Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1753-1754, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain.
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00201-3

Deracemization of (±)-2,2-Disubstituted Epoxides *via* Enantioconvergent Chemoenzymatic Hydrolysis using *Nocardia* EH1 Epoxide Hydrolase and Sulfuric Acid

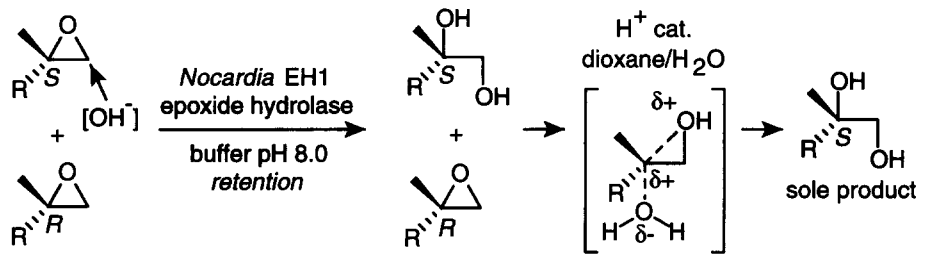
Romano V. A. Orru, Wolfgang Kroutil and Kurt Faber*

Institute of Organic Chemistry, Graz University of Technology, Stremayrgasse 16, A-8010 Graz, Austria. <Faber@ORGC.TU-GRAZ.AC.AT>

Abstract: 2-Substituted (*S*)-1,2-diols were prepared in a one-pot procedure with >90% ee and >90% isolated yield *via* deracemization of (±)-2,2-disubstituted oxiranes through sequential (i) biocatalytic asymmetric hydrolysis using *Nocardia* EH1 epoxide hydrolase and (ii) acid catalyzed hydrolysis of the remaining oxirane enantiomer.
© 1997 Elsevier Science Ltd. All rights reserved.

Recently, microbial epoxide hydrolases from fungi or bacteria have become highly versatile biocatalysts for the kinetic resolution of epoxides.[1] As a rule, the enzymatic hydrolysis proceeds by following a classical kinetic resolution pattern, *i.e.* optically enriched epoxide and the corresponding enantiomeric vicinal diol are obtained in 50% theoretical yield at 50% conversion. On the other hand, procedures which would lead to the formation of a single product enantiomer in 100% theoretical yield would clearly be advantageous over the classic resolution pattern.[2] A recent communication[3] on the deracemization of a cyclic trisubstituted oxirane by tandem bio- and chemocatalytic hydrolysis using *Corynebacterium* C12 and perchloric acid prompts us to disclose some of our preliminary results. We have recently shown[4] that the enzymatic hydrolysis of 2,2-disubstituted epoxides proceeds *via* attack at the less substituted C-atom with excellent regioselectivity thus leading to *retention* of configuration at the stereogenic center. On the other hand, it is known that the acid-catalyzed hydrolysis of an epoxide can result in ring opening with *inversion*[5] at the more substituted oxirane carbon atom under carefully controlled reaction conditions. These considerations led us to anticipate that the combination of bio- and chemocatalysis might provide access to enantiomerically enriched vicinal diols as the sole product from racemic 2,2-disubstituted epoxides in 100% theoretical yield.

In the first step, 2,2-disubstituted epoxides[6] (±)-**1-3** were hydrolyzed using lyophilized whole cells of *Nocardia* EH1.[1c] With R being *n*-pentyl (**1**) or 4-pentenyl (**2**), the selectivity was found to be absolute (E >200); with substrate **3** the selectivity was slightly reduced, but still in a preparatively useful range (E = 80). When the remaining (*R*)-epoxides were isolated and treated with conc. sulfuric acid in dioxane/water (97:3), the corresponding (*S*)-diols were formed within minutes. No trace of racemization was observed (entries 1-3).[7] Aiming at a simple deracemization technique, which could be performed in a one-pot reaction sequence,[8] both of the reactions were coupled (entries 4-6). Consequently, the enzymatic hydrolysis of (±)-**1-3** was run to the optimum degree of conversion,[9] and the crude reaction mixture was directly treated with conc. H_2SO_4 in dioxane/water (97:3). In this way, racemic epoxides (**1-3**) were directly converted to the corresponding (*S*)-diols **1a-3a** in >90 % isolated yield and >90 % e.e.



(±)-**1** R = $(CH_2)_4CH_3$ (*R*)-**1** (*S*)-**1a**
(±)-**2** R = $(CH_2)_3CH{=}CH_2$ (*R*)-**2** (*S*)-**2a**
(±)-**3** R = CH_2Ph (*R*)-**3** (*S*)-**3a**

Entry	Process	Epoxide	E.e. [%]	Diol	Yield [%]	E.e. [%]
1	2-step	(*R*)-**1**	96	(*S*)-**1a**	97	96
2	2-step	(*R*)-**2**	99	(*S*)-**2a**	99	99
3	2-step	(*R*)-**3**	83	(*S*)-**3a**	87	83
4	one-pot	(±)-**1**	—	(*S*)-**1a**	98	98
5	one-pot	(±)-**2**	—	(*S*)-**2a**	97	99
6	one-pot	(±)-**3**	—	(*S*)-**3a**	94	92

In summary, we have developed a simple one-pot procedure for the deracemization of 2,2-disubstituted epoxides based on (i) biocatalytic resolution using *Nocardia* EH1 epoxide hydrolase and (ii) acidic hydrolysis of the remaining epoxide enantiomer (H_2SO_4 cat., dioxane/water). Thus, the enantiomerically enriched corresponding 1,2-diols were obtained close to the theoretical limit of 100% yield and 100% ee. The scope and limitations of this method as well as full experimental details will be reported in due course.

Acknowledgements: The authors wish to express their cordial thanks to C. Syldatk (Stuttgart) for providing *Nocardia* EH1. This project was performed within the Spezialforschungsbereich Biokatalyse (SFB-A4). Financial support from the Fonds zur Förderung der wissenschaftlichen Forschung (F 104), the European Community (BIO4-CT95-0005) and the Austrian Federal Ministry of Sciences is gratefully acknowledged.

References and Notes

1. a) For a review see: Faber, K.; Mischitz, M.; Kroutil, W. *Acta Chem. Scand.* **1996**, *50*, 249. b) Pedragosa-Moreau, S.; Archelas, A.; Furstoss, R. *Tetrahedron* **1996**, *52*, 4593. c) Osprian, I.; Kroutil, W.; Mischitz, M.; Faber, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1.
2. For a review on 'second-generation biotransformations' see: Stecher, H.; Faber, K. *Synthesis* **1997**, in press.
3. Archer, I. V. J.; Leak, D. J.; Widdowson, D. A. *Tetrahedron Lett.* **1996**, *37*, 8819.
4. Mischitz, M.; Mirtl, C.; Saf, R., Faber, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2041.
5. Via a borderline S_N2-mechanism: Biggs, J.; Chapman, N. B.; Finch, A. F.; Wray, V. *J. Chem. Soc. (B)* **1971**, 55.
6. Mischitz, M.; Kroutil, W.; Wandel, U.; Faber, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1261.
7. Using $HClO_4$, no diols were formed and elimination and/or rearrangement was the major reaction.
8. Typically, racemic epoxide (300mg, 2.00-2.40 mmol) was hydrolyzed using *Nocardia* EH1 cells[1c] (300mg) in Tris-buffer (5 mL, 50 mM, pH 8.0) by shaking the mixture at 30°C with 120 rpm. After an appropriate degree of conversion was reached (*i.e.* slightly beyond 50%)[9] the reaction was quenched by extraction of (*R*)-**1-3** and (*S*)-**1a-3a** using CH_2Cl_2. After evaporation, the crude mixture was treated for ~5 min. with aq. dioxane (150 mL, 3% H_2O) containing containing 1.5 mL of conc. sulfuric acid. After neutralization (sat. aq. $NaHCO_3$), diols (*S*)-**1a-3a** were extracted with EtOAc (5 x 10 mL) and analyzed as described in ref. 1c.
9. *I.e.* slightly beyond 50%, see: Vänttinen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 1779.

(*Received in Germany* 23 *December* 1996; *revised* 26 *January* 1997; *accepted* 28 *January* 1997)