Pergamon

Tetrahedron Letters 39 (1998) 7741–7744

TETRAHEDRON LETTERS

Asymmetric Synthesis of Chiral 2-Fluorinated 1,3-Propanediols and Its Application to the Preparation of Monofluorinated Chiral Synthon[1)]

Hajime Yokoyama†, Ryo Hyodo†, Akiko Nakada†, Seiji Yamaguchi†, Yoshiro Hirai†*, Tadashi Kometani‡, Michimasa Goto‡, Norio Shibata§ and Yoshio Takeuchi§*

†Department of Chemistry, Toyama University, Gofuku 3190, Toyama 930-8555, Japan

‡Toyama National College of Technology, Hongo 13, Toyama 930-8630, Japan

§Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

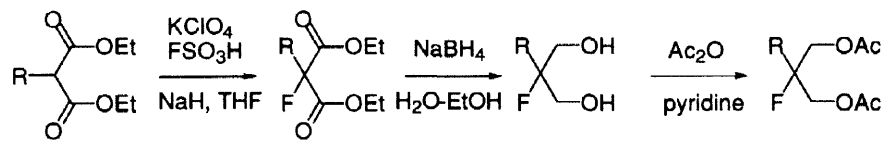
Received 17 July 1998; revised 6 August 1998; accepted 7 August 1998

Abstract: Asymmetric synthesis of optically active 2-fluorinated 1,3-propanediols was achieved by enzymatical resolution and applied to obtain a chiral monofluorinated synthon for lignan derivatives.

Since significant physical and biological properties are shown by compounds possessing a fluorine atom, the synthesis of fluorinated derivatives of biologically active natural products is of interest[2)]. Synthetic studies have been directed toward syntheses by chiral building blocks[3)] as the current topics for research. Especially chiral 1,3-propanediol[4,10)] are useful synthon for the synthesis of interested compounds. We are currently interested in the construction of chiral 2-fluorinated propanediols, as building blocks for the synthesis of antitumor lignan derivatives[5)]. We report here an asymmetric construction of chiral 2-fluorinated propanediols via enzymatic resolution of a σ-symmetrical diol system and its application to the synthesis of an optically active fluorinated lactone as a synthon.

The diesters **1a-c**, which were easily prepared from the corresponding malonate esters, were fluorinated using $FClO_3$ to give the corresponding fluorinated diesters **2a-c** in 81-82% yields[6)]. The fluorinated diesters **2a-c** were converted to the diols **3a-c** by reduction ($NaBH_4$, H_2O-EtOH, rt) and then acetylation with acetic anhydride afforded the diacetates **4a-c** (Scheme 1).

Scheme 1



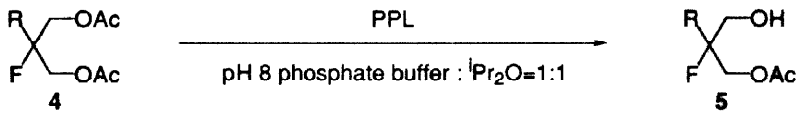
1a : R = ^{i}Pr	**2a** : 82%	**3a** : 81%	**4a** : 45%
1b : R = cyclohexyl	**2b** : 81%	**3b** : 74%	**4b** : 92%
1c : R = Bn	**2c** : 82%	**3c** : 96%	**4c** : 68%

Next we examined the dissymmetrization of the glycol system, by enantioselective enzymatic hydrolysis of the diacetates **4** and by lipase-catalyzed transesterification of the diols **3** based on our previous work[7)]. PPL-catalyzed hydrolysis of the 2-fluorinated diacetates **4** proceeded smoothly in a mixed solution[8)] (pH 8 phosphate buffer : diisopropylether = 1 : 1) to afford the optically active monoalcohols **5**. It is noteworthy that all the 2-

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01687-6

fluorinated diacetates **4** gave the corresponding monoalcohols **5** in 76-96%ee. The results are summarized in Table 1.

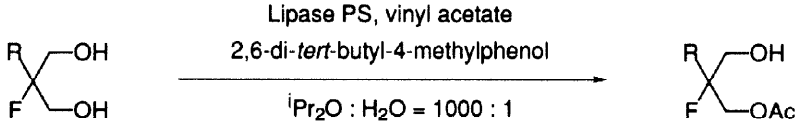
Table 1 Enantioselective Hydrolysis of the Diacetates 4



Substrate		Reaction Time	Product	Yield (%)	Optical Purity (%ee)	$[\alpha]_D$ (*c* in $CHCl_3$)
4a	R = ^{i}Pr	5.5 h	**5a**	55	76	+10.1° (c 0.82)
4b	R = cyclohexyl	1.5 h	**5b**	57	96	+ 9.8° (c 0.50)
4c	R = Bn	1 h	**5c**	65	80	- 7.1° (c 1.04)

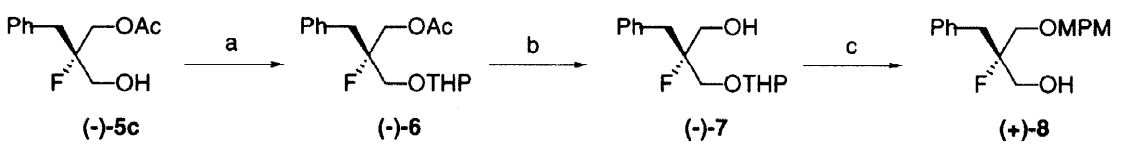
Next enzymatic acetylation of the diols **3** was carried out using Lipase PS. These results are summarized in Table 2. The enzymatic acetylation afforded the monoalcohols **5** with high enantioselectivity except in the acetylation of **3a**.

Table 2 Lipase-catalyzed Transesterification of the Diols 3



Substrate		Reaction Time	Product	Yield (%)	Optical Purity (%ee)	$[\alpha]_D$ (*c* in $CHCl_3$)
3a	R = ^{i}Pr	3.5 h	**5a**	34	6	+0.4° (c 0.90)
3b	R = cyclohexyl	4 h	**5b**	67	91	-8.0° (c 1.20)
3c	R = Bn	1 h	**5c**	91	95	-8.8° (c 0.98)

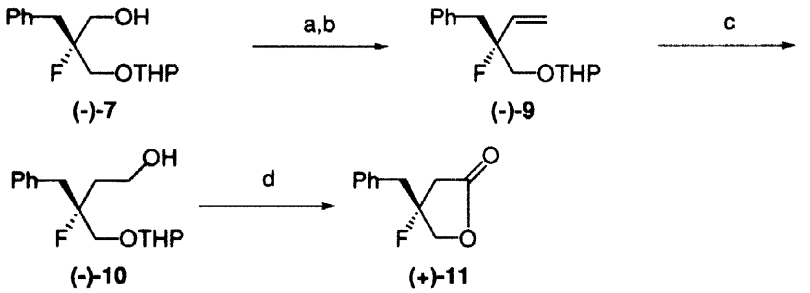
The absolute configuration of the (-)-monoalcohol **5c** was determined by correlation with a known compound as follows[9,10] (Scheme 2). The (-)-monoalcohol **5c** (95%ee) was converted into the monoalcohol **8** in 3 steps. A comparison of the specific rotation of **8** thus obtained with the reported value of the (*R*)-isomer indicated that our synthetic product **8** has (*S*)-configuration.



Scheme 2 a) DHP, *p*-TsOH, CH_2Cl_2, 99%, b) K_2CO_3, MeOH, 91%, c) MPMCl, NaH, $^{n}Bu_4NI$, THF, 74 %.

In order to demonstrate the usefulness of the optically active 2-fluorinated propanediols **5** as chiral building blocks for the synthesis of biologically active chiral compounds, the mono alcohol **7** was converted to the optically pure lactone **11**. Swern oxidation of the monoalcohol **7** followed by Wittig reaction provided the alkene **9** in 2 steps in 78% yield. Hydroboration-oxidation reaction of the alkene **9** using diborane and

subsequent oxidation of the resulting alcohol **10** with PCC afforded the desired lactone **11**[11] , which is an important synthon for the lignan synthesis (Scheme 3).



Scheme 3 a) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, b) $MeP^+Ph_3I^-$, KHMDS, THF, 2 steps 78%, c) BH_3·THF and then H_2O_2, NaOH, 55%, d) PCC, CH_2Cl_2, 51% .

Thus we have developed an efficient synthesis of chiral 2-fluorinated 1,3-propanediols and its application to synthon for the synthesis of lignans. Further studies on total synthesis of various lignan derivatives with the use of these synthons are under way.

Acknowledgment. This work was financially supported by Grant-in Aid for Scientific Research (No. 090 442 77) from the Ministry of Education, Science, Sports, and Culture of Japan.

References and Notes

1) Yokoyama, H.; Hyodo, R.; Nakada, A.; Yamaguchi, S.; Hirai, Y.; Kometani, T.; Goto, M.; Takeuchi, Y. 74th National Meeting of the Japan Chemical Society, Kyoto, 1998, March 29, 3D539.

2) (a) Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley and Sons: New York, 1991. (b) Feller, R.; Kobayashi, Y. Eds. *Biomedical Aspects of Fluorine Chemistry*; Kodansha and Elsevier Ltd.: Tokyo, 1982. (c) Welch, J. T. *Tetrahedron*, **1987**, *43*, 3123.

3) Reviews (a) Iseki, K. Kobayashi, Y. *Yuki Gousei Kagaku Kyoukaishi* **1994**, *52*, 54. (b) Yamazaki, T.; Kitazume, T. *Yuki Gousei Kagaku Kyoukaishi* **1991**, *49*, 721.

4) (a) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525-535. (b) Ihara, M.; Kai, T.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2357-2358. (c) Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413-5415. (d) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 897-903. (e) Ihara, M.; Takahashi, M.; Taniguchi, N.; Fukumoto, K; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 619-620.

5) Recently reports: (a) Ward, R. S. *Tetrahedron*, **1990**, *46*, 5029. (b) Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717-5723.

6) The improved fluorination with $FClO_3$ was reported by Y. Takeuchi ; Takeuchi, Y.; Satoh, A.; Suzuki, T.; Kameda, A.; Dohrin, M.; Satoh, T.; Koizumi, T.; Kirk, K. L. *Chem. Pharm. Bull.* **1997**, *45*, 1085 and references cited therein.

7) Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21.

8) Typical procedure for asymmetric hydrolysis of the diacetates **4** is as follows.

To a mixture of the diacetate **4c** (38 mg, 0.142 mmol) in isopropyl ether (8.9 mL) and phosphate buffer solution (pH 8, 8.9 mL) was added PPL (19 mg) at 30°C. After having been stirred for 1 hr, the reaction mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was diluted with ethyl acetate. The filtrate was washed with brine. The organic layer was dried and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane : ethyl acetate = 75 : 15) to afford a monoalcohol **5c** (21 mg, 65 %) as a colorless oil; IR (neat) 3456, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$);δ= 2.13 (3H, s), 2.29 (1H, brs), 3.05 (2H, d, *J* =21.5 Hz), 3.61 (2H, d, *J* =15.9 Hz), 4.12 (1H, dd, *J* =15.9, 12.2 Hz), 4.24 (1H, dd, *J* =19.0, 12.2 Hz), 7.15-7.34 (5H, m). The optical purity of **5c** was determined by HPLC analysis (Chiralcel OJ-R, pH 2 phosphate buffer / CH_3CN).

Monoalcohols **5a** and **5b** were prepared similarly.

5a: IR (neat) 3444 , 1747cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$);δ= 1.01 (6H, d, *J* =7.1 Hz), 1.68 (1H, brs), 2.12 (3H, s), 2.08-2.28 (1H, m), 3.74 (1H, dd, *J* =23.4, 12.7 Hz), 3.78 (1H, dd, *J* =19.8, 12.7 Hz), 4.30 (1H, dd, *J* =13.7, 12.4 Hz), 4.35 (1H, dd, *J* =16.3, 12.4 Hz).

The optical purity of **5a** was determined by HPLC analysis (Chiralcel OJ, 2-propanol / hexane) after tosylation of the hydroxyl group and hydrolysis of the acyl group.

5b: IR (neat); 3466, 1748cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$);δ= 1.08-1.35 (5H, m), 1.67-1.95 (6H, m), 2.12 (3H, s), 3.73 (1H, dd, *J* =16.6, 12.4 Hz), 3.77 (1H, dd, *J* =14.6, 12.4 Hz), 4.29 (1H, dd, *J* =14.9, 12.4 Hz), 4.34 (1H, dd, *J* =17.8, 12.4 Hz). The optical purity was determined by HPLC analysis (Chiralcel OJ, 2-propanol / hexane) after tosylation of the hydroxyl group and hydrolysis of the acyl group.

9) (*S*)- (+)- **8**: $[\alpha]_D$ + 6.6° (c 1.33, in $CHCl_3$), (lit.[10] - 5.3° (*R*))

10) (a) Ihara, M.; Kawabuchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron: Asymmetry*, **1994**, *5*, 1041. (b) Ihara, M.; Taniguchi, N.; Kai, T.; Satoh, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 221-227. (c) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J. T. *J. Org. Chem.* **1986**, *51*, 1003-1006.

11) (*R*)-(+)-**11**: $[\alpha]^{29}_D$ +29.9° (c 0.55 in $CHCl_3$); IR (neat) 1791cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$);δ= 2.63-2.80 (2H, m), 3.12 (1H, dd, *J* =23.0 , 14.4 Hz), 3.18 (1H, dd, *J* =21.7, 14.4 Hz), 4.30 (1H, dd, *J* =40.5, 11.0 Hz), 4.36 (1H, dd, *J* =29.3, 11.0 Hz), 7.22-7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 39.11 and 39.38 (d, *J* =26.5 Hz), 41.16 and 41.40 (d, *J* =24.0 Hz), 75.39 and 75.67 (d, *J* =27.3 Hz), 98.13 and 99.94 (d, *J* =182.0 Hz), 127.71, 128.85, 129.82, 133.83 and 133.86 (d, *J* =2.48 Hz), 173.61; ^{19}F NMR (376 MHz, $CDCl_3$+ C_6F_6) - 146.20 (m).