Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2403–2407

TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic synthesis of anti-inflammatory drugs in enantiomerically pure form

Amit Basak,* Ahindra Nag, Gautam Bhattacharya, Subrata Mandal and Sikha Nag

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

Received 20 April 2000; accepted 10 May 2000

Abstract

A novel chemoenzymatic route to chiral anti-inflammatory drugs in enantiomerically pure form is described.

1. Introduction

The synthesis of drugs exhibiting chirality in one enantiomeric form is an area of high priority in pharmaceutical research.[1] There are several reasons for this new trend: in many cases[2] one enantiomer of a chiral drug has a therapeutically useful action while the other does not, one enantiomer is toxic and the other is safe or one enantiomer is an agonist and the other is an antagonist. In addition, the new regulation[3] regarding the introduction of drugs in one chiral form (racemates are allowed but in that case pharmacological and toxicological effects of individual enantiomers need to be evaluated) has forced industries to look for other ways to prepare homochiral drugs.

One of our prime objectives was to develop protocols for the preparation of drugs in one enantiomerically pure form. We have chosen the nonsteroidal anti-inflammatory agents, mainly the 2-aryl propionic acid derivatives for which the (*S*)-enantiomer is the pharmacologically more active isomer.[4] For Naproxen, the (*S*)-isomer is 28 times more active in vivo than its (*R*)-counterpart.

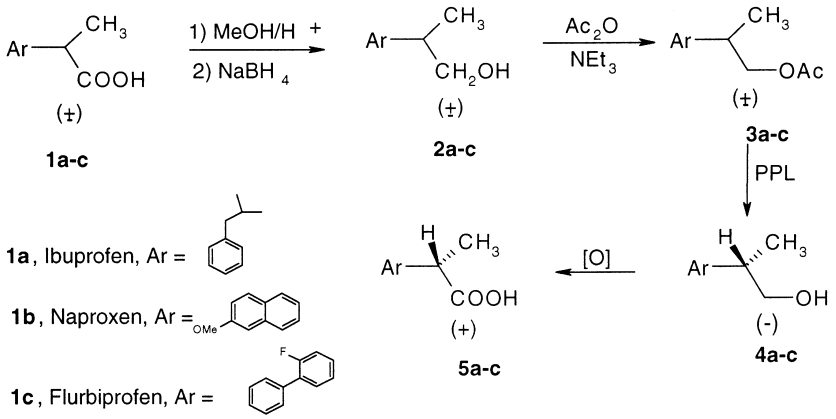
2. Discussion

Our initial approach to access these drugs was the enzyme-catalyzed hydrolysis of the corresponding racemic esters using the well known hydrolytic enzymes porcine pancreatic lipase (PPL) and porcine liver esterase (PLE). However, the results were disappointingly similar to those reported earlier.[5] The enantiomeric excess of the hydrolyzed product in the case of Ibuprofen was ~30%. This prompted us to replace the carbomethoxy group with the carbinol acetate and then

* Corresponding author.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00184-1

study the hydrolysis using PLE and PPL. We were pleased to discover that PPL performed favourably in the hydrolytic reaction of (±)-acetates **3a**,**b**, derived from (±)-Ibuprofen and (±)-Naproxen, giving the corresponding (*S*)-alcohols in high enantiomeric excess (Scheme 1). We have extended the hydrolysis to the carbinol acetate **3c** derived from (±)-Flurbiprofen for which the gastrointestinal toxicity is greatly enhanced by the presence of the (*R*)-isomer.[6] In all cases, the ee's were very high (as judged from the specific rotation) (Table 1). The hydrolytic reactions were carried out up to a conversion of 35–48% (determined by ^{1}H NMR of the crude reaction mixture after work up). The alcohols and the unconverted acetates were separated by column chromatography over silica gel. Previously, Sih and Gu[7] prepared the homochiral acetates by a PPL-mediated transesterification of the corresponding racemic alcohols using vinyl acetate. Our method offers an alternate route to these chiral alcohols by exploiting the enantioselective hydrolytic ability of PPL. The steric course of hydrolysis could be explained on the basis of the Jones model[8] as shown in Fig. 1.



Scheme 1.

Table 1

Substrate	Product	$[\alpha]_{D\,(obs)}$	$[\alpha]_{D\,(lit)}$[10]	Enantiomeric Excess (ee)[a]	percent conversion (c)[b]	Enantiomeric ratio (E)[c]
Acetate (3a)	Alcohol (4a)	-13	-14	89	40	76
Acetate (3b)	Alcohol (4b)	-17	-18	94	48	91.7
Acetate (3c)	Alcohol (4c)	-14.4	----	94	35	54

a enantiomeric excess was determined from the ratio of the observed and literature specific rotations. For the alcohol from flurbiprofen, the ee was calculated from the ratio of specific rotations of the oxidized product, i.e. (*S*)-(+)-Flurbiprofen and the one reported in the literature.
b percent conversion was determined by recording the ^{1}H-NMR of the crude reaction mixture after work up.
c enantiomeric ratio was calculated from the formula $E=\ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$[9]

The absolute configurations of the alcohols were determined by comparison with the literature values for the (*S*)-isomer.[10] For Flurbiprofen, we could not get a literature value of the specific rotation of the corresponding alcohol. However, simply by analogy with the sign of rotation of the alcohols derived from Ibuprofen and Naproxen and also from the rotation of the oxidation product, the absolute configuration was assumed to be *S*.

Figure 1.

2.1. Oxidation of the chiral alcohols to the chiral drugs

The oxidations of the (*S*)-(+)-alcohols were carried out with pyridinium dichromate (PDC)[11] using DMF as solvent. The yield of (*S*)-(+)-acid was ~60%. The specific rotations of (*S*)-(+)-Ibuprofen, (*S*)-(+)-Naproxen and (*S*)-(+)-Flurbiprofen all matched well with the literature values[12] (Table 2). The same oxidation to (*S*)-(+)-Flurbiprofen had been carried out previously by Griesbach et al.[13] using Jones' conditions (CrO_3, H_2SO_4). Although Jones' oxidation might be economically more viable, one advantage of the PDC reaction is that the rest of the material in the oxidation, the aldehyde, can again be reoxidized to the acid, thus improving the yield.

In conclusion, a chemoenzymatic route to the anti-inflammatory drugs in one chiral form has been developed. The method is operationally simple and produces the pharmacologically active form in high enantiomeric purity.

Table 2

Substrate	Product	$[\alpha]_{D\ (obs)}$	$[\alpha]_{D\ (lit)}$[5,12]
S(-) Alcohol (4a)	**S(+) Ibuprofen (5a)**	**+56**	**+59**
S(-)Alcohol (4b)	**S(+) Naproxen (5b)**	**+62**	**+66**
S(-)Alcohol (4c)	**S(+)Flurbiprofen (5c)**	**+39**	**+41.4**

3. Experimental

3.1. General procedure for the synthesis of 2-aryl substituted propanol derivatives

3.1.1. Preparation of alcohols *2a–c*

The methyl ester **1a–c** (5 mmol) was reduced with sodium borohydride (5 mmol) in methanol (25 ml). The mixture was allowed to stir for 4 h after which the reaction volume was reduced to 5 ml. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate and then evaporated. The product was purified by silica gel chromatography using hexane:ethyl acetate = 3:1.

Spectral data. Alcohol **2a**: δ_H 7.10 (4H, m, Ar-H), 3.65 (2H, d, $J = 6.8$ Hz, CH_2OH), 2.90 (1H, m, CH-CH_2OH), 2.45 (2H, m, $J = 7.1$ Hz, Ar-CH_2), 1.89 (1H, m, CH_3CHCH_3), 1.27 (3H, d, $J = 6.7$ Hz, CHCH_3), 0.91 {6H, d, $J = 6.7$ Hz, CH(CH_3)$_2$}. Alcohol **2b**: δ_H 7.69 (2H, dd, $J = 5.3$, 8.4 Hz, Ar-H), 7.60 (1H, s, Ar-H), 7.33 (1H, dd, $J = 1.8$, 8.5 Hz, Ar-H), 7.12 (2H, m, Ar-H), 3.89

(3H, s, OMe), 3.75 (2H, d, $J=6.8$ Hz, CH_2OH), 3.07 (1H, m, CH-CH_2OH), 1.33 (3H, d, $J=7.0$ Hz, CHCH_3). Alcohol **2c**: δ_H 7.26–7.56 (6H, complex, Ar-H), 7.02–7.13 (2H, m, Ar-H), 3.75 (2H, d, $J=6.8$ Hz, CH_2OH), 2.99 (1H, m, CH-CH_2OH), 1.31 (3H, d, $J=6.9$ Hz, CHCH_3).

3.1.2. Preparation of acetate

The alcohol **2a–c** (2 mmol) was then acetylated with acetic anhydride, triethylamine (2.2 mmol) and a catalytic amount of DMAP (5 mg) using dichloromethane as solvent. The mixture was allowed to stir for 1 h at room temperature, and then washed with water and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and then evaporated to leave a white solid from which the product was isolated by silica gel chromatography using hexane:ethyl acetate = 7:1.

Spectral data. Acetate **3a**: δ_H 7.23–7.20 (4H, m, Ar-H), 4.34, 4.27 (2H, ABX, $J_{AB}=10.8$ Hz, $J_{AX}=6.8$ Hz, $J_{BX}=5.4$ Hz, CH_2OAc), 3.21 (1H, m, CHCH$_3$), 2.61 (2H, d, $J=7.0$ Hz, CH_2CH), 2.18 (3H, s, COCH_3), 2.01 {1H, m, CH(CH$_3$)$_2$}, 1.46 (3H, d, $J=7.0$ Hz, CH_3CH), 1.06 {6H, d, $J=7.0$ Hz, (CH_3)$_2$CH}. Acetate **3b**: δ_H 7.62 (2H, d, $J=8.5$ Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.31 (1H, dd, $J=1.7$, 8.5 Hz, Ar-H), 7.12 (2H, m, Ar-H), 4.25, 4.17 (2H, AB of ABX, $J_{AX}=7.0$ Hz, $J_{BX}=7.3$ Hz, $J_{AX}=10.8$ Hz, CH_2OH), 3.90 (3H, s, OCH_3), 3.21 (1H, m, CHCH$_3$), 2.05 (3H, s, OCOCH_3), 1.33 (3H, d, $J=7.1$ Hz, CHCH_3). Acetate **3c**: δ_H 7.35–7.57 (6H, complex, Ar-H), 7.00–7.11 (2H, m, Ar-H), 4.14 (2H, m, CH_2OCOCH$_3$), 3.14 (1H, m, CHCH$_3$), 2.05 (3H, s, OCOCH_3), 1.33 (3H, d, $J=7.1$ Hz, CHCH_3).

*3.1.3. Enzymatic hydrolysis of acetyl derivatives **3a–c***

The acetyl derivative was hydrolyzed with the help of the enzyme pig pancreatic lipase (PPL). The reaction mixture contained the acetyl derivative (2 mmol), phosphate buffer (pH 8.0, 50 ml), acetone (10 ml) and the enzyme (100 mg). The pH was maintained at 8.0 by intermittent addition of 1N NaOH. After 50% conversion (estimated by TLC), the mixture was extracted with ethyl acetate, dried over Na_2SO_4 and solvent was evaporated. The residue, upon chromatography on silica gel, furnished the product which was isolated from hexane:ethyl acetate (1:1).

Specific rotation ($CHCl_3$, *c* 1): alcohol **4a**: $[\alpha]_D=-13$; alcohol **4b**: $[\alpha]_D=-17$; alcohol **4c**: $[\alpha]_D=-14.4$.

*3.1.4. Oxidation of the alcohols **4a–c** to acids **5a–c***

The alcohol **4a–c** was reacted with 3.5 equivalents of pyridinium dichromate (PDC) in the presence of DMF (10 ml). After 72 h, the mixture was partitioned between ethyl acetate and aqueous $NaHCO_3$. The aqueous layer was adjusted to pH 2 and then re-extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and evaporated to leave the acid as a white solid (yield ~50%) having identical ^{1}H NMR with the authentic racemic sample.

Specific rotation ($CHCl_3$, *c* 1): (*S*)-(+)-Ibuprofen: $[\alpha]_D=+56$, lit.[12] $[\alpha]_D=+59$; (*S*)-(+)-Naproxen: $[\alpha]_D=+62$, lit.[12] $[\alpha]_D=+66$; (*S*)-(+)-Flurbiprofen: $[\alpha]_D=+39$, lit.[5] $[\alpha]_D=+41.4$.

Acknowledgements

We are grateful to the Department of Biotechnology, Government of India, for funding the research.

References

1. (a) Patel, R. N. *J. Am. Oil. Chem. Soc*. **1999**, *76*, 1275; (b) Stinson, S. C. *Chem. Eng. News* Oct 9, 1995, p. 44; (c) Margolin, A. L. *Enzyme Microb. Technol*. **1993**, *15,* 266.
2. (a) Beckett, A. *Biochem. Soc. Trans*. **1991**, *19*, 443; (b) Ariens, E. J. *Med. Res. Rev*. **1986**, *6*, 41.
3. FDA policy statement for the development of new stereoisomeric drugs *Chirality* **1992**, *4*, 338.
4. Brune, K.; Beck, W. S.; Geisslinger, G.; Menzel-Soglowek, S.; Peskar, B. M.; Peskar, B. A. *Experientia* **1991**, *47*, 257.
5. Morrone, R.; Nicolosi, G.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1773.
6. Wechter, W. J.; Bigornia, A. E.; Murray, E. D.; Levine, B. H.; Young, J. W. *Chirality* **1993**, *5*, 492.
7. Sih, C. J.; Gu, R. L. *Tetrahedron: Asymmetry* **1995**, *6*, 37.
8. Hulting, P. G.; Jones, J. B. *Tetrahedron Lett*. **1992**, *33*, 1999.
9. Chen, C.-S.; Fuzimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294.
10. (a) Chiarino, D.; Ferrario, F.; Pellacini, F.; Sale, A. *J. Heterocycl. Chem*. **1989**, *26*, 589; (b) Harrison, I.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem*. **1970**, *13*, 203.
11. Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, 399.
12. *Dictionary of Organic Compounds*, Fifth Ed., Vol. 3 and 4; Buckingham, J.; Donaghy, S. M., Eds.
13. Griesbach, R. C.; Hamon, D. P. G.; Kennedy, R. J. *Tetrahedron: Asymmetry* **1997**, *8*, 507.