DOI: 10.1002/adsc.200((will be filled in by the editorial staff))

Chemo- and Stereodivergent Preparation of Terminal Epoxides and Bromohydrins through *One-Pot* Biocatalysed Reactions: Access to Enantiopure Five- and Six-Membered *N*-Heterocycles

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Received: ((will be filled in by the editorial staff))

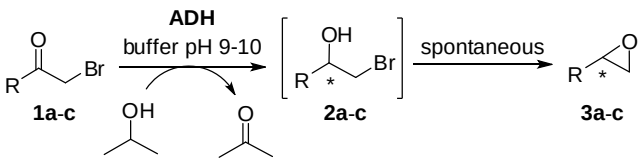
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200######.

Abstract. Different enantiopure terminal epoxides or bromohydrins have chemoselectively been synthesised in *one-pot* starting from the corresponding α-bromoketones through alcohol dehydrogenase (ADH)-catalysed processes adding an organic co-solvent and tuning appropriately the medium pH and the temperature. Thus, at neutral pH enantiopure bromohydrins were obtained while using basic conditions (pH 9.5-10) epoxides were isolated as the main product. Furthermore, by simple selection of the biocatalyst, chemo- and stereodivergent transformations were achieved to obtain, *e.g.* enantiopure prolinol or piperidin-3-ol.

Keywords: *one-pot* reaction; alcohol dehydrogenases; epoxides; bromohydrins; prolinol; medium engineering

Enantiopure terminal halohydrins and epoxides are valuable functionalities in pharmaceutical industry and natural products synthesis due to their high reactivity allowing the obtaining of a huge variety of compounds.[1] In the last three decades, organo- and transition metal-based approaches have successfully been developed to synthesise these derivatives.[2] Otherwise, environmental friendly enzymatic processes leading to enantioenriched oxiranes and halohydrins have been less developed.[3] Among them, kinetic resolutions using epoxide hydrolases (EHs)[4] and halohydrin dehalogenases (Hhes)[5] have been employed to catalyse the regio- and enantioselective oxirane ring-opening with H_2O or other nucleophiles, affording the enantioenriched substrate and product with a 50% maximum yield. Recently, an elegant chemoenzymatic dynamic kinetic resolution procedure leading to aromatic terminal epoxides has been published.[6] Thus, coupling an Ir catalyst which promoted the racemisation of the halohydrins with an Hhe, several (*R*)-oxiranes could be achieved with moderate to high conversions and high enantioselectivities. Another approach has been the P450 monooxygenase-catalysed asymmetric epoxidation of terminal olefins.[7] Halohydrins have been obtained through stereoselective reduction of α-haloketones using alcohol dehydrogenases (ADHs).[8] Likewise, terminal epoxides have also been prepared through ADH-based sequential or cascade protocols.[9] In those systems, a terminal α-chloroketone was stereoselectively reduced with an ADH to the corresponding enantiopure chlorohydrin that subsequently cyclised through Hhe-[9a-c] or base-catalysed[9d] intramolecular S_N2 reaction, leading to the epoxides with moderate to high conversions and excellent *ee*s. Similarly, a "designer-cell"-based two-step procedure was developed to synthesise (*S*)-octene oxide.[10] It is noteworthy that pH around 13 was set in order to accomplish the oxirane ring-formation,[9d,10] that can be incompatible with other functionalities.

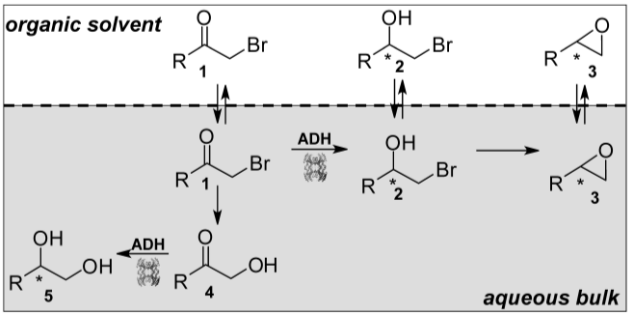
With this scenario we assumed that employing α-bromoketones[10,11] instead of α-chloroketones, we could synthesise enantioenriched terminal oxiranes or bromohydrins in *one-pot* by simple use of a catalyst (an ADH) and a catalytic amount of cofactor employing 2-propanol to recycle it ('substrate-coupled' approach)[12] at suitable pH conditions for the enzyme (Scheme 1). Furthermore, an application to obtain *N*-heterocyclic compounds is also shown.



a, C_6H_{13}; **b**, *p*-NO_2-C_6H_4; **c**, N_3-$(CH_2)_3$

Scheme 1. *One-pot* synthesis of enantiopure terminal epoxides.

For this purpose, we chose 1-bromooctan-2-one (**1a**)[10] as model substrate. Using *Lactobacillus brevis* ADH (LBADH)[13] as catalyst at pH 7.5, only 10% of enantiopure (*S*)-epoxide **3a** was obtained after 24 h, so Tris.SO_4 buffers ranging from pH 7.5 until 10 were tested (see Supporting Information). Obviously, the best conversion into **3a** (47%) was found with the highest pH, although we observed that other minor compounds were also formed. In this sense, blank experiments demonstrated that the corresponding hydroxyketone (**4a**) was formed by S_N2 reaction over substrate **1a**, and diol **5a** appeared due to the ADH-catalysed reduction of **4a**.[14] To circumvent this fact it was envisaged that an amount of a water-immiscible solvent could result in a reservoir for both substrate and products (Scheme 2).



Scheme 2. (Bio)transformations in a biphasic aqueous-organic system.

Consequently, several organic solvents such as *n*-pentane, *n*-hexane, cyclohexane, *n*-heptane and *n*-decane were assayed at 5% v v^{-1} leading to almost exclusive formation of **2a** and **3a** after 24 h, although the cyclisation rate diminished (see Supporting Information). Since no relevant difference was noticed among them, *n*-hexane was selected as the organic co-solvent. The addition of the organic phase was advantageous to suppress the undesired S_N2 reaction over α-bromoketone **1a**, but also delayed the enzymatic reduction to obtain **2a** and the ring-closure to achieve **3a**, so a compromise had to be found. To optimise the reaction outcome, a study of the *n*-hexane concentration (3-20% v v^{-1}) was carried out (Figure 1). As expected, it was observed that at higher percentages of the organic co-solvent, less quantity of by-products was formed although going in hand with a lower cyclisation rate. Hence, 5% v v^{-1} of *n*-hexane was the compromise concentration.

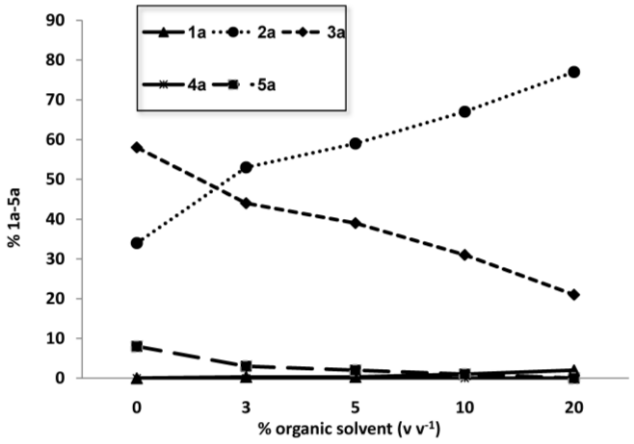


Figure 1. Co-solvent concentration effect on the products ratio in the biotransformation of **1a** into **3a** after 24 h.

In these conditions, we observed a clean reaction with complete consumption of **1a** and a promising 42% of **3a** after 24 h. In an attempt to maximise the oxirane formation, it was designed a thermally controlled experiment consisting of the enzymatic bioreduction at 30ºC followed by the intramolecular S_N2 transformation at 45ºC by simply setting a temperature program. Thus, the reaction progress at 30ºC was studied (Figure 2) to check the time needed to consume α-bromoketone **1a**. As can be noted after 12 h this compound disappeared, only forming traces (<2%) of diol **5a**.

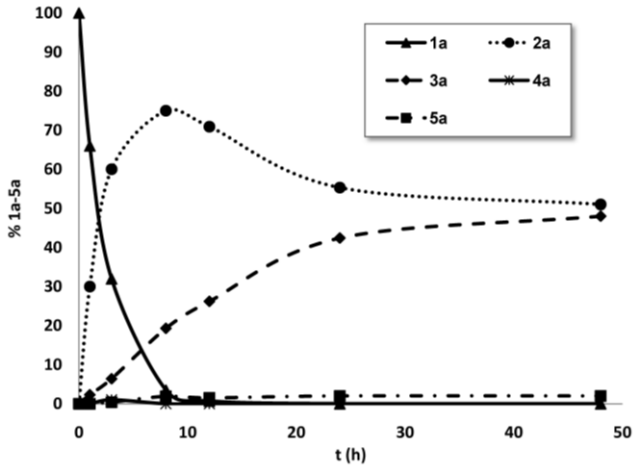


Figure 2. Time-course of the enzymatic transformation of **1a** into **3a** catalysed by LBADH in Tris.SO_4 buffer pH 10 at 30ºC in the presence of 5% v v^{-1} of *n*-hexane.

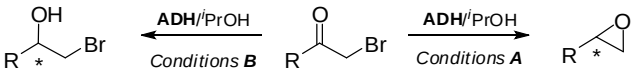
Table 1. Biocatalysed synthesis of enantiopure epoxides and bromohydrins in a biphasic system.[a]

entry	**1**	conv.[b]	*ee*[c,d]	**2**[b]	**3**[b]	T program	pH	**ADH**
1	**1a**	98	>99 (*S*)	56	42	24h 30ºC	10	LB
2	**1a**	99	>99 (*S*)	<1	98	13h 30ºC /18h 45ºC	10	LB
3	**1a**	>99	>99 (*R*)	9	90	13h 30ºC /18h 45ºC	10	T
4[e]	**1b**	>99	>99 (*S*)	<1	84	13h 30ºC /18h 45ºC	9.5	LB
5	**1b**	99	>99 (*R*)	<1	98	13h 30ºC /18h 45ºC	9.5	T
6	**1c**	87	>99 (*S*)	4	83	36h 30ºC	9.5	LB
7	**1a**	>99	>99 (*S*)	99	<1	18h 30ºC	7.5	LB
8	**1a**	99	>99 (*R*)	98	<1	18h 30ºC	7.5	T
9	**1b**	>99	>99 (*S*)	85	15	18h 30ºC	7	LB
10	**1b**	>99	>99 (*R*)	93	7	18h 30ºC	7	T
11	**1c**	>99	>99 (*S*)	99	<1	18h 30ºC	7.5	LB

[a] For reaction conditions, see Supporting Information. [b] Measured by GC. [c] Measured by chiral GC or HPLC. [d] Switch in Cahn-Ingold-Prelog (CIP) priority. [e] 15% of by-products were formed.

Thus, employing a program that comprised 13 h at 30ºC followed by 18 h at 45ºC excellent epoxide conversion was achieved (Table 1). This *one-pot* sequential process enabled the formation of enantiopure (*S*)- or (*R*)-**3a** with excellent yields by simple selection of the biocatalyst, using either LBADH (entry 2) or ADH from *Thermoanaerobacter* sp.[15] (ADH-T, entry 3), respectively.

Since this *one-pot* two-step procedure rendered excellent results for this aliphatic substrate, we decided to apply this methodology with an aromatic ketone such as α-bromo-*p*-nitroacetophenone (**1b**), obtaining with ADH-T a complete conversion of enantiopure (*R*)-*p*-nitrostyrene oxide (**3b**), and a conversion of 84% and >99% *ee* of (*S*)-**3b** using LBADH (Table 1, entries 4-5). For this derivative a slightly lower pH (9.5) was chosen, since at pH 10 higher amounts of by-products were detected.

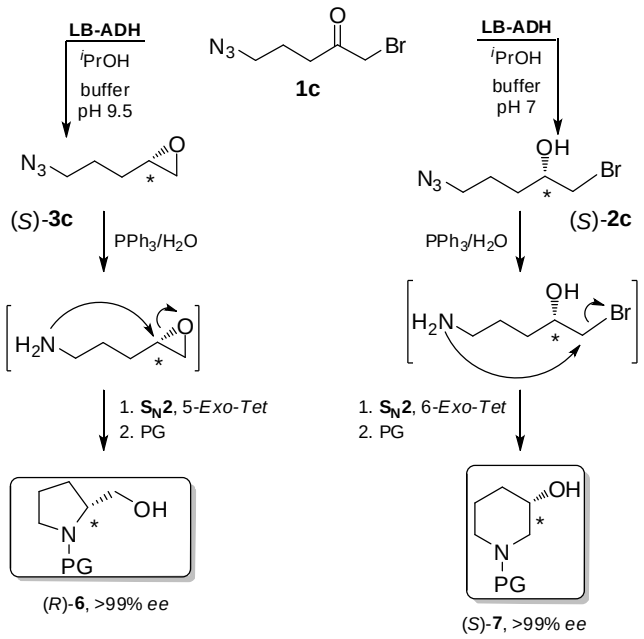


Scheme 3. Chemo- and stereodivergent preparation of β-bromo alcohols and epoxides starting from α-bromoketones. *Conditions A*: ADH, 2-propanol, Tris.SO_4 buffer pH 9.5-10, *n*-hexane, 30ºC plus a 45ºC period. *Conditions B*: ADH, 2-propanol, Tris.SO_4 buffer pH 7-7.5, *n*-hexane, 30ºC.

Furthermore, taking benefit from the versatility of the medium parameters, we can use this methodology to synthesise selectively the corresponding bromohydrins with high conversions and optical purities. Since it was observed in previous experiments that lower pHs and the presence of an organic co-solvent diminished the cyclisation rate, we exploited this to obtain the bromohydrins **2a-b** (Scheme 3). Therefore, experiments were carried out at lower pH (7-7.5) and 30ºC with 5% v v^{-1} *n*-hexane (entries 7-10). Thus, enantiopure derivatives (*S*)- and (*R*)-**2a-b** were preferentially obtained using both ADHs. To show the feasibility of these protocols, enantiopure (*S*)-alcohol **2a** and (*S*)-epoxide **3a** were prepared on a higher scale starting from 120 mg of the α-bromoketone **1a** with excellent isolated yields (see SI).

At this point we were interested in applying this methodology to obtain other valuable derivatives. Enantiopure prolinol and related structures are important chiral auxiliaries in hydrogen transfer protocols as well as asymmetric epoxidations and catalysts in aldol condensations, Michael type additions and other C-C bond-forming reactions.[16] Moreover, chiral *N*-containing heterocycles are quite common in natural alkaloids and derivatives,[17] and therefore, it becomes interesting to develop new strategies for their preparation.[18] Epoxides and halohydrins are considered as similar chemical functionalities but they can offer different features that can be exploited chemoselectively. To show this, 5-azido-1-bromopentan-2-one (**1c**) was reduced with LBADH, affording enantiopure bromohydrin **2c** or epoxide **3c** in high conversions (Table 1, entries 6 and 10). These reactions were performed at 100 mg-scale obtaining similar results. It was envisaged that these derivatives could be reduced to the highly reactive (non isolated) amino compounds that would spontaneously cyclisise[19] affording prolinol or piperidin-3-ol through S_N2 reactions (Scheme 4). We firstly decided to optimise the reduction step using some reducing reagents such as $NaBH_4$ and H_2-Pd/C but in case of **3c** the oxirane moiety was unstable. However, by means of the Staudinger reaction using PPh_3 and H_2O,[20] the desired reduction was successfully accomplished. In case of the amino epoxide, it spontaneously evolved into prolinol with inversion of the configuration following a 5-*Exo-Tet* process, instead of piperidin-3-ol through an impeded 6-*Endo-Tet* route according to Baldwin' rules (Scheme 4, left).[21] On the other hand, bromohydrin **2c** afforded the piperidine derivative as the sole product through a favoured 6-*Exo-Tet* pathway (Scheme 4, right).[21] Once optimised all individual steps, enantiopure (*R*)-prolinol and (*S*)-piperidin-3-ol were obtained as the corresponding *N*-Boc and N-CBz derivatives, respectively, through this three-step

procedure. These transformations could be performed following a *one-pot* protocol, although better yields were achieved when the Staudinger reduction was performed after isolation of (*S*)-**2c** or (*S*)-**3c**. This procedure shows an elegant chemodivergent strategy that can be applied to the synthesis of different heterocyclic-bearing scaffolds with good yields and optical purities.



Scheme 4. Biocatalysed chemodivergent synthesis of enantiopure *N*-protected (*R*)-prolinol and (*S*)-piperidin-3-ol.

In conclusion, we have developed an efficient *one-pot* chemo- and stereodivergent enzymatic process applied to the preparation of both enantiopure terminal epoxides or β-bromo alcohols starting from the corresponding α-bromoketones just tuning the reaction conditions. This is a nice example of the application of the *medium engineering*[22] to an enzymatic process to perform transformations using mild reaction conditions to achieve the selective formation of several derivatives in high yields choosing the stereochemistry by employing the appropriate biocatalyst. Furthermore, applying this chemodivergent methodology very interesting compounds such as prolinol or piperidin-3-ol could readily be synthesised. Other heterocycles may be prepared by selecting the suitable precursor. A more comprehensive study of the presented system is currently under way in our laboratories.

Experimental Section

Synthesis of (*S*)-*N*-CBz-piperidin-3-ol (*S*)-7.[23] 100 mg of **1c** were incubated in Tris.SO_4 buffer 50 mM pH 7.5 (20 mL) containing NADPH (1 mM) and $MgBr_2$ (1 mM) in the presence of 2-propanol (5% v v^{-1}) and *n*-hexane (5% v v^{-1}) with LBADH (10 U) for 18 h at 30 ºC. The reaction was extracted with Et_2O (3 x 5 mL) and the organic layers were dried and evaporated. The crude was dissolved in THF (4 mL), and PPh_3 (2 equiv.) and H_2O (2 equiv.) were added. The reaction was stirred for 24 h at room temperature. Then, the solvent was evaporated and the crude was extracted with CH_2Cl_2/HCl 3N. The aqueous phase obtained (10 mL) was set to pH 8-9 with a satd. solution of Na_2CO_3 3N and then CH_2Cl_2 (5 mL) and CBz-Cl (1.2 equiv.) were added and the biphasic system was stirred for 12 h. The crude was extracted with CH_2Cl_2 and was subjected to *flash* chromatography over silica gel eluted with EtOAc/CH_2Cl_2 (from 1:1 to 2:1) affording enantiopure (*S*)-**7** (40%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.40-1.50 (*m*, 2H, H_4), 1.65-1.80 (*m*, 2H, H_5), 1.91 (*br s*, 1H, H_{OH}), 3.01-3.13 (*m*, 2H, H_6) 3.49-3.74 (*m*, 3H, H_2+H_3), 5.03 (*s*, 2H, H_b) and 7.24 (*m*, 5H, H_{ar}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.2 (CH_2, C_4), 32.2 (CH_2, C_5), 44.0 (CH_2, C_6), 50.6 (CH_2, C_2), 65.8 (CH, C_3), 67.9 (CH_2, C_b), 127.7 (C, C_i), 127.9 (2 CH, C_m), 128.4 (2 CH, C_o), 136.6 (CH, C_p) and 155.6 (C, C=O).

Acknowledgements

F.R.B. is supported by the Programme Alβan, the European Union Program of High Level Scholarships for Latin America (scholarship No. E07D402519AR). A.C. thanks Universidad de Oviedo for a pre-doctoral fellowship. A.A.O. is a postdoctoral CONICET fellow. M.K.-S. is member of the Research Career of CONICET. I.L. thanks the Spanish Ministerio de Ciencia e Innovación (MICINN) for personal funding (Ramón y Cajal Program). Financial support from MICINN (Project CTQ2007-61126) and the Spanish Ministerio de Asuntos Exteriores y de Cooperación (Programa de Cooperación Interuniversitaria, PCI Iberoamérica MAEC-AECID, Project A/8856/07) is gratefully acknowledged. Dedicated to Prof. Oscar S. Giordano on the occasion of his retirement.

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COMMUNICATION

Chemo- and Stereodivergent Preparation of Terminal Epoxides and Bromohydrins through *One-Pot* Biocatalysed Reactions: Access to Enantiopure Five- and Six-Membered *N*-Heterocycles

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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