Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 12–14

Lipase-catalysed resolution by an esterification reaction in organic solvent of axially chiral (±)-3,3′-bis(hydroxymethyl)-2,2′-bipyridine *N*,*N*-dioxide

Claudia Sanfilippo,* Nicola D'Antona and Giovanni Nicolosi

Istituto di Chimica Biomolecolare del CNR, Via del Santuario 110, I-95028 Valverde CT, Italy

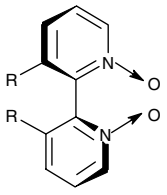
Received 4 November 2005; accepted 29 November 2005
Available online 9 January 2006

Abstract—The enzymatic kinetic resolution of atropisomeric (±)-3,3′-bis(hydroxymethyl)-2,2′-bipyridine *N*,*N*-dioxide (±)-**3** was investigated via enantioselective esterification in the unusual medium of alcohol/vinyl acetate (20:80). Lipase from *Mucor miehei* (immobilised lipase preparation, Lipozyme®) was found to give good enantioselectivity with an (a*S*)-enantiopreference in the axial recognition, and allowed to efficiently perform the preparation of both enantioforms with ee >98%. Lipase from *Pseudomonas cepacia* (immobilised lipase preparation, PS-D) also catalysed the reaction although with low enantioselectivity and showing opposite stereopreference.

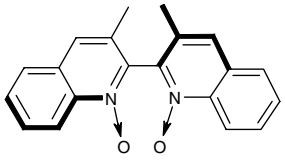
1. Introduction

Chiral 2,2′-bipyridine-type ligands (bipys) have recently received considerable attention in the field of stereoselective organic synthesis and transition metal catalysis.[1] Among them, a promising class of bipyridine-type ligands can be envisaged in the 2,2′-bipyridine *N*,*N*-dioxides, possessing high coordinating power due to its Lewis-base nature.[2] Moreover the presence of *N*-oxide groups in derivatives of structure **1** imposes a rotation restriction around the 2,2′-bipyridine bond making these bipys atropisomeric. Due to this structural characteristic, C_2-symmetric axially chiral 2,2′-bipyridine *N*,*N*-dioxides, such as biquinoline **2** or bipyridines **3** and **3a**, find valuable applications as catalysts in organocatalysis, for example: the asymmetric allylation of aldehydes with allyl(trichloro)silane,[3] enantioselective ring opening of *meso*-epoxides with tetrachlorosilane[4] and the addition of silyl enolates to ketones.[5]

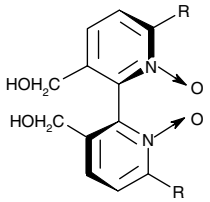
Chiral 2,2′-bipyridine *N*,*N*-dioxide derivatives with axial chirality only are difficult to prepare in non-racemic form and only a few examples have been reported to date. Enantiomers of 2,2′-bipyridine-3,3′-dicarboxylic acid *N*,*N*-dioxides have been obtained by crystallisation of the corresponding brucine salts.[6] Recently, others have been prepared by an elegant approach developed by Hayashi,[3b] based on the formation of a cyclic diester



1



2



3, R=H
3a, R=Ph

* Corresponding author. Tel.: +39 0957212136; fax: +39 0957212141; e-mail: claudia.sanfilippo@icb.cnr.it

0957-4166/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2005.11.028

by reaction of an enantiopure chiral binaphthyl acid with a conformationally free 3,3′-disubstituted-2,2′-bipyridine, and successively restricting the axial rotation of the pyridine rings by sp^2-nitrogen oxidation. Biocatalytic procedures aimed at the resolution of bipy scaffolds have not been reported to date although this approach has proven successful in the enantiomeric resolution of axially chiral biaryls.[7] Prompted by our experience in the resolution of atropisomeric biphenyls by lipase catalysis in an organic medium,[8] we have considered obtaining enantiopure 2,2′-bipyridine *N*,*N*-dioxides using the same procedure. As a first case we have considered 3,3′-dihydroxymethyl-2,2′-bipyridine *N*,*N*-dioxide, (±)-**3**, with a basic structure that, due to easy metallation *ortho* to the *N*-oxide, can act as a useful starting material for the preparation of chiral 6- and 6,6′-substituted derivatives.[9]

2. Results and discussion

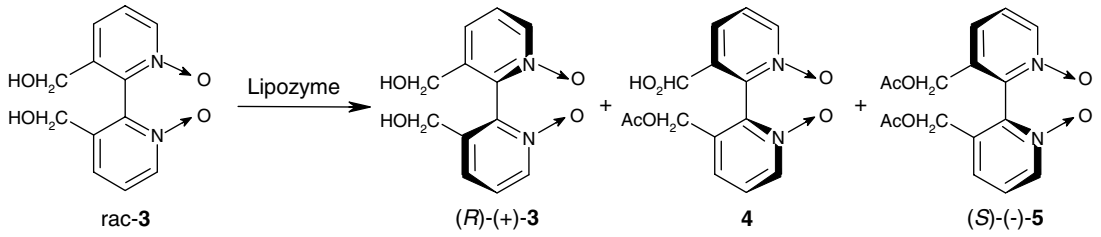
Compound (±)-**3** was obtained in three steps starting from commercially available (±)-2,2′-bipyridine-3,3′-dicarboxylic acid including esterification of the carboxylic groups, successive reduction of the methyl ester derivative and final nitrogen oxidation using *m*-chloroperbenzoic acid (*m*-CPBA) as oxygen donor.[3b,10]

In our previous work, we had observed that the lipases from *Mucor miehei* (immobilised lipase preparation, Lipozyme®) and from *Pseudomonas cepacia* (immobilised lipase preparation, PS-D) in the presence of vinyl acetate as an acyl donor in *tert*-butyl methyl ether (*t*-BME), behaved as suitable catalysts for the enantioselective esterification of axial chiral biphenyls. A direct use of this procedure was not feasible in the resolution of (±)-**3**, due to its insolubility in the above solvent, as such as in all the organic media commonly used for the lipase catalysis.[11] The presence of the N=O functions, in the framework of **3**, requires the use of a protic organic solvent, hence we resorted to utilising methanol as *medium*, though it is a substrate for the lipase. To this end, bipy *N*,*N*-dioxide (±)-**3** was easily dissolved in methanol, then vinyl acetate was added until a final methanol/vinyl acetate ratio of 13:87 was reached, followed by the addition of Lipozyme® to start the reaction.

Under these conditions, with a reaction time of 3 h, fast esterification of methanol was associated with a 20% conversion of (±)-**3**, and two products, mono- and diacetylated bipyridine **4** and **5**, respectively (Scheme 1), were detected in the solution. While methanol allowed us to perform the esterification of (±)-**3** with vinyl acetate, its effect on the lipase is deleterious, as reported,[12] and a decline in the activity degree for the enzyme was evidenced. Consequently, we chose the more compatible 2-propanol to continue our studies, with the benefit of a more efficient process in terms of both reaction rate and better stability of the lipase (Table 1, entry 2). As an alternative, in order to operate in the absence of the parallel esterification of the solvent component, the dissolution of dioxide (±)-**3** was attempted by exploiting the property of pyridine *N*-oxide to form molecular associations with acids via OH···O and CH···O hydrogen bonds.[13] *N*,*N*-Dioxide (±)-**3** treated with acetic acid, proved soluble in vinyl acetate and Lipozyme® was added to the solution. Under these conditions, the esterification of (±)-**3** occurred quickly but with a lower enantioselectivity (Table 1, entry 3).

In order to find a further active lipase the esterification of (±)-**3** in 2-propanol/vinyl acetate mixture was repeated using PS-D lipase as catalyst. The chromatographic profile of the reaction revealed monoester **4** as the main product (51%) associated with diol (−)-**3** (ee 21%) and diester (+)-**5** (ee 30%) both having low enantiomeric excess. The result indicated that PS-D had a lower efficiency, but an opposite enantiopreference in the axial recognition of **3** was observed with respect to Lipozyme®.

Taking into the account the above preliminary experiments, a preparative enantiomeric resolution of (±)-**3** was performed in 2-propanol/vinyl acetate.[14] After



Scheme 1. Lipozyme®-catalysed esterification of (±)-**3** in protic solvent/vinyl acetate mixture.

Table 1. Lipozyme-catalysed esterification of (±)-**3** in different protic solvent/vinyl acetate mixtures

Entry	Solvents, protic agent/vinyl acetate	Time (h)	% Conv.[b]	% **3** (ee%)[b]	% **4**[b]	% **5** (ee%)[b]	Stereo preference
1	Methanol, 13:87	30	61	39 (64)	48	13 (90)	*S*
2	2-Propanol, 16:84	24	80	20 (>99)	30	50 (92)	*S*
3	Acetic acid, 2:98	24	85	15 (>99)	56	29 (73)	*S*

[a] Enzymatic reaction conditions: 0.04 mmol (10 mg), 50 mg lipase, solution 3 ml, 45 °C, 300 rpm.
[b] Substrate conversion and enantiomeric excesses were determined by chiral HPLC, see Ref. 14.

30 h, HPLC analysis of the reaction mixture displayed the presence of 23% of (+)-**3** (ee 97%), 40% of **4** and 37% of (−)-**5** (ee 88%). Diol (+)-**3** isolated by silica gel chromatography after crystallisation from methanol was obtained with an ee >99%. The comparison of the specific rotation with the literature data,[3b] revealed an (a*R*)-configuration of (+)-**3**, also indicating an (a*S*)-enantiopreference of the enzyme in the recognition of the chiral axis. The enantiomeric excess of diester (−)-**5** was increased to ee 97% by crystallisation from methanol/*t*-BME mixture. The easy hydrolysis of the ester in aqueous NH_4OH allowed us to obtain (−)-**3** from diester (−)-**5** and an almost-racemic **3** from monoester **4**, the latter can be recycled thus improving the chemical yield of the process.

3. Conclusion

In conclusion we have achieved the first example of a biocatalytic resolution of a bipyridine *N*,*N*′-dioxide, considering diol (±)-**3**, as a synthon for more structurally complex bipy-type derivatives. The use of the unusual medium alcohol/vinyl acetate, required by the nature of the substrate, proves to be tolerated by lipase from *P. cepacia* (PS-D) and from *M. miehei* (Lipozyme®). This latter in particular allowed us to conveniently perform the preparative enantiomeric separation of (±)-**3**. The biocatalytic procedure developed for **3** represents an opportunity in the resolution of bipy *N*,*N*′-dioxides and further investigations will be made using other derivatives bearing an additive central/axial and planar/axial chirality.

References

1. For recent reviews, see: (a) Malkov, A. V.; Kočovskŷ, P. *Curr. Org. Chem.* **2003**, *7*, 1737–1757; (b) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129–3170; (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831–1842.
2. For a review on the synthesis and application in asymmetric catalysis of chiral pyridine *N*-oxides, see: Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373–1389.
3. (a) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219–3222; (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329–6337; (c) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799–2801; (d) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.
4. Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827–8829.
5. (a) Nakajima, M.; Yokota, T.; Saito, M.; Hashimoto, S. *Tetrahedron Lett.* **2004**, *45*, 61–64; (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235.
6. Tichý, M.; Závada, J.; Podlaha, J.; Vojtíšek, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1279–1282.
7. (a) Juarez-Hernandez, M.; Johnson, D. V.; Holland, H. L.; McNulty, J.; Capretta, A. *Tetrahedron: Asymmetry* **2003**, *14*, 289–291; (b) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1989**, *53*, 1879–1884.
8. (a) Sanfilippo, C.; Nicolosi, G.; Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3267–3270; (b) Sanfilippo, C.; Nicolosi, G.; Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1079–1084.
9. Abramovitch, R. A.; Saha, M.; Smith, E. M.; Coutts, R. T. *J. Am. Chem. Soc.* **1967**, *89*, 1537.
10. Wiederholt, K.; McLaughlin, L. W. *Nucleic Acids Res.* **1999**, *27*, 2487–2493.
11. Considering the weak solubility of (±)-**3**, an attempt at resolution was tried by resorting to alcoholysis of the corresponding diacetyl derivative (±)-**5** obtained by conventional acetylation with pyridine/acetic anhydride of 3,3′-dihydroxymethyl-2,2′-bipyridine and successive N-oxidation by *m*-CPBA. Both the lipase from *P. cepacia* and *M. miehei* were able to catalyse the alcoholysis with *n*-butanol in *t*-BME, but a poor enantioselectivity was observed and consequently this approach was not considered further.
12. Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707.
13. (a) Bowers, J. R.; Hopkins, G. W.; Yap, G. P. A.; Wheeler, K. A. *Cryst. Growth Des.* **2005**, *5*, 727–736; (b) Baures, P. W.; Wiznycia, A.; Beatty, A. M. *Bioorg. Med. Chem.* **2000**, *8*, 1599–1605.
14. Preparative enzymatic reaction involved 200 mg (0.8 mmol) of (±)-**3**, dissolved in 16% 2-propanol/vinyl acetate vol/vol mixture (60 ml) started by adding the Lipozyme® (Fluka) (1 g). The reaction was shaken for 30 h (45 °C and 300 rpm) and then the mixture purified on silica gel chromatography eluting with $CH_3OH/CHCl_3$ from 10% to 40% vol/vol.
Compound (+)-**3**: (18% yield), ee >99%, after crystallisation from methanol, $[\alpha]_D = +181.9$ (*c* 0.26, CH_3OH).
Compound **4**: (29% yield); ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.97 (3H, s), 4.28 (1H, d, $J = 13.0$ Hz), 4.33 (1H, d, $J = 13.0$ Hz), 4.75 (1H, d, $J = 13.6$ Hz), 4.95 (1H, d, $J = 13.6$ Hz), 7.42 (2H, m), 7.51 (1H, d, $J = 7.9$ Hz), 7.53 (1H, d, $J = 7.6$ Hz), 8.27 (1H, d, $J = 6.5$ Hz), 8.31 (1H, d, $J = 6.8$ Hz). ^{13}C NMR (100.03 MHz, $CDCl_3$) δ 20.43, 61.71, 61.96, 126.43, 126.72, 126.85, 126.89, 137.65, 138.69, 139.44, 139.49, 141.07, 141.57, 170.13.
Compound (−)-**5**: (33% yield), ee = 97% after crystallisation from methanol/*t*-BME $[\alpha]_D = -203.1$ (*c* 0.25, CH_3OH), mp 147 °C; ^1H NMR (400.13 MHz, $CDCl_3$) δ 2.03 (6H, s), 4.87 (2H, d, $J = 13.8$ Hz), 5.00 (2H, d, $J = 13.8$ Hz), 7.44 (4H, m), 8.33 (2H, d, $J = 6.1$ Hz). ^{13}C NMR (100.03 MHz, $CDCl_3$) δ 20.52, 61.66, 125.26, 126.47, 137.38, 139.13, 139.96, 170.02.
For ee determination, a Daicel Chiralcel OD-H was used (100% 2-propanol, flow rate 0.4 ml/min): t_R (a*S*)-(−)-**3** 11.0 min; t_R (a*R*)-(+)-**3** 12.9 min; t_R (a*S*)-(−)-**5** 24.7 min; t_R (a*R*)-(+)-**5** 28.7. Due to an anomalous chromatographic behaviour, the accurate determination of the ee of monoester **4** was not possible since the more retained enantiomer was eluted as an asymmetric very broad peak.