PREPARATION OF A CHIRAL BUILDING BLOCK BASED ON 1,3-SYN-DIOL USING PSEUDOMONAS FLUORESCENS LIPASE AND ITS APPLICATION TO THE SYNTHESIS OF A HUNGER MODULATOR

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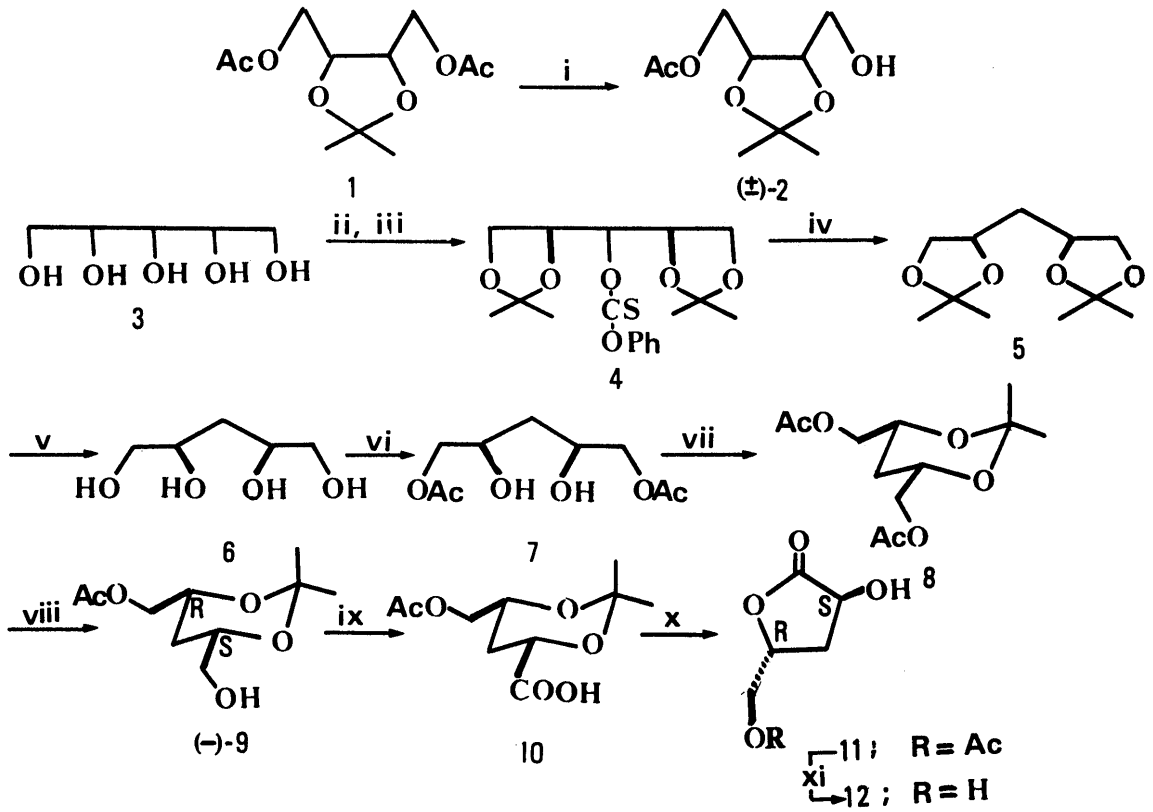
A novel, chiral building block (**9**) consisting of 1,3-syn-diol was obtained by highly enantioselective hydrolysis of the meso-diacetate (**8**) with Pseudomonas fluorescens lipase (PFL), and (-)-**9** was used to synthesize one of four possible stereoisomers of 2-hydroxy-4-hydroxymethyl-4-butanolide, which has hunger modulating activities.

KEYWORDS Pseudomonas fluorescens lipase; 1,3-syn-diol; meso-compound; enantioselective hydrolysis; 2-hydroxy-4-hydroxymethyl-4-butanolide

We have already reported that PFL is of great value in asymmetric induction[1] as shown in the synthesis of (-)-muscone.[2] We describe here PFL-catalyzed highly enantioselective hydrolysis of the meso-acetate (**8**) consisting of 1,3-syn-diol to a novel, chiral building block (**9**), and its application to the synthesis of one of four possible stereoisomers of 2-hydroxy-4-hydroxymethyl-4-butanolide, which has hunger modulating activities. In a preliminary experiment, we found that the hydrolysis of 2,2-dimethyl-4,5-cis-bisacetoxymethyl-1,3-dioxolane (**1**)[3] with PFL results in the formation of the optically inactive mono-acetate (**2**). One reason may be the inherent feature of the five-membered ring system as observed in the case of PLE-catalyzed hydrolysis of cyclopentane diester.[4] The other reason may be the acetyl migration attributable to either the enzymes[1] or the work up.[5] To overcome these obstacles, we envisaged the conformationally rigid compound (**8**) as a preferable substrate, in which two acetoxymethyl groups should be located in the 1,3-equatorial positions.[6] Our starting material for preparing **8** was commercially available adonitol (**3**), which was converted to the phenoxythiocarbonyl ester (**4**) in 71% yield via acetalization with 2,2-dimethoxypropane/p-TsOH and subsequent treatment with PhOCSCl/4-(dimethylamino)pyridine. **4** was converted to the diacetonide (**5**) by treatment with Bu_3SnH[7] in 87% yield. Deacetalization of **5** with p-TsOH/MeOH followed by careful acetylation with acetic anhydride/pyridine under ice-water cooling afforded, in 63% yield, the diacetate (**7**), which was again converted to the acetonide using 2,2-dimethoxypropane/p-TsOH. Hydrolysis of the meso-diacetate (**8**) (0.017 M solution in 0.1 M phosphate buffer (pH 7)) with PFL (91 mg/1 mmol substrate) afforded, in accord with our expectation, the monoacetate (**9**)($[\alpha]_D^{25}$ -4.64°(c=0.99, $CHCl_3$)) in 96% e.e.[8] and 79% chemical yield.[9] The above procedure provides practical, efficient synthesis of chiral 1,3-syn-diol.[10] Next, this compound was used to synthesize 2-hydroxy-4-hydroxymethyl-4-



Reagents and conditions: i) PFL, 30°C, 4h, 16%; ii) $Me_2C(OMe)_2$/p-TsOH/ dimethylformamide, 20°C, 81%; iii) PhOCSCl/4-(dimethylamino)pyridine/MeCN, 25°C, 12h, 87%; iv) n-Bu_3SnH/AIBN/benzene/N_2, 75°C, 8h, 87%; v) p-TsOH/ MeOH, 20°C, 5h, 85%; vi) Ac_2O/pyridine, 0-20°C, 8h, 61%; vii) see ii, 89%; viii) PFL, 50min, 25°C, 79%; ix) PDC/DMF, 16h; x) p-TsOH/ CH_2Cl_2, 41% from (-)-9; xi) 4% K_2CO_3/MeOH, then, 5% aqueous HCl, 62%.

butanolide which has hunger modulating activities.[11] Oxidation of (-)-9 with pyridinium dichromate (PDC) in N,N-dimethylformamide followed by treatment with p-toluenesulfonic acid in CH_2Cl_2 afforded the lactone (-)-(11). Hydrolysis of (-)-11 with 4% K_2CO_3/MeOH and subsequent lactonization with 5% aqueous HCl afforded one of four possible stereoisomers of 2-hydroxy-4-hydroxymethyl-4-butanolide, (2S,4R)-isomer (12), which was identical in terms of the spectral data with the authentic sample.[12]

REFERENCES AND NOTES

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3) Compound (1) was prepared from meso-dimethyl tartrate via (i) acetalization

with 2,2-dimethoxypropane/p-TsOH, (ii) reduction with $LiAlH_4$, (iii) acetylation with Ac_2O/Py. In the hydrolysis of **1** with PFL, (±)-**2** was isolated, in addition to the recovery (19%) of **1** and the diol (20%).

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8) Enantiomeric excess was determined by the 270 MHz ^{1}H-NMR spectra of (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester, and the absolute configuration was determined by transformation of **9** into (R)-1,2,4-butantriol via deketalization with p-TsOH, followed by treatment with $NaIO_4$, and then reduction with $NaBH_4$.

9) All yields refer to isolated and purified products.
Selected spectroscopic data for **4**; ^{1}H-NMR ($CDCl_3$) δ: 4.05 (2H, dd, J=8.6, 6.5 Hz), 4.16 (2H, dd, J=8.6, 6.7 Hz), 4.43 (2H, dt, J=6.7, 4.3 Hz), 5.77 (1H, t, J=4.2 Hz). IR (neat): 1590, 1480, 1455 cm^{-1}. **5**: ^{1}H-NMR ($CDCl_3$) δ: 1.35 (6H, s), 1.41 (6H, s), 1.78 (1H, dt, J=13.9, 6.1 Hz), 2.01 (1H, dt, J=14.1, 6.1 Hz), 3.61 (2H, dd, J=7.5, 7.4 Hz), 4.08 (2H, dd, J=7.5, 5.9 Hz), 4.15-4.25 (2H, m). ^{13}C-NMR($CDCl_3$) δ: 25.67 (q), 26.87 (q), 36.72 (t), 69.25 (t), 72.83 (d), 108.85 (s). MS m/z: 216 (M^+), 201. **7**; ^{1}H-NMR($CDCl_3$) δ: 1.66 (2H, t, J=6.1 Hz), 2.11 (6H, s), 3.55 (2H, br), 3.85-4.20 (6H, m). MS m/z: 221 (M+1), 203, 161. **8**; ^{1}H-NMR($CDCl_3$) δ: 1.29-1.53 (2H, m), 1.43 (3H, s), 1.47 (3H, s), 2.09 (6H, s), 4.02-4.20 (6H, m). ^{13}C-NMR($CDCl_3$) δ: 19.60 (q), 20.90 (q), 29.34 (t), 29.85 (q), 66.90 (d), 67.02 (t), 99.07 (s), 170.94 (s). MS m/z: 245(M^+-15), 203, 187. **9**; ^{1}H-NMR($CDCl_3$) δ: 1.26-1.45 (2H, m), 1.43 (3H, s), 1.48 (3H, s), 2.09 (3H, s), 3.52 (1H, J=11.6, 6 Hz), 3.64 (1H, dd, J=11.6, 3.3 Hz), 3.98-4.19 (4H, m). MS m/z: 218 (M^+), 200, 186. **11**; $[\alpha]_D^{25}$-53.8°(c=0.53, $CHCl_3$). ^{1}H-NMR($CDCl_3$) δ: 2.10 (3H, s), 2.30-2.51 (2H, m), 4.21 (1H, dd, J=19.6, 12.5 Hz), 4.25 (1H, dd, J=12.5, 8.6 Hz), 4.60 (1H, t, J=8.4 Hz), 4.70-4.95 (1H, m). **12**; $[\alpha]_D^{25}$-47.5°(c=0.72, EtOH).

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