Tetrahedron: Asymmetry Vol. 1, No. 9, pp. 575-578, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

LIPASE-CATALYSED RESOLUTION OF HYDROXY SULFONES[+]

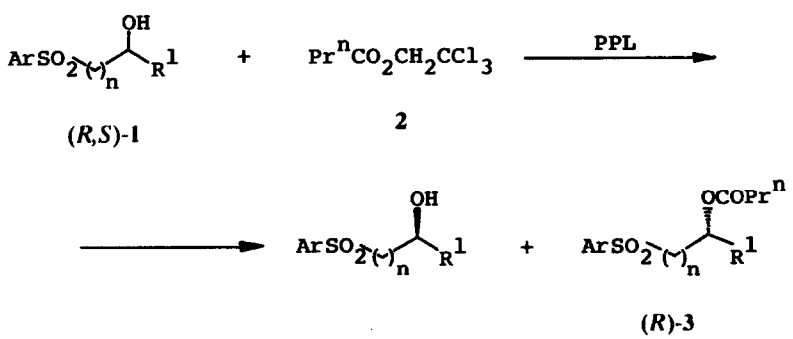
Rafael Chinchilla, Carmen Nájera*, José Pardo, and Miguel Yus

División de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Aptdo. 99, 03690 Alicante, Spain

(*Received* 6 *July* 1990)

Abstract: Porcine pancreatic lipase catalyses the enantioselective transesterification of β-, γ-, and δ-hydroxy sulfones with 2,2,2-trichloroethyl butyrate in ethyl ether.

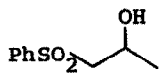
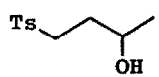
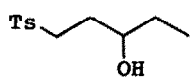
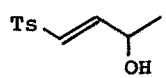
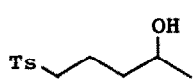
The ability of the sulfone group to stabilyse a carbanionic centre has been widely used in organic synthesis.[1] The functionalysed β-, γ-, and δ-hydroxy sulfones can therefore be used as precursors of d^2, d^3, and d^4 reagents.[2] The corresponding chiral derivatives have been used as building blocks for the synthesys of chiral lactones,[3] tetrahydrofurans,[4] calcidiol lactone,[5] (+)-desespoxiasperdiol,[6] prostaglandines,[7] and precursors of lathrane diterpenes.[8] Chiral β-hydroxy sulfones have been obtained by oxidation of chiral β-hydroxy sulfoxides,[3c] by opening of chiral β,γ-epoxi sulfones,[4] and by baker yeast-mediated reduction of β-keto sulfones.[9] Hovewer, there is a lack of a general simple method for the preparation of *R*- and *S*-hydroxy sulfones. Since Klibanov[10] discovered enzymatic activity in anhydrous organic solvents, specially inexpensive lipases have been widely used for the resolution of alcohols, esters and carboxylic acids.[11] We report here that porcine pancreatic lipase (PPL) catalyses the enantioselective esterification of hydroxy sulfones in organic solvents.



Scheme 1

[+] Dedicated to the memory of Prof. F. Gaviña.

Table. Enantioselective esterification of racemic hydroxy sulfones

No.	Sulfone	Reaction time (d)	T (°C)	(*S*)-1			(*R*)-1[a]		
				Yield (%)[b]	$[\alpha]_D^{25}$[c] deg	ee (%)	Yield (%)[b]	$[\alpha]_D^{25}$[c] deg	ee (%)
1a		12	20	25	+15.1 (c 1.3)	95[d]	20[e]	+ 2.5 (c 3.1)[e]	65[f]
		2	34	40	+ 8.3 (c 2.7)	53[d]	21[e]	+ 1.5 (c 2.1)[e]	37[f]
1b		13	20	43	+12.4 (c 5.0)	62[g]	37	-13.2 (c 2.5)	66[g]
		3	34	49	+ 7.2 (c 5.0)	36[g]	36	-13.6 (c 1.0)	68[g]
1c		7	20	44	+16.4 (c 2.1)	75[h]	39	-13.0 (c 1.6)	81[h]
		4	34	50	+ 4.9 (c 2.2)	12[h]	26	-12.2 (c 1.8)	78[h]
1d		8	20	38	+11.5 (c 3.0)	33[i]	30	+ 7.6 (c 3.0)[j]	53[g]
		2	34	36	+14.2 (c 4.4)	41[i]	28	-14.6 (c 2.0)[k]	73[i]
1e		8	20	46	+ 7.2 (c 1.8)	78[k]	35	- 6.1 (c 1.9)	74[k]
		5	34	48	+ 3.5 (c 2.0)	25[k]	28	- 9.1 (c 1.7)	80[k]

[a] This enantiomer was obtained by alkaline hydrolysis of the corresponding compound **3**. [b] Referred to the racemic compound **1**. [c] In chloroform. [d] Lit.[9] $[\alpha]_D^{25}$ +15.7° (c 1, $CHCl_3$). [e] For compound **3a**. [f] Deduced from the prepared ester (*R*)-**3a**. [g] Deduced from the $[\alpha]_D^{25}$ corresponding to a chemically synthesised optically pure sample.[14] [h] Using $Eu(tfc)_3$ (^1H n.m.r., 300 MHz). [i] From the $[\alpha]_D^{25}$ corresponding to compound **1b**[14] obtained by reduction with $NaBH_4$ of compound **1d** or its ester. [j] For the butyrate derived from **1b**. [k] By ^1H n.m.r. (300 MHz) analysis of the Mosher ester obtained by DCC esterification of compound **1e**.

The reaction of β-, γ-, and δ-hydroxy sulfones[1] with 2,2,2-trichloroethyl butyrate and PPL[12] in anhydrous ethyl ether[13] in the presence of molecular sieves at room temperature or under reflux gave the corresponding ester derived from the *R*-hydroxy sulfone and the *S*-hydroxy sulfone (Scheme 1 and Table). The obtained compounds were separated by column chromatography (silica gel) and the esters **3** were hydrolyzed with methanolic potassium hydroxide to yield compound (*R*)-**1**, in the case of the β-hydroxy sulfone derivative **1a** partial racemization occurred.

The esterification was carried out at room temperature for several days or under ether reflux and shorter time. The first reaction conditions gave in general better ee for the unreacted alcohol, the *S* enantiomer (see Table).

Other lipase catalised esterification methods[11] using vinyl acetate,[11f] acetic anhydride,[11c] *O*-acetylcyclohexanone oxime[16] as esterification agents failed or afforded very low yields. Very poor results were also obtained by hydrolysis with yeast lipase and n-butanol of the corresponding acetates.[11h]

From the results described in this paper we conclude that PPL can be used as a catalyst for the resolution of β-,γ-, and δ-hydroxy sulfones, which are interesting starting materials in organic synthesis.[3-8,17]

In a *typical reaction*, a suspension of hydroxy sulfone (1 mmol), PPL (0.4 g), 4 Å molecular sieves (0.5 g) and 2,2,2-trichloroethyl butyrate (1.2 mmol, 123 μl) in dry ethyl ether (5 ml) was stirred at room temperature or under reflux (see Table). The reaction was monitorised by t.l.c. and after the reaction time the mixture was filtered off and the residue was evaporated and purified by flash chromatography on silica gel.

Acknowledgement

This work was supported by DGICYT (no. PB88-0287) from Ministerio de Educación y Ciencia, Spain.

References and Notes

1. (a) Schank, K. in *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag. Stuttgart, 1985; Vol. E/11. (b) Posner, G.H. "The Chemistry of Sulphones and Sulphoxides", Ed. Patai, S., Rappoport, Z. and Stirling, C., John Wiley & Sons, New York (1988), Chapter 16.
2. Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
3. (a) Kozikowski, A.P.; Mugrage, B.B.; Li, C.S.; Felder, L. *Tetrahedron Lett.* **1986**, *18*, 4817. (b) Tanaka, K.; Ootake, K.; Imai, K.; Tanaka. N.; Kaji, A. *Chem. Lett.* **1983**, 633. (c) Solladié, G.; Frenchon, C.; Demailly, G.; Greck, C. *J. Org.Chem.* **1986**, *51*, 1912.

4. Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1799.

5. Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 2591.

6. Tius, M.A.; Fauq, A.H. *J. Am. Chem. Soc.* **1986**, *108*, 1053.

7. (a) Donaldson, R.E.; Fuchs, P.L. *J. Am. Chem. Soc.* **1981**, *103*, 2108. (b) Saaler, J.C.; Donaldson, R.E.; Fuchs, P.L. *J. Am. Chem. Soc.* **1981**, *103*, 2110.

8. Braish, T.F.; Saddler, J.C.; Fuchs, P.L. *J. Org. Chem.* **1988**, *53*, 3347.

9. Crumbie, R.L.; Deol, B.S.; Nemorin, J.E.; Ridley, D.D. *Aust. J. Chem.* **1978**, *31*, 1965.

10. Klibanov, A.M. *CHEMTECH* **1986**, *16*, 354.

11. (a) Kirchner, G.; Scollar, M.P.; Klibanov, A.M. *J. Am. Chem. Soc.* **1985**, *107*, 7072. (b) Francalanci, F.; Cesti, W.; Cabri, W.; Bianchi, D.; Martinengo, T.; Foà, M. *J. Org. Chem.* **1987**, *52*, 5079. (c) Gotor, V.; Brieva, R.; Rebolledo, F. *J. Chem. Soc., Chem. Commun.* **1988**, 957. (d) Theisen, P.D.; Heathcock, C.H. *J. Org. Chem* **1988**, *53*, 2374. (e) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531. (f) Wang, Y.-F.; Lalonde, J.J.; Momongan, M.; Bergbreiter, D.E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. (g) Okahata, Y.; Fujimoto, Y.; Ijiro, K. *Tetrahedron Lett.* **1988**, *29*, 5133. (h) Bevinakatti, H.S.; Banerji, A.A.; Newadkar, R.V. *J. Org. Chem.* **1989**, *54*, 2453. (i) Terao, Y.; Tsuji, K.; Murata, M.; Achiwa, K.; Nishio, T.; Watanabe, N.; Seto, K. *Chem. Pharm. Bull.* **1989**, *37*, 1653. (j) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189. (k) Chen, C.-S.; Liu, Y.-C. *Tetrahedron Lett.* **1989**, *30*, 7165. (l) Macfarlane, E.L.A.; Roberts, S.M.; Turner, N.J. *J. Chem. Soc., Chem. Commun.* **1990**, 569. (m) Burgess, K.; Jennings, L.D. *J. Org. Chem.* **1990**, *55*, 1138. (n) Wu, S.-H.; Guo, Z.-W.; Sih, C.J. *J. Am. Chem. Soc.* **1990**, *112*, 1990. (o) Babiak, K.A.; Ng, J.S.; Dygos, J.H.; Weyker, C.L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377. (p) Wallace, J.S.; Reda, K.B.; Williams, M.E.; Morrow, C.J. *J. Org. Chem.* **1990**, *55*, 3544. (q) Gutman, A.L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.

12. Sigma, E.C.3.1.1.3, Type II crude.

13. In other solvents such as hexane, acetone, acetonitrile, or ethyl acetate the reaction failed.

14. Optically pure compound (*S*)-**1b** was prepared by reaction of methyl *p*-tolyl sulfone with Bu^nLi at -78°C followed by addition of $Ti(OPr^i)_4$ and (*S*)-methyloxirane.[15]

15. Scherkenbeck, J.; Barth, M.; Thiel, U.; Metten, K.-H.; Heimmann, F.; Welzel, P. *Tetrahedron* **1988**, *44*, 6325.

16. Ghogare, A.; Kumar, G.S. *J. Chem. Soc., Chem. Commun.* **1989**, 1533.

17. See, for instance: (a) Nájera, C.; Yus, M. *J. Org. Chem.* **1989**, *54*, 1491. (b) Nájera, C.; Sansano, J.M. *Tetrahedron* **1990**, *46*, 3993.