SYNTHESIS OF ALL FOUR POSSIBLE ENANTIOMERS OF SITOPHILATE, AGGREGATION PHEROMONE OF THE GRANARY WEEVIL

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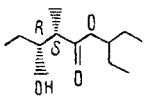
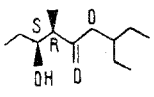
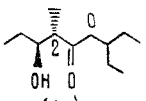
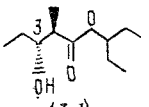
An efficient synthesis of the 3-pentyl ester of 2S-methyl-3R-hydroxypentanoic acid (sitophilate) and its 2S,3S-, 2R,3R-, and 2R,3S-isomers has been carried out starting from the available 2R-methyl-3-butenyl acetate as sole monochiral precursor.

The granary weevil is one of the most widespread storage pests of cereals. It has recently been shown that the primary component of the aggregation pheromone of this insect (Sitophilus granarius) is the erythro isomer of sec-amyl-2-methyl-3-hydroxypentanoate [1], which has been given the name sitophilate. The initially published synthesis of its racemate in admixture with its diastereomer [1] was soon supplemented by the diastereoselective synthesis of the individual (±)-erythro-(Ia + b) and (±)-threo-(Ic + d) isomers [2]. The chiral syn enantiomers (Ia) and (Ib) were originally obtained from Sharpless epoxidaton of 2Z-pentenol [3] and somewhat later from Mitsunobu inversion of the anti-methylcarbinols of (Ic) and (Id), respectively, prepared in turn from chiral 3-hydroxypentanoates [4].


(Ia)


(Ib)


(Ic)


(Id)

Bioassays conducted in the process showed that sitophilate has the 2S,3R configuration (Ia), although its enantiomer (Ib) does not inhibit the attractant activity of the pheromone [5]. In the present communication we discuss a new and efficient synthetic route to all four optically pure enantiomers of (I) based on readily available 4R-methyl-5-acetoxypentanoic acid [6], which we have used previously with success in a number of chiral natural product syntheses [7, 8].

Because of the opportunity of simple conversion of this acetoxy acid into the C_5 building block (II) [7], the planned route to targets (I) was in essence the generation of the C^2 chiral centers of the latter molecules by means of their conservation in the monochiral precursor molecule subjected to a set of required transformations including C_1 homologation. However, in view of the lack of reliable control methods at the formation step of the configuration at C^3, this choice of approach led to nonselective formation of diastereomeric mixtures of (Ia + c) and (Ib + d) at the final stage, making separation necessary. This proved nonetheless easily done by flash chromatography of these pairs on SiO_2.

In accordance with the plan of synthesis of the 2S isomers (Ia, c) (Scheme 1), hydroxylation of acetoxyolefin (II) with OsO_3 in the presence of N-methylmorpholine-N-oxide (MFO) [9] and subsequent ketalization of the intermediate diols without further purification gave in high yield a mixture of acetoxyacetonides (III) epimeric at C^3 whose saponification gave the alcohols (IV) nearly quantitatively. Oxidation of these with pyridinium chlorochromate (PCC) [10] led smoothly to the aldehydes (V), which were readily converted by Grignard reaction to carbinols (VI), from which were then obtained benzyloxyacetonides (VII). Acid-catalyzed removal of the protecting group from the latter gave glycols (VIII), which were cleaved with periodate to the corresponding aldehydes, subjected without further purification to oxidation by pyridinium dichromate (PDC) [11] to yield a mixture of β-benzyloxyacids S-(IX) having the required C_6 carbon skeleton. Esterification with sec-amyl alcohol using dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP) under

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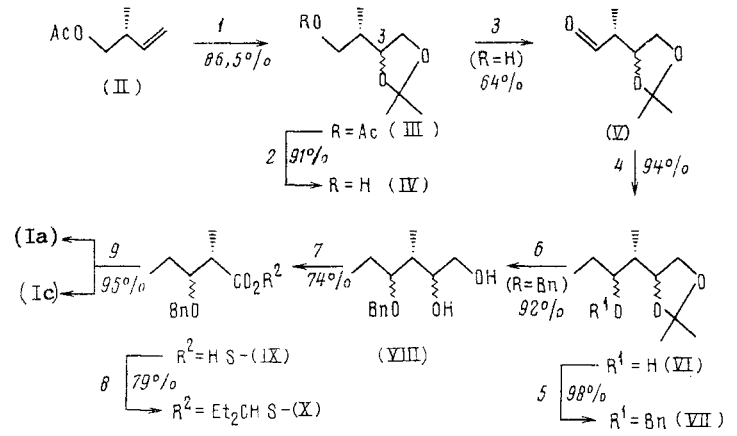
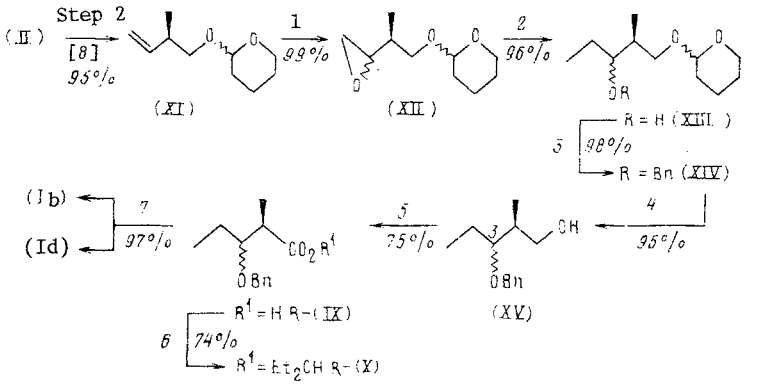
Scheme 1



Reagents and conditions: 1) MFO, cat. OsO_4, t-BuOH/Me_2CO/H_2O, 25°C, 4 h; then cat. TsOH, $Me_2C(OMe)_2$/Me_2CO, 25°C, 30 min; 2) KOH, Et_2O/MeOH/H_2O, 25°C, 30 min; 3) PCC/AcONa, CH_2Cl_2, 25°C, 4 h; 4) EtMgBr/Et_2O, −78 → 0°C, 1 h; 5) NaH/DMF; then BnBr, 25°C, 12 h; 6) CF_3CO_2H, MeCN/H_2O, 25°C, 15 min; 7) HIO_4/H_2O/Et_2O, 25°C, 1 h; then PDC/DMF, 25°C, 12 h; 8) Et_2CHOH, DCC, cat. DMAP, CH_2Cl_2, −10 → 25°C, 3 h; 9) H_2, 5% Pd/C, EtOH, 25°C, 6 h; then chromatography on SiO_2.

Scheme 2



Reagents and conditions: 1) 3-$ClC_6H_4CO_3H$/AcONa, CH_2Cl_2, 0 → 25°C, 4 h; 2) Me_2CuLi/Et_2O, −60 → 0°C, 1 h; 3) NaH/DMF; then BnBr, 25°C, 12 h; 4) cat. TsOH·Py/EtOH, 55°C, 6 h; 5) PDC/DMF, 25°C, 10 h; 6) Et_2CHOH, DCC, cat. DMAP, CH_2Cl_2, −10 → 25°C, 3 h; 7) H_2, 5% Pd/C, EtOH, 25°C, 6 h; then chromatography on SiO_2.

the conditions of [12] smoothly furnished the C^3 epimers of benzyl ethers S-(X). Finally, hydrogenolysis of the latter gave a mixture of the target alcohols (Ia, c) in overall yield of 25% for the 9-step synthesis.

The mixture, as noted above, was readily separated by chromatography into the individual isomers. The proportion (Ia)/(Ic) = 1:1 found in this operation was confirmed by analysis of the product mixture by GLC and PMR (comparison of integrated intensities of CH_3 doublet signals, $\delta \approx 1.2$ ppm). In accordance with the same data, acetonides (III)-(V) and benzyl ethers S-(IX) and S-(X) had very nearly the same diastereomeric ratio, which reliably attests to the absence of racemization of the intermediate carbonyl compounds at the steps (3, 4, and 7 of Scheme 1) most vulnerable in this regard. The optical purity of alcohols (Ia) and (Ic) prepared by the above method was found to be ≥95%, comparable with that of the starting acetate (II) (>97% [6, 7]).

A shorter synthesis of the 2R isomers (Ib, d) was carried out (Scheme 2) starting from tetrahydropyranyl ether (XI), readily obtainable from the same acetate (II) [8]. Thus, epoxidation of olefin (XI) and the regiospecific opening of the intermediate epoxides (XII) with Me_2CuLi gave in almost quantitative yield secondary alcohols (XIII) having the required C_6 carbon skeleton, which were transformed, after formation of benzyl ethers (XIV), into a mixture of C^3 epimers of primary alcohols (XV). Oxidation of the latter with PDC smoothly produced acids R-(IX), whose yield was much reduced if Jones' reagent (8 N H_2CrO_4/Me_2CO) [13] or the recently proposed $KMnO_4/CuSO_4 \cdot 5H_2O/KOH$ system [14] were employed, due to competing β-elimination of the benzyloxy group. The final conversion of R-(IX) to esters R-(X) and further to the target alcohols (Ib, d) was identical to that described above for their enantiomers (Ia, c), and the overall yield was 48% for the 7-step synthesis.

Flash chromatography of the final mixture on SiO_2 separated the individual isomers in a ratio (Ib)/(Id) ≈ 1:1, confirmed by GLC and PMR analysis and in agreement with analysis of the diastereomeric precursors (XV), R-(IX), and R-(X) by the same methods. The optical purity of alcohols (Ib) and (Id) prepared in this manner was respectively >95 and ≈100%. The structures of compounds discussed above and previously undescribed (III)-(X) and (XII)-(XV) were established from elemental and spectral analysis.

Thus a standard set of transformations of monochiral R-acetoxyolefin (II) provides an efficient synthesis of sitophilate (Ia) and three of its stereoisomers (Ib-d).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in $CHCl_3$ solution, UV spectra of ethanolic solutions on a Specord UV-VIS spectrophotometer. PMR spectra were taken in $CDCl_3$ relative to TMS on a Bruker WM-250 instrument. Mass spectra were acquired at 70 eV ionization potential on a Varian MAT CH-6. GLC was performed on a LKhM-80 chromatograph (column 3 m × 3 mm with 15% Carbowax 20 M on N-AW-DMCS packing). TLC was performed on Silufol plates in ether:hexane (1:1). Values of $[\alpha]_D$ were determined on a Jasco DIP-360 polarimeter in $CHCl_3$.

3R/S, 4-Isopropylidenedioxy-2S-methylbutyl Acetate (III). To a solution of 2.27 g (17.7 mmoles) of (II) [7] and 5.42 g (35.4 mmoles) of MFO dihydrate in 8 ml acetone and 1 ml water, stirred at 25°C under Ar, was added over 5 min a solution of 0.22 g (0.87 mmole) of OsO_4 in 4.5 ml t-BuOH. The reaction mixture was stirred 4 h at 25°C and then diluted with ether and a saturated aqueous solution of $Na_2S_2O_5$. Within 12 h the mixture was extracted with ether. The extract was washed with saturated aqueous $NaHSO_3$ and NaCl solutions, dried with $MgSO_4$, and concentrated under vacuum. A solution of the residue (2.9 g) in 0.34 g (1.8 mmoles) $TsOH \cdot H_2O$ in 16 ml acetone and 9 ml $Me_2C(OMe)_2$ was stirred 30 min at 25°C and extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried with $MgSO_4$, and concentrated under vacuum, and the residue (3.3 g) was chromatographed on 150 g SiO_2. Gradient elution from hexane to ether (to 20% of the latter) gave 3.1 g (86.5%) of (III), bp 65-66°C (3 mm), n_D^{20} 1.4331, $[\alpha]_D^{24}$ −0.3° (s 5.6). IR spectrum (ν, cm^{-1}): 855, 905, 985, 1035, 1065, 1115, 1160, 1230, 1260, 1370, 1385, 1455, 1735, 2880, 2940, 2990, 3015, 3510, 3655. PMR spectrum (δ, ppm; J, Hz): 0.91 and 1.00 d (3H, CH_3–C^2, J = 7), 1.33 and 1.38 s (6H, CH_3), 2.03 s (3H, CH_3CO), 1.9-2.0 m (1H, HC^2), 3.6-4.3 m (5H, HC^1, HC^3, HC^4). Mass spectrum, m/z (I, %): M^+ 202 (2), 187 (76), 151 (7), 145 (8), 127 (25), 101 (53), 99 (10), 86 (11), 85 (100), 84 (13), 83 (13), 73 (26), 72 (74), 71 (19). Found, %: C 58.98, H 8.90. $C_{10}H_{18}O_4$. Calculated, %: C 59.39, H 8.97.

3R/S, 4-Isopropylidenedioxy-2S-methyl-1-butanol (IV). To a solution of 2.3 g (11.4 mmoles) of (III) in 20 ml ether stirred at 25°C was added over 5 min a solution of 1.59 g (28.4 mmoles) of KOH in 3 ml water and 3 ml MeOH. Within 30 min the mixture was extracted with ether. The extract was washed with saturated NaCl solution, dried with $MgSO_4$, and concentrated under vacuum and the residue was redistilled. Yield 1.65 g (91%) of (IV), bp 63-64°C (3 mm), n_D^{20} 1.4421, $[\alpha]_D^{23}$ +11.2° (s 2.2). IR spectrum (ν, cm^{-1}): 850, 900, 985, 1035, 1055, 1085, 1230, 1370, 1380, 1455, 1625, 2880, 2930, 2985, 3510, 3625, 3655. PMR spectrum (δ, ppm; J, Hz): 0.83 and 0.96 d (3H, CH_3–C^2, J = 7), 1.36 and 1.42 s (6H, CH_3), 1.8-2.0 m (1H, HC^2), 3.5-4.2 m (5H, HC^1, HC^3, HC^4). Mass spectrum, m/z (I, %): M^+ 160 (2), 145 (93), 129 (27), 101 (53), 99 (20), 85 (100), 83 (15), 73 (19), 72 (73), 71 (19). Found, %: C 59.94, H 10.08. $C_8H_{16}O_3$. Calculated, %: C 59.98, H 10.07.

3R/S, 4-Isopropylidenedioxy-2S-methylbutanal (V). To a suspension of 5.98 g (27.8 mmoles) of PCC [10] and 0.76 (9.3 mmoles) of AcONa in 50 ml CH_2Cl_2, stirred at 25°C under

Ar, was added in one portion a solution of 2.96 g (18.5 mmoles) of (IV) in 5 ml CH_2Cl_2. Within 4 h the mixture was diluted with ether and filtered through a 5-cm layer of SiO_2. The filtrate was concentrated under vacuum and the residue was redistilled. Yield 1.87 g (64%) of (V), bp 45-46°C (3 mm), n_D^{22} 1.4350, $[\alpha]_D^{26}$ −5.9° (s 0.9). IR spectrum (ν, cm^{-1}): 865, 905, 960, 1025, 1065, 1155, 1205, 1240, 1375, 1390, 1460, 1540, 1730, 2735, 2880, 2940, 2995, 3515, 3585. PMR spectrum (δ, ppm; J, Hz): 1.07 and 1.20 d (3H, CH_3–C^2, J = 7), 1.36 and 1.41 s (6H, CH_3), 2.58 m (1H, HC^2), 3.5-4.3 m (3H, HC^3, HC^4), 9.77 d (1H, HC^1, J = 2). Mass spectrum, m/z (I, %): M^+ 158 (3), 143 (100), 129 (24), 101 (35), 83 (65), 73 (24), 72 (64), 71 (35). Found, %: C 61.05, H 9.15. $C_8H_{14}O_3$. Calculated, %: C 60.74, H 8.92.

5R/S, 6-Isopropylidenedioxy-4S-methyl-3R/S-hexanol (VI). To a solution of 0.24 g (1.5 mmoles) of (V) in 4 ml ether stirred at −78°C under Ar was added over 30 min 2.9 ml of a 0.8 M solution of EtMgBr (2.3 mmoles) in ether. The reaction mixture was warmed to 0°C over 1 h, decomposed with a saturated aqueous solution of NH_4Cl, and extracted with ether. After the usual workup the extract was dried with $MgSO_4$ and concentrated under vacuum and the residue was redistilled. Yield 0.27 g (94%) of (VI), bp 68-69°C (3 mm), n_D^{19} 1.4453, $[\alpha]_D^{27}$ +18.3° (s 1.7). IR spectrum (ν, cm^{-1}): 860, 965, 1060, 1160, 1205, 1240, 1375, 1385, 1415, 1460, 2880, 2940, 2990, 3515, 3585. PMR spectrum (δ, ppm; J, Hz): 0.8-1.0 m (6H, HC^1, CH_3–C^4), 1.32 and 1.38 s (6H, CH_3), 1.2-1.8 m (3H, HC^2, HC^4), 3.4-4.3 m (4H, HC^3, HC^5, HC^6). Mass spectrum, m/z (I, %): 174 (16), 173 (57), 145 (25), 115 (25), 113 (50), 101 (100), 95 (33), 85 (51), 73 (33), 72 (92), 69 (35). Found, %: C 63.44, H 10.63. $C_{10}H_{20}O_3$. Calculated, %: C 63.80, H 10.71.

Benzyl Ether of 5R/S, 6-Isopropylidenedioxy-4S-methyl-3R/S-hexanol (VII). To a suspension of 0.49 g of 80% NaH (16.3 mmoles) (previously degreased with pentane) in 5 ml DMF under Ar was added over 5 min a solution of 0.94 g (5.0 mmoles) of (VI) in 5 ml DMF. The reaction mixture was stired 30 min at 25°C, then treated with 1.71 g (10.0 mmoles) of BnBr, held 12 h, diluted with water, and extracted with ether:hexane (1:1). The extract was washed with saturated NaCl solution, dried with $MgSO_4$, and concentrated under vacuum and the residue (1.7 g) chromatographed on 100 g SiO_2. Gradient elution from hexane to ether (to 15% of the latter) gave 1.36 g (98%) of (VII) as a colorless oil, R_f 0.58, $[\alpha]_D^{23}$ +0.05° (s 1.7). IR spectrum (ν, cm^{-1}): 865, 965, 1060, 1160, 1245, 1260, 1385, 1460, 1500, 1675, 2880, 2940, 2975, 3060. UV spectrum (λ_{max}, nm): 207 (ε 8800), 258 (ε 300). PMR spectrum (δ, ppm; J, Hz): 0.8-1.0 m (6H, HC^1, CH_3–C^4), 1.38 and 1.44 s (6H, CH_3), 1.3-1.9 m (3H, HC^2, HC^4), 3.2-4.2 m (4H, HC^3, HC^5, HC^6), 4.5-4.7 m (2H, CH_2Ph), 7.3-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): M^+ 278 (13), 263 (37), 219 (30), 171 (20), 170 (27), 150 (30), 149 (90), 145 (25), 130 (67), 129 (40), 118 (30), 114 (83), 113 (27), 107 (67), 101 (100), 99 (60), 92 (60), 91 (100), 85 (25), 72 (79), 71 (63), 69 (40). Found, %: C 73.12, H 9.29 $C_{17}H_{26}O_3$. Calculated, %: C 73.35, H 9.41.

4R/S-Benzyloxy-3S-methyl-1,2R/S-hexanediol (VIII). A solution of 0.42 g (1.5 mmoles) of (VII) in 5 ml of a mixture of CF_3CO_2H:MeCN:water (4:4:1) was stirred 15 min at 25°C, then neutralized with $NaHCO_3$ and extracted with ether. The extract was washed with a saturated aqueous NaCl solution, dried with $MgSO_4$, and concentrated under vacuum and the residue (0.4 g) was chromatographed on 20 g SiO_2. Gradient elution from hexane to ether (to 95% of the latter) gave 0.33 g (92%) of (VIII) as a colorless oil, R_f 0.37 (ether), $[\alpha]_D^{24}$ +11.8° (s 1.0). IR spectrum (ν, cm^{-1}): 955, 1060, 1215, 1355, 1385, 1455, 1500, 1675, 2880, 2935, 2970, 3010, 3450, 3535. UV spectrum (λ_{max}, nm): 207 (ε 8800), 258 (ε 300). PMR spectrum (δ, ppm; J, Hz): 0.8-1.0 m (6H, HC^6, CH_3–C^3), 1.4-2.2 m (3H, HC^3, HC^5), 3.4-3.9 m (4H, HC^1, HC^2, HC^4), 4.4-4.7 m (2H, CH_2Ph), 7.3-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): M^+ 238 (8), 220 (13), 207 (29), 189 (19), 150 (21), 149 (90), 148 (44), 134 (21), 114 (42), 108 (69), 107 (100), 101 (49), 92 (78), 91 (100), 89 (30), 85 (25), 83 (28), 81 (28), 79 (54), 71 (93), 70 (56), 69 (45). Found, %: C 70.52, H 9.32. $C_{14}H_{22}O_3$. Calculated, %: C 70.56, H 9.30.

3R/S-Benzyloxy-2S-methylpentanoic Acid S-(IX). To a solution of 0.16 g (0.67 mmole) of (VIII) in 10 ml ether stirred at 25°C was added in one portion 0.5 g (2.4 mmoles) of $HIO_4 \cdot 2H_2O$ in 5 ml water. Within 1 h the mixture was extracted with ether, this extract was dried with $MgSO_4$ and concentrated under vacuum, and a solution of the residue (0.14 g) in 1 ml DMF was added to a suspension of 0.47 g (1.3 mmoles) of PDC [11] in 4 ml DMF. The reaction mixture was stirred 12 h at 25°C, then diluted with water, acidified with 5% HCl to pH 3 and extracted with hexane:ether (1:1). The extract was dried with $MgSO_4$ and

concentrated under vacuum and the residue (0.2 g) was chromatographed on 10 g SiO_2. Gradient elution from hexane to ether (to 20% of the latter) gave 0.11 g (74%) of S-(IX) as a colorless oil, R_f 0.35, $[\alpha]_D^{22}$ +10.7° (s 2.3). IR spectrum (ν, cm^{-1}): 695, 930, 950, 1025, 1060, 1090, 1110, 1230, 1285, 1345, 1380, 1410, 1455, 1495, 1710, 1745, 2880, 2950, 2970, 3005, 3030, 3510. UV spectrum (λ_{max}, nm): 208 (ε 12,500), 258 (ε 350). PMR spectrum (δ, ppm; J, Hz): 0.98 t (3H, HC^5, J = 7), 1.19 and 1.26 d (3H, CH_3-C^2, J = 7), 1.5-1.8 m (2H, HC^4), 2.75 and 2.85 quint (1H, CH_2, J = 7), 3.71 m (1H, HC^3), 4.58 and 4.60 s (2H, CH_2PH), 7.3-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): M^+ 222 (26), 186 (35), 149 (30), 122 (23), 107 (39), 105 (21), 91 (100), 85 (13), 77 (19), 73 (19). Found, %: C 70.39, H 8.09. $C_{13}H_{18}O_3$. Calculated, %: C 70.24, H 8.16.

3-Pentyl Ester of 3R/S-Benzyloxy-2S-methylpentanoic Acid S-(X). To a solution of 0.74 g (3.3 mmoles) of S-(IX), 0.88 g (10.0 mmoles) of Et_2CHOH, and 40 mg (0.33 mmole) of DMAP in 15 ml CH_2Cl_2, stirred at −10°C under Ar, was added over 5 min 0.78 g (3.7 mmoles) of DCC. The reaction mixture was warmed to 25°C over 30 min, stirred 2.5 h and filtered. The filtrate was washed with 5% HCl and saturated aqueous $NaHCO_3$ and NaCl solutions, dried with $MgSO_4$, and concentrated under vacuum and the residue (1.5 g) was chromatographed on 80 g SiO_2. Gradient elution from hexane to ether (to 10% of the latter) gave 0.77 g (79%) of S-(X) as a colorless oil, R_f 0.53, $[\alpha]_D^{26}$ +3.2° (s 1.1). IR spectrum (ν, cm^{-1}): 695, 890, 915, 955, 1030, 1065, 1100, 1190, 1230, 1260, 1305, 1330, 1350, 1385, 1460, 1495, 1725, 2880, 2940, 2975, 3005, 3030, 3060, 3090. UV spectrum (λ_{max}, nm): 208 (ε 10,400), 258 (ε 300). PMR spectrum (δ, ppm; J, Hz): 0.8-1.0 m (9H, CH_3), 1.13 and 1.26 d (3H, CH_3-C^2, J = 7), 1.4-1.7 m (6H, CH_2), 2.69 and 2.82 quint (1H, HC^2, J = 7), 3.70 m (1H, HC^3), 4.54 and 4.56 s (2H, CH_2Ph), 4.79 quint (1H, COOCH, J = 7), 7.2-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): M^+ 292 (2), 222 (5), 206 (10), 187 (37), 164 (15), 116 (85), 115 (24), 107 (90), 92 (37), 91 (100), 87 (39), 79 (18), 71 (20), 70 (23), 69 (27), 65 (36). Found, %: C 73.63, H 9.53. $C_{18}H_{28}O_3$. Calculated, %: C 73.92, H 9.67.

3-Pentyl Esters of 3R- and 3S-Hydroxy-2S-methylpentanoic Acid (Ia) (Sitophilate) and (Ic). A suspension of 0.41 g (1.4 mmoles) of S-(X) and 0.7 g 5% Pd/C in 15 ml EtOH was hydrated at 25°C and atmospheric pressure until hydrogen absorption ceased (6 h). The catalyst was filtered out, the filtrate was concentrated under vacuum, and the residue (0.4 g) was chromatographed on 40 g SiO_2. Gradient elution from hexane to ether (to 15% of the latter) gave, in order of elution, 0.12 g (42%) of (Ic) and 0.15 g (53%) of (Ia). For (Ia): bp 80-81°C (3 mm), n_D^{24} 1.4312, $[\alpha]_D^{29}$ −3.7° (s 0.6); compare data of [3]: $[\alpha]_D^{24}$ −3.1° (s 1.7, $CHCl_3$); [4]: $[\alpha]_D^{24}$ −3.9° (s 1.74, $CHCl_3$). PMR spectrum (δ, ppm; J, Hz): 0.89 t (6H, CH_3, J = 7), 0.98 t (3H, HC^5, J = 7), 1.19 d (3H, CH_3-C^2, J = 7), 1.4-1.7 m (6H, CH_2), 2.55 q.d (1H, HC^2, J = 7 and 4), 3.81 m (1H, HC^3), 4.79 quint (1H, COOCH, J = 7). For (Ic): bp 77-78°C (3 mm), n_D^{24} 1.4288, $[\alpha]_D^{29}$ + 5.7° (s 0.5); lit. [4]: $[\alpha]_D^{21}$ +6.00° (s 1.04, $CHCl_3$). PMR spectrum (δ, ppm; J, Hz): 0.90 t (6H, CH_3, J = 7), 0.99 t (3H, HC^5, J = 7), 1.24 d (3H, CH_3-C^2, J = 7), 1.4-1.7 m (6H, CH_2), 2.54 quint (1H, HC^2, J = 7), 3.58 m (1H, HC^3), 4.81 quint (1H, COOCH, J = 7).

3R-Methyl-4-(2R/S-tetrahydropyranyloxy)-1,2-R/S-epoxybutane (XII). To a suspension of 1.75 g (10.3 mmoles) of (XI) [8] and 1.43 g (17.4 mmoles) of AcONa in 20 ml CH_2Cl_2 stirred at 0°C was added over 15 min 3.41 g of 78% $3-ClC_6H_4CO_3H$ (15.4 mmoles). The reaction mixture was stirred 1 h at 0°C and 4 h at 25°C and then diluted with pentane:ether (1:1) and filtered through a 3-cm layer of Al_2O_3. The filtrate was concentrated under vacuum and the residue (2 g) chromatographed on 100 g SiO_2. Gradient elution from pentane to ether (to 25% of the latter) gave 1.9 g (99%) of (XII), bp 62-63°C (3 mm), n_D^{27} 1.4494, $[\alpha]_D^{26}$ +3.5° (s 1.1). IR spectrum (ν, cm^{-1}): 815, 870, 905, 975, 1020, 1040, 1065, 1080, 1120, 1140, 1185, 1200, 1215, 1235, 1260, 1275, 1285, 1325, 1350, 1355, 1380, 1445, 1455, 1485, 1575, 1620, 1725, 2470, 2660, 2880, 2940, 3005, 3050, 3500, 3665. PMR spectrum (δ, ppm; J, Hz): 0.95-1.05 m (3H, CH_3), 1.4-1.9 m (7H, HC^3, CH_2), 2.5-3.0 m (3H, HC^1, HC^2), 3.3-3.9 m (4H, OCH_2), 4.58 m (1H, OCHO). Mass spectrum, m/z (I, %): M^+ 186 (2), 156 (5), 128 (13), 127 (15), 115 (16), 101 (25), 86 (15), 85 (100), 84 (20), 83 (15). Found, %: C 64.38, H 9.79. $C_{10}H_{18}O_3$. Calculated, %: C 64.49, H 9.74.

4R-Methyl-5-(2R/S-tetrahydropyranyloxy)-3-R/S-pentanol (XIII). To a suspension of 7.37 g (38.7 mmoles) of CuI in 50 ml ether stirred at −30°C under Ar was added over 10 min 46 ml of a 1.47 M solution of MeLi (67.6 mmoles) in ether. The mixture was held 30 min at 0°C, cooled to −60°C, and within 30 min treated with a solution of 1.2 g (6.4 mmoles) of (XII) in 10 ml ether, warmed over 1 h to 0°C, decomposed with aqueous NH_4Cl, and extracted with ether. The extract was washed with a saturated aqueous NaCl solution, dried with $MgSO_4$,

and concentrated under vacuum and the residue (1.4 g) chromatographed on 70 g SiO_2. Gradient elution from hexane to ether (to 40% of the latter) gave 1.25 g (96%) of (XIII), bp 77-78°C (3 mm), n_D^{21} 1.4572, $[\alpha]_D^{28}$ +7.8° (s 2.0). IR spectrum (ν, cm^{-1}): 870, 890, 900, 975, 1030, 1075, 1120, 1140, 1215, 1315, 1345, 1380, 1410, 1440, 1460, 1730, 2860, 2880, 2940, 2965, 3005, 3620. PMR spectrum (δ, ppm; J, Hz): 0.9-1.0 m (6H, CH_3), 1.4-1.9 m (9H, HC^4, CH_2), 3.3-4.0 m (5H, HC^3, OCH_2), 4.5-4.6 m (1H, OCHO). Mass spectrum, m/z (I, %): 162 (25), 155 (10), 144 (52), 143 (59), 119 (32), 117 (86), 116 (25), 115 (33), 104 (30), 103 (85), 102 (62), 101 (100), 100 (49), 99 (38), 86 (67), 85 (100), 84 (91), 87 (72), 82 (41), 81 (20). Found, %: C 64.94, H 10.91. $C_{11}H_{22}O_3$. Calculated, %: C 65.31, H 10.96.

Benzyl Ether of 4R-Methyl-5-(2R/S-tetrahydropyranyloxy)-3-R/S-pentanol (XIV). As described above for (VII), from 0.44 g (2.2 mmoles) of (XIII), 0.21 g 80% NaH (7.1 mmoles), and 0.74 g (4.4 mmoles) of BnBr in 5 ml DMF was obtained 0.9 g of product, which was chromatographed on 50 g SiO_2. Gradient elution from hexane to ether (to 10% of the latter) gave 0.62 g (98%) of (XIV) as a colorless oil, R_f 0.48, $[\alpha]_D^{27}$ −0.5° (s 1.7). IR spectrum (ν, cm^{-1}): 700, 810, 840, 865, 905, 975, 1025, 1065, 1075, 1120, 1135, 1185, 1200, 1240, 1260, 1275, 1325, 1355, 1380, 1440, 1455, 1495, 1605, 2880, 2940, 2970, 3000, 3065, 3090, 3665. UV spectrum (λ_{max}, nm): 208 (ε 12,100), 258 (ε 540). PMR spectrum (δ, ppm; J, Hz): 0.9-1.0 m (6H, CH_3), 1.4-1.9 m (8H, CH_2), 2.0-2.2 m (1H, HC^4), 3.3-4.0 m (5H, HC^3, OCH_2), 4.5-4.5 m (3H, OCHO, CH_2Ph), 7.2-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): 209 (4), 208 (14), 207 (67), 161 (12), 149 (14), 132 (12), 117 (12), 108 (20), 107 (75), 106 (24), 105 (48), 101 (45), 92 (48), 91 (100). Found, %: C 73.86, H 9.55. $C_{18}H_{28}O_3$. Calculated, %: C 73.92, H 9.67.

3R/S-Benzyloxy-2S-methyl-1-pentanol (XV). A solution of 0.43 g (1.5 mmoles) of (XIV) and 35 mg (0.15 mmole) of TsOH·Py [15] in 10 ml EtOH was stirred 6 h at 55°C, then concentrated under vacuum and the residue (0.4 g) chromatographed on 25 g SiO_2. Gradient elution from hexane to ether (to 40% of the latter) gave 0.29 g (95%) of (XV) as a colorless oil, R_f 0.26 $[\alpha]_D^{25}$ −16.2° (s 1.5). IR spectrum (ν, cm^{-1}): 700, 815, 910, 950, 985, 1030, 1050, 1070, 1110, 1140, 1180, 1210, 1240, 1285, 1355, 1380, 1420, 1455, 1495, 1610, 2880, 2920, 2975, 3005, 3030, 3070, 3095, 3490, 3625, 3665. UV spectrum (λ_{max}, nm): 208 (ε 9200), 258 (ε 250). PMR spectrum (δ, ppm; J, Hz): 0.9-1.0 m (6H, CH_3), 1.5-2.2 m (3H, HC^2, HC^4), 3.4-3.7 m (3H, HC^1, HC^3), 4.4-4.7 m (2H, CH_2Ph), 7.3-7.4 m (5H, C_6H_5). Mass spectrum, m/z (I, %): M^+ 208 (1), 190 (6), 179 (31), 108 (15), 107 (15), 92 (28), 91 (100), 84 (17), 77 (16), 69 (16), 65 (19). Found, %: C 75.18, H 9.67. $C_{13}H_{20}O_3$. Calculated, %: C 74.96, H 9.68.

3R/S-Benzyloxy-2R-methylpentanoic Acid R-(IX). A mixture of 0.1 g (0.5 mmole) of (XV) and 1.26 g (3.4 mmoles) of PDC in 3 ml DMF was held 10 h at 25°C, then treated and the product chromatographed as for S-(IX). Yield 80 mg (75%) of R-(IX) as a colorless oil, $[\alpha]_D^{25}$ −17.6° (s 0.6). Physicochemical characteristics (R_f, IR, PMR, and mass spectra) were identical with those above for S-(IX).

3-Pentyl Ester of 3R/S-Benzyloxy-2R-methylpentanoic Acid R-(X). This was obtained as described for S-(X) from 0.47 g (2.1 mmoles) of R-(IX), 0.56 g (6.4 mmoles) of Et_2CHOH, 30 mg (0.24 mmole) of DMAP, and 0.48 g (2.3 mmoles) of PDC in 10 ml CH_2Cl_2. Yield 0.46 g (74%), colorless oil, $[\alpha]_D^{27}$ −4.0° (s 2.0). Physicochemical characteristics (R_f, IR, PMR, and mass spectra) were identical with those above for S-(X).

3-Pentyl Esters of 3S- and 3R-Hydroxy-2R-methylpentanoic Acid (Ib and Id). As described above for (Ia, c), from 0.43 g (1.5 mmoles) of R-(X) and 0.5 g 5% Pd/C in 15 ml EtOH was obtained, in order of elution, 0.15 g (50%) of (Id) and 0.14 g (47%) of (Ib). For (Ib): bp 71-72°C (2 mm), n_D^{25} 1.4331, $[\alpha]_D^{29}$ +3.9° (s 1.3); compare data in [3]: $[\alpha]_D^{24}$ +3.0° (s 1.5, $CHCl_3$); [4]: $[\alpha]_D^{21}$ +4.1° (s 1.46, $CHCl_3$). The PMR spectrum was identical to that given for (Ia). For (Id): bp 67-68°C (2 mm), n_D^{23} 1.4331, $[\alpha]_D^{28}$ −5.8° (0.9); compare data in [4]: $[\alpha]_D^{17}$ −5.76° (s 1.03, $CHCl_3$). The PMR spectrum was identical to that given for (Ic).

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