, ddd, J=4.3, 9.2, and 18.3 Hz, C3-H), 3.73 and 3.79 (each 3H, each s, 2×OMe), 4.03 (1H, dq, J=6.7 and 18.3 Hz, C2'-H), 4.82 (1H, ddd, J=6.7, 7.9, and 12.8 Hz, C5-H). MS *m/z* 258 (M^+) (Found 258.1100. Calcd for $C_{12}H_{18}O_6$: 258.1102. $[\alpha]_D$ -55° (c=0.4, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O_6$: C 55.80; H 7.03. Found: C 55.50; H 7.23.

The Over-Reduction Product (12) --- A solution of **10** (80 mg, 0.32 mmol) in methanol (2 ml) in the presence of rhodium on alumina (0.16 g) was stirred under 7 atm of hydrogen at room temperature for 1 h. After removal of an insoluble material by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (85:15 v/v) afforded the over-reduction product (**12**)(82.3 mg, 100%) as a mixture of diastereomers. IR($CHCl_3$) 3450, 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 0.89-0.98 (2H, m), 1.19 (3H, d, J=6.1 Hz, Me), 1.13-1.95 (18H, m), 3.13 and 3.34 (each 1H, each dd, J=6.1 and 8.5 Hz, $CHOCH_2$), 3.37 and 3.40 (each 0.5 H, each d, J=7.3 Hz, $CHCO_2$), 3.70-3.76 (1H, m), 3.74 (6H, s, 2×OMe), 3.80-3.95 (1H, m). MS *m/z* 261 (M^+-97)(Found: 261.1340. Calcd for $C_{12}H_{21}O_6$: 261.1339).

(5*R*)-[(2*R*)-Benzyloxypropyl]-2-[1-di(methoxycarbonyl)ethyl]tetrahydrofuran (13) --- To a stirred solution of **10**(100 mg, 0.4 mmol) in THF (2 ml) was added dropwise 1M solution of L-Selectride in THF (0.6 ml, 0.6 mmol) at -78 °C under an atmosphere of argon. After the stirring had been continued for 10 min at the same temperature, methyl iodide (0.09 ml, 2 mmol) was added to the solution and the resulting mixture was warmed up to room temperature over the period of 1 h and further stirred for 3 h. The mixture was treated

with 10% ammonium chloride solution and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1 : 1 v/v) afforded the diester (**13**)(86 mg, 82%) as a mixture of the diastereomers at the 2-position (2α : 2β = 1 : 3) as a colorless oil. IR($CHCl_3$) 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.18 (3H, d, J=6.1 Hz, C3'-Me), 1.42 and 1.44 (each 1.5H, each s, Me), 1.53-2.09 (6H, m), 3.69 and 3.70 (each 3H, each s, 2×OMe), 3.69-3.71 (1H, m), 3.96-4.06 (1H, m), 4.43 and 4.56 (each 1H, each d, J=11.6 Hz, OC*H*$_2$Ph), 4.43-4.60 (1H, m). MS *m/z* 364 (M^+) (Found: 364.1885. Calcd for $C_{20}H_{28}O_6$: 364.1885). Anal. Calcd for $C_{20}H_{28}O_6$: C 65.91; H 7.74. Found: C 66.22; H 7.92.

(5*R*)-[(2*R*)-Hydroxypropyl]-(2*S*)-[di(methoxycarbonyl)methyl]tetrahydrofuran (14) and (5*R*)-[(2*R*)-Hydroxypropyl]-(2*R*)-[di(methoxycarbonyl)methyl]tetrahydrofuran --- A solution of the unsaturated ester (**10**)(1.5 g, 4.3 mmol) in methanol-5 % hydrochloric acid (15 ml, 10 : 1 v/v) in the presence of a catalytic amount of Pd-C (0.75 g) was stirred for 48 h at ambient temperature under 7 atm of hydrogen. After removal of the insoluble material by filtration, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4 : 6 v/v) gave (5*R*)-[(2*R*)-hydroxypropyl]-(2*R*)-[di(methoxycarbonyl)methyl]tetrahydrofuran (180 mg, 16%), homogeneous by TLC [Rf 0.42; hexane-ethyl acetate (1:1 v/v)], as a colorless oil. IR($CHCl_3$) 3500, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ 1.20 (3H, d, J=6.1 Hz, C3'-Me), 1.58-2.30 (7H, m), 3.52 (1H, d, J=9.2 Hz, $CHCO_2$), 3.74 and 3.76 (each 3H, each s, 2×OMe), 3.98-4.05 (1H, m, C2'-H), 4.19-4.29 (1H, m, C5-H), 4.58 (1H, dt, J= 6.7 and 9.2 Hz, C2-H). MS *m/z* 261(M^++1)(Found 261.1326. Calcd for $C_{12}H_{21}O_6$: 261.1336). $[\alpha]_D$ -30° (c=0.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_6$: C 55.37; H 7.75. Found: C 55.39; H 7.95. Further elution with the same solvent gave the diester (**14**)(710 mg, 64%), homogeneous by TLC [Rf 0.39; hexane-ethyl acetate (1:1 v/v)], as a colorless oil. IR($CHCl_3$) 3500, 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.20 (3H, d, J=6.1 Hz, C3'-Me), 1.58-2.30 (7H, m), 3.51 (1H, d, J=9.2 Hz, $CHCO_2$), 3.74 and 3.76 (each 3H, each s, 2×OMe), 3.98-4.05 (1H, m, C2'-H), 4.07-4.20 (1H, m, C5-H), 4.45 (1H, dt, J=6.7 and 9.2 Hz, C2-H). MS *m/z* 261(M^++1)(Found 261.1326. Calcd for $C_{12}H_{21}O_6$: 261.1336). $[\alpha]_D$ +1° (c=0.2, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_6$: C 55.37; H 7.75. Found: C 55.09; H 7.97.

(5*R*)-[(2*R*)-*tert*-Butyldimethylsilyloxypropyl]-(2*S*)-[di(methoxycarbonyl)methyl]-tetrahydrofuran (15) --- A solution of the alcohol (**14**)(170 mg, 0.65 mmol) , *tert*-butyldimethylsilyl chloride (150 mg, 0.98 mmol) and imidazole (53 mg, 0.78 mmol) in DMF (8 ml) was stirred at ambient temperature for 1 h. After treatment with 10% ammonium chloride solution, the mixture was extracted with ether and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (9:1 v/v) provided the silyl ether (**15**)(244 mg, 100%) as a colorless oil. IR($CHCl_3$) 1730 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 0.04 (6H, s, 2×Me), 0.88 (9H, s, *tert*-Bu), 1.11 (3H, d, J= 6.1 Hz, C3'-Me), 1.47-2.25 (6H, m), 3.46 (1H, d, J=9.2 Hz, $CHCO_2$), 3.73 and 3.75 (each 3H, each s, 2×OMe), 3.95 (1H, dq, J=6.1 and 12.8 Hz, C2'-H), 4.03-4.13 (1H, m, C5-H), 4.55 (1H, dt, J=6.7 and 9.2 Hz, C2-H). MS *m/z* 374(M^+). $[\alpha]_D$ -43° (c=0.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{34}O_6Si$: C 57.72; H 9.15. Found: C 57.81; H 9.44.

(5*R*)-[(2*R*)-*tert*-Butyldimethylsilyloxypropyl]-(2*S*)-[1-di(methoxycarbonyl)ethyl]-tetrahydrofuran (16) --- To a stirred solution of the ester (**15**)(40 mg, 0.11 mmol) in THF (2 ml) in the presence of potassium *tert*-butoxide (18 mg, 0.17 mmol) was added methyl iodide (0.03 ml, 0.55 mmol) at room temperature and the mixture was further stirred for 2 h. After dilution with ether, the mixture was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (93:7 v/v) gave the methylated product (**16**)(41.5 mg, 100%) as a yellow oil. IR($CHCl_3$) 1735 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 0.05 (6H, s, 2×Me), 0.88 (9H, s, *tert*-Bu), 1.16 (3H, d, J=6.1 Hz, C3'-Me), 1.42 (3H, s, Me), 1.46-2.12 (6H, m), 3.70-3.73 (each 3H, each s, 2×OMe), 3.89-4.12 (2H, m), 4.53 (1H, dd, J=6.1 and 7.9 Hz, C2-H). $[\alpha]_D$ -39° (c=0.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}O_6Si$: C 58.73; H 9.34. Found: C 58.71; H 9.67.

(5*R*)-[(2*R*)-Hydroxypropyl]-(2*S*)-[1-di(methoxycarbonyl)ethyl]tetrahydrofuran (17) --- To a stirred solution of the silyl ether (**16**)(41.5 mg, 0.11 mmol) in THF (2 ml) was added 1M solution of tetrabutylammonium fluoride in THF (0.13 ml, 0.13 mmol) at ambient temperature and the mixture was further stirred for 16 h. After treatment with 10% ammonium chloride solution, the mixture was extracted with ethyl acetate and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (6:4 v/v) afforded the alcohol (**17**)(30.6 mg, 100%) as a colorless oil. IR($CHCl_3$) 3540, 1735 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.20 (3H, d, J=6.1 Hz, C3'-Me), 1.43 (3H, s, Me), 1.60-2.16 (6H, m), 2.70-3.20 (1H, br s, OH), 3.72 and 3.74 (each 3H, each s, 2×OMe), 4.00-4.06 (1H, m, C2'-H), 4.18-4.28 (1H, m, C5-H), 4.58 (1H, dd, J=6.1 and 8.6 Hz, C2-H). $[\alpha]_D$ -17° (c=0.2, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}O_6$: C 56.92; H 8.08. Found: C 56.93; H 8.31.

Methyl Nonactate (18) and 2-epi-Methyl Nonactate (19) --- A solution of the diester (**17**)(16 mg, 0.056 mmol) and sodium chloride (26 mg, 0.448 mmol) in dimethyl sulfoxide (0.8 ml) and water (0.08 ml) was refluxed for 3 h, then the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (6:4 v/v) gave 2-epi-methyl nonactate (**19**)(5 mg, 39%), homogeneous by TLC [Rf 0.70; hexane-ethyl acetate (9:1 v/v)], as a colorless oil. IR($CHCl_3$) 3100-3700, 1700 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.21 (3H, d, J=6.1 Hz, Me), 1.22 (3H, d, J=6.7 Hz, Me), 1.61-2.05 (7H, m), 2.59 (1H, m, $CHCO_2$), 3.68 (3H, s, OMe), 3.95-4.22 (3H, m). $[\alpha]_D$ -17° (c=0.05, CH_2Cl_2). Further elution with the same solvent system afforded methyl nonactate (**18**)(5 mg, 39%), homogeneous by TLC [Rf 0.63; hexane-ethyl acetate (9:1 v/v)], as a colorless oil. IR($CHCl_3$) 3100-3700, 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ 1.13 (3H, d, J=7.3 Hz, Me), 1.21 (3H, d, J=6.1 Hz, Me), 1.25-2.09 (7H, m), 2.54 (1H, m, $CHCO_2$), 3.70 (3H, s, OMe), 3.94-4.28 (3H, m). $[\alpha]_D$ +21° (c=0.02, CH_2Cl_2).

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