

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

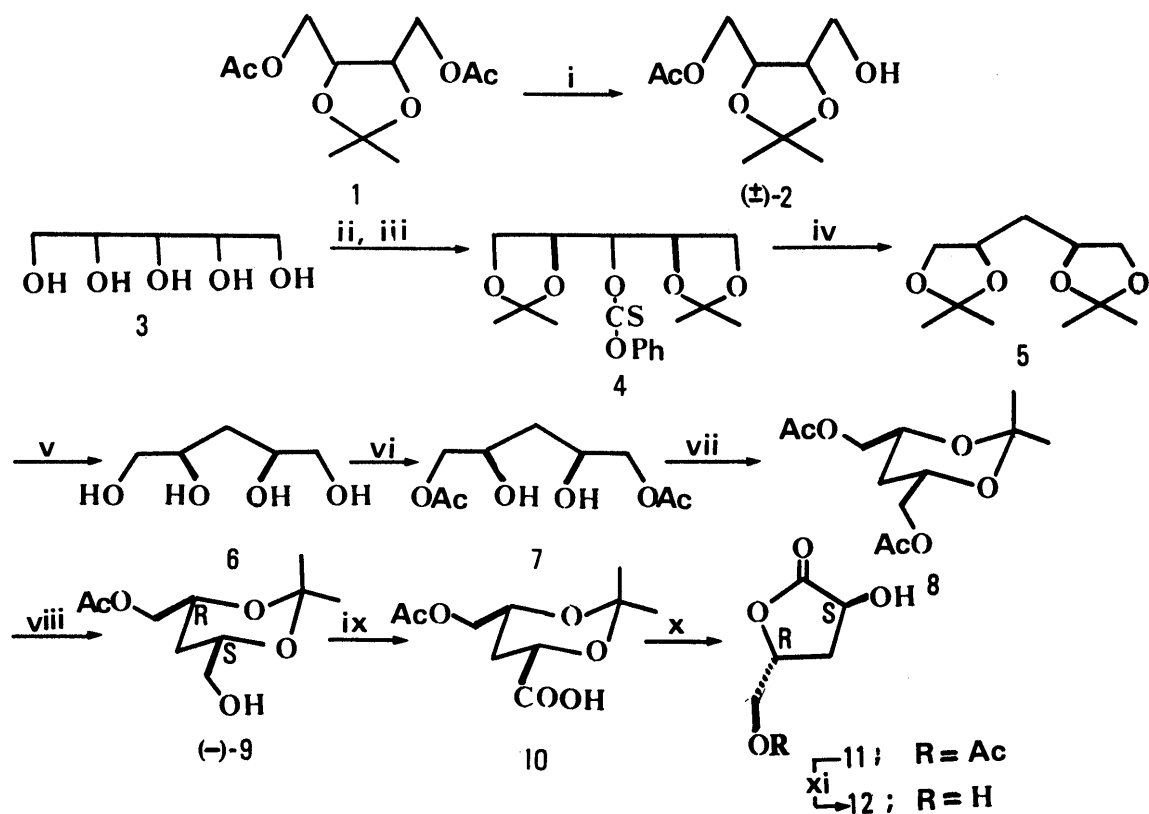
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A novel, chiral building block (9) consisting of 1,3-syn-diol was obtained by highly enantioselective hydrolysis of the meso-diacetate (8) with Pseudomonas fluorescens lipase (PFL), and (-)-9 was used to synthesize one of four possible stereoisomers 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 induction¹⁾ 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 enzymes¹⁾ 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 diacetone (5) by treatment with Bu₃SnH⁷⁾ 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 acetone 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/l mmol substrate) afforded, in accord with our expectation, the monoacetate (9) ($[\alpha]_D^{25} -4.64^\circ$ (c=0.99, CHCl₃)) 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) $\text{Me}_2\text{C}(\text{OMe})_2/\text{p-TsOH}/\text{dimethylformamide}$, 20°C, 81%; iii) $\text{PhOCSCl}/4\text{-(dimethylamino)pyridine}/\text{MeCN}$, 25°C, 12h, 87%; iv) $n\text{-Bu}_3\text{SnH}/\text{AIBN}/\text{benzene}/\text{N}_2$, 75°C, 8h, 87%; v) $\text{p-TsOH}/\text{MeOH}$, 20°C, 5h, 85%; vi) $\text{Ac}_2\text{O}/\text{pyridine}$, 0-20°C, 8h, 61%; vii) see ii, 89%; viii) PFL, 50min, 25°C, 79%; ix) PDC/DMF, 16h; x) $\text{p-TsOH}/\text{CH}_2\text{Cl}_2$, 41% from (-)-9; xi) 4% $\text{K}_2\text{CO}_3/\text{MeOH}$, 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% $\text{K}_2\text{CO}_3/\text{MeOH}$ and subsequent lactonization with 5% aqueous HCl afforded one of four possible stereoisomers of 2-hydroxy-4-hydroxymethyl-4-butanolide, (2*S*,4*R*)-isomer (12), which was identical in terms of the spectral data with the authentic sample.¹²⁾

REFERENCES AND NOTES

- 1) For PFL-catalysed hydrolysis of acetates, see Z.-F.Xie, I.Nakamura, H.Suemune, and K.Sakai, *J. Chem. Soc., Chem. Commun.*, 1988, 966, and references cited therein.
- 2) Z.-F.Xie, H.Suemune, and K.Sakai, *J. Chem. Soc., Chem. Commun.*, 1988, 1638.
- 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 $\text{Ac}_2\text{O}/\text{Py}$. 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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 - 6) The preferred orientation for hydrolysis of ester was postulated to be equatorial when it attached to the cyclohexane ring; see L.K.P.Lam and J.B.Jones, *J. Org. Chem.*, **53**, 2637 (1988) and also see ref. 1 and 4.
 - 7) M.J.Robins and J.S.Wilson, *J. Am. Chem. Soc.*, **103**, 932 (1981).
 - 8) Enantiomeric excess was determined by the 270 MHz ^1H -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-butanetriol 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**; ^1H -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**: ^1H -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**: ^1H -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 ($\text{M}+1$), 203, 161. **8**: ^1H -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**: ^1H -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**: $[\alpha]_{\text{D}}^{25} -53.8^\circ$ ($c=0.53$, CHCl_3). ^1H -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**: $[\alpha]_{\text{D}}^{25} -47.5^\circ$ ($c=0.72$, EtOH).
 - 10) For chemical synthesis of chiral 1,3-syn-diol moiety, see a: K.C.Nicolaou, R.A.Daines, J.Uenishi, W.S.Li, D.P.Papahatjis, and T.K.Chakraborty, *J. Am. Chem. Soc.*, **109**, 2205 (1987). b: I.Nakata, S.Nagao, S.Takao, T.Tanaka, and T.Oishi, *Tetrahedron Lett.*, **73**, 26 (1985). c: S.Masamune and W.Choy, *Aldrichimica Acta*, **15**, 47 (1982).
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