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Development of Tetrahydrofuran Chiral Synthons by Enzymatic Approach: Improved Synthesis of a Strong Agonist of Platelet Activating Factor

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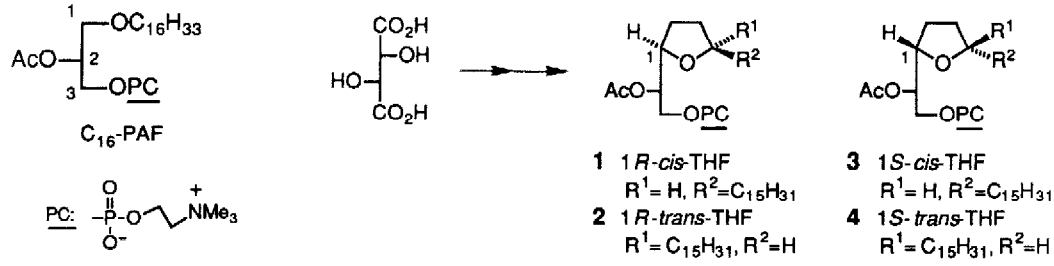
Key Words: pig liver esterase; enantioselective hydrolysis; tetrahydrofuran; chiral synthon; platelet activating factor

Abstract: *Bicyclic meso diester 7 was found to undergo enantioselective hydrolysis with PLE (pig liver esterase) generating the chiral monoester 8 in excellent yield with high enantiomeric excess. The chiral monoester 8 was successfully utilized in the improved synthesis of 1R-cis-THF derivative (1), a strong agonist of PAF which we previously developed.*

During the course of our continuing interests in the molecular design based on the structure of platelet activating factor (PAF),[1] we synthesized tetrahydrofuran derivatives **1**~**4** in which the PAF structure is partially fixed as a part of the tetrahydrofuran skeleton.[2] (Scheme 1) Among the four stereoisomers prepared, 1*R-cis*-THF derivative (**1**) was found to have strong agonistic activity almost equivalent to that of natural C_{18}-PAF. Then it became necessary to develop a practical route to **1** for further investigation on biological tests.

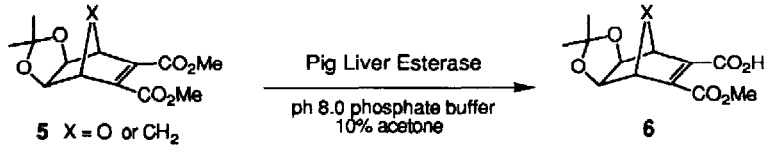
Scheme 1



The synthetic approach taken in the previous study was devised to synthesize all stereoisomers in a stereochemically unambiguous manner, and L-tartaric acid was employed as a starting material. We report here the improved synthesis of **1** by enzymatic approach using pig liver esterase (PLE).

In relation to the enzymatic approach to nucleoside antibiotics, we previously demonstrated the PLE-mediated hydrolysis of tricyclic meso diester **5** furnishing the corresponding chiral monoester **6** with 80~85% enantiomeric excess.[3] Therefore, we were particularly interested in the hydrolysis of the meso diester **7** with PLE, since ozonolysis of the carbon-carbon double bond of the 7-oxabicyclo[2.2.1]heptene skeleton would provide a new entry to chiral 2,5-*syn*-disubstituted tetrahydrofurans.

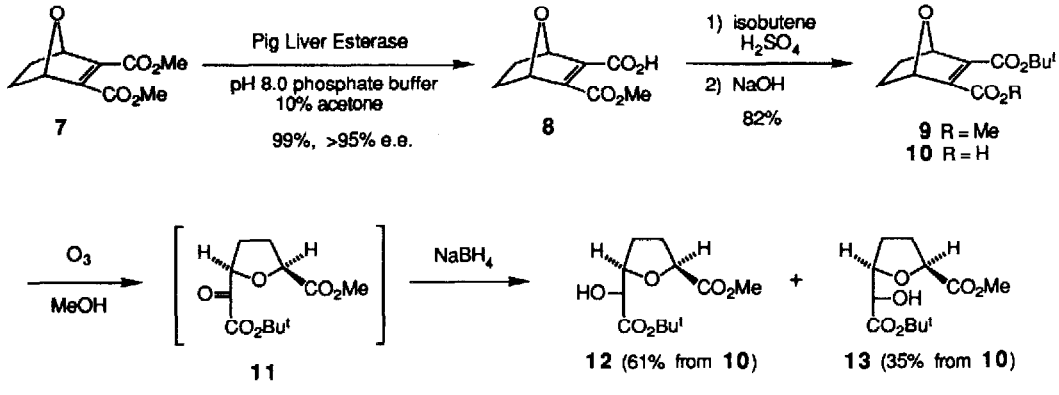
Scheme 2



5 X = O or CH_2 **6**

Bicyclic meso diester **7** was prepared by the selective hydrogenation (5% Pd-C, H_2, 96%) of the Diels-Alder adduct[4] of furan and dimethyl acetylenedicarboxylate. When the diester **7** (0.344g, 1.6 mmole) was treated with PLE[5] (100μl, *ca* 180 units/mmole **7**) in pH 8.0 phosphate buffer (27m*l*) and acetone (3m*l*) at room temperature for 18hr, the monoester **8** was obtained in 99% yield (0.317g).[6] The crude monoester **8** was converted to the mixed diester **9** (isobutene, cat. H_2SO_4 / CH_2Cl_2, 82%), and the enantiomeric excess of **9** (*viz.* that of **8**) was determined to be higher than 95% by ^{1}H-NMR experiments using Eu(hfc)$_3$ as a chiral shift reagent. The absolute configuration of **8** was tentatively assigned as shown by analogy with those of other bicyclo[2.2.1]hept-2-ene derivatives,[3] and was unambiguously confirmed by correlating to the known intermediate **16**.[2] Excellent enantiomeric excess is noteworthy because the enantiomeric excesses range between 80 and 85% in the case of other bicyclic derivatives. Enantiomerically pure monoester **8**[7] could easily be obtained by recrystallization from ethyl acetate-hexane, and the following experiments were carried out using pure **8**.

Scheme 3



7 **8** **9** R = Me **10** R = H

11 **12** (61% from **10**) **13** (35% from **10**)

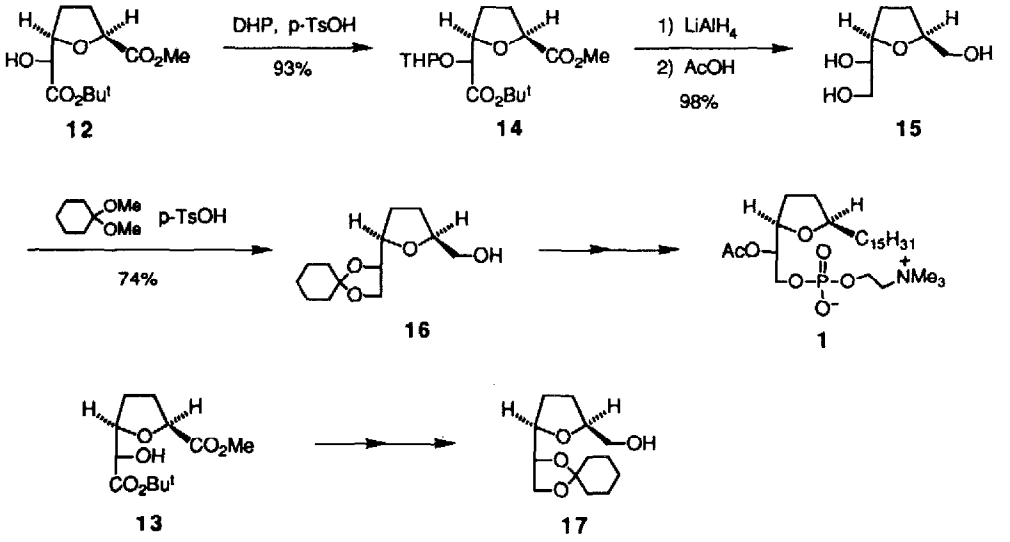
Selective hydrolysis (0.25*M* NaOH-acetone, 0°C, 0.5hr) of the mixed dicarboxylate **9** gave the *t*-butyl monoester **10**[8] in quantitative yield. Ozonolysis of the resulting monoester **10** proceeded smoothly in methanol at -78°C accompanying decarboxylation to form α-ketoester **11**, which without isolation was directly treated with

sodium borohydride to obtain hydroxy diesters **12** and **13** in 61% and 35% yields, respectively.[9] ((i) O_3 / MeOH, -78°C, (ii) $NaBH_4$ / MeOH, -78°C → 0°C) (Scheme 3)

The stereochemistry of **12** and **13** was determined later by correlation to the known **16** and **17**, respectively.[2] Scheme 4 shows the transformation of the polar isomer **12** to **16**, the key intermediate of **1**. Thus, the protection of the hydroxyl group with tetrahydropyranyl ether (dihydropyran, cat. p-TsOH / CH_2Cl_2, r.t. 1.5hr, 93%). Reduction of the ester group followed by deprotection of the THP ether ((i) $LiAlH_4$ / Et_2O (ii) AcOH / THF-H_2O, 98%) gave the triol **15**. Treatment of **12** with $LiAlH_4$ resulted in the formation of unidentified material as a by-product, and higher overall yields was obtained by stepwise procedure. Vicinal diol was selectively protected as a cyclohexylidene acetal to obtain **16**,[10] which was identical in all respects with the intermediate of **1**.[2] The transformation of **16** to **1** was already established.[2]

In a similar manner, less polar isomer **13** was converted to **17**,[10] and the latter proved to be the enantiomer of the intermediate of 1*S*-*cis*-THF derivative (**3**).[2]

Scheme 4



Although the reduction of α-ketoester **11** with $NaBH_4$ is not stereoselective, the present method is superior to the previous one starting from L-tartaric acid in terms of overall yields (33% from **7** to **16**) and experimental operation. Furthermore, the present enzymatic approach provides a new route to chiral tetrahydrofuran derivatives which are considered potential intermediates for the synthesis of many biologically interesting compounds having tetrahydrofuran skeleton.

Acknowledgement

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References and Notes

1. *Platelet Activating Factor and Related Lipid Mediators*; Snyder, F. Ed.; Plenum Press: New York & London; 1987.
2. Ohno, M.; Kobayashi, S.; Shiraiwa, M.; Yoshiwara, H.; Eguchi, Y. Molecular Design Toward Biologically Significant Compounds based on Platelet Activating Factor: Agonists and Antagonists. In *New Aspects of Organic Chemistry I*; Yoshida, Z.; Shiba, T.; Ohshiro, Y. Eds.; Kodansha Ltd.: Tokyo, 1989; pp. 549-560.
3. (a) Ito, Y.; Shibata, T.; Arita, M.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 6739-6741. (b) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *ibid.* **1983**, *105*, 4049-4055.
4. Diels, O.; Alder, K. *Annalen*, **1931**, *490*, 243-257.
5. Purchased from Sigma Co., Ltd.; E3128.
6. Enzymatic hydrolysis of **7** on a preparative scale: PLE (2m*l*) was added to the diester **7** (55.4g, 0.261 mole) in pH 8.0 phosphate buffer (3*l*) and acetone (300m*l*). The amount of PLE used was about 22 units/mmole **7**. The whole mixture was gently stirred at ambient temperature (20~25°C) for 4 days. The solution was saturated with NaCl and acidified to pH 3.0 with 2*N* HCl. The mixture was extracted with AcOEt (0.5*l* x 3), and the combined AcOEt solution was washed (H_2O, sat. NaCl), dried (Na_2SO_4), and concentrated to give crude monoester **8** (47.1g, 91%) as a white solid. Recrystallization from AcOEt-hexane afforded enantiomerically pure monoester **8**.
7. m.p. 88.0~88.5°C (AcOEt-hexane). *Anal.* Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.43; H, 4.96. $[\alpha]_D^{20}$ -69.4°(*c* 0.95, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.18~1.45 (m, 2H), 1.88~2.14 (m, 2H), 3.90 (s, 3H), 5.24~5.42 (m, 2H).
8. Colorless powder. *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.32; H, 7.01. $[\alpha]_D^{24}$ +18.0°(*c* 0.95, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.30~1.50 (m, 2H), 1.59 (s, 9H), 1.76~2.16 (m, 2H), 5.24~5.38 (m, 1H), 5.40~5.52 (m, 1H).
9. **12**: R_f 0.44 (hexane:AcOEt=1:1). *Anal.* Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.01; H, 7.78. $[\alpha]_D^{25}$ +4.86°(*c* 1.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.77~1.85 (m, 1H), 1.96~2.07 (m, 1H), 2.15~2.36 (m, 2H), 3.76 (s, 3H), 4.25 (brd, 1H), 4.45 (ddd, *J*=8.8, 6.5, 3.2Hz, 1H), 4.51~4.56 (m, 2H). **13**: R_f 0.46 (hexane:AcOEt=1:1). m.p. 56.0~57.0°C (Et_2O-hexane). *Anal.* Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.56; H, 7.95. $[\alpha]_D^{25}$ -4.40°(*c* 1.33, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.97~2.5 (m, 4H), 3.76 (s, 3H), 3.99 (dd, *J*=10.9, 1.5Hz, 1H), 4.32 (d, *J*=11.2Hz, 1H), 4.48~4.54 (m, 2H).
10. **16**: $[\alpha]_D^{23}$ +21.3°(*c* 1.05, $CHCl_3$). HRMS Calcd for $C_{13}H_{22}O_4$ 242.1519, Found 242.1522. ^{1}H-NMR ($CDCl_3$) δ 1.39 (m, 2H), 1.52~1.67 (m, 8H), 1.86~2.02 (m, 4H), 2.43 (dd, *J*=7.7, 4.3Hz, 1H), 3.47 (ddd, *J*=11.7, 8.0, 4.4Hz, 1H), 3.73 (dd, *J*=8.4, 6.2Hz, 1H), 3.79 (td, *J*=7.0, 5.5Hz, 1H), 4.07 (dd, *J*=8.4, 7.0Hz, 1H), 4.10 (m, 1H), 4.18 (dd, *J*=11.7, 6.2Hz, 1H). **17**: $[\alpha]_D^{22}$ +5.28°(*c* 1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.35 (m, 2H), 1.80~2.01 (m, 4H), 1.50~1.71 (m, 8H), 2.51 (dd, *J*=7.7, 4.5Hz, 1H), 3.49 (ddd, *J*=11.7, 8.1, 7.7Hz, 1H), 4.01 (dd, *J*=8.1, 6.6Hz, 1H), 4.11 (ddd, *J*=7.7, 6.6, 4.8Hz, 1H), 4.13 (m, 1H). *ent*-**17**[2] prepared from L-tartaric acid; $[\alpha]_D^{24}$ -4.60°(*c* 1.13, $CHCl_3$).

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