Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4483–4487

TETRAHEDRON: *ASYMMETRY*

Enzymatic resolution of (±)-*cis*-2-aminocyclopentanol and (±)-*cis*-2-aminocyclohexanol

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Received 3 November 1998; accepted 25 November 1998

Abstract

(±)-*cis*-*N*-Benzyloxycarbonyl-2-aminocyclopentanol was efficiently resolved by *O*-acylation with *Pseudomonas cepacia* lipase, as was (±)-*cis*-*N*-benzyloxycarbonyl-2-aminocyclohexanol when *Candida antarctica* lipase was used.

1. Introduction

In recent years, we have been exploring the use of enzymes, and particularly lipases, in organic solvents, for the synthesis and resolution of nitrogen-containing organic compounds.[1] 1,2-Amino alcohols were resolved via an enzymatic aminolysis reaction,[2] although the enzymatic transesterification of *N*-protected amino alcohols has been reported by ourselves[3] and others[4] as an efficient procedure for the resolution of some amino alcohols.

Surprisingly, very little attention has been paid to the enzymatic resolution of cyclic 1,2-amino alcohols. The importance of these compounds is evident by virtue of their biological and pharmacological properties,[5] and *cis*-1,2-amino alcohols are also of great interest in asymmetric catalysis and asymmetric synthesis.[6] Considerable efforts have been made to obtain optically active (±)-*trans*-2-aminocyclopentanol and (±)-*trans*-2-aminocyclohexanol.[7] However, their isomers (±)-*cis*-2-aminocyclopentanol and (±)-*cis*-2-aminocyclohexanol, whose structures are present in a wide variety of biologically active compounds,[8] have scarcely been studied.

We recently reported[9] a practical and efficient procedure for the resolution of (±)-*trans*-2-aminocyclopentanol and (±)-*trans*-2-aminocyclohexanol. On the basis of these initial results, our aim was to develop a similar strategy for the resolution of (±)-*cis*-2-aminocyclopentanol and (±)-*cis*-2-aminocyclohexanol. We report here the enzymatic resolution of these amino alcohols.

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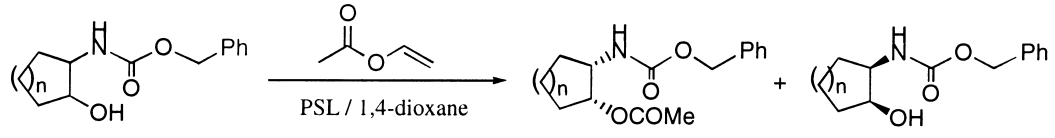
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00482-0

Table 1

Entry	t, d	product (1*R*,2*S*)			remaining substrate (1*S*,2*R*)			conv.[c] (%)	*E*[c]
			yield[a] (%)	ee[b] (%)		yield[a] (%)	ee[b] (%)		
1, n=1	2	**2**	100	99	**1**	86	79	44	>200
2, n=1	6	**2**	100	99	**1**	100	99	50	>200
3, n=2	13	**4**	91	99	**3**	89	4	4	>200

[a] After flash chromatography. [b] determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD.
[c] See ref. 10.

As in the previously-mentioned resolution of the *trans* isomers, we began our experiments with the corresponding *N*-benzyloxycarbonyl derivatives as starting material, in order to obtain enantiomerically pure (±)-*cis*-2-aminocyclopentanol and (±)-*cis*-2-aminocyclohexanol.



(±)-*cis*-**1**, n = 1
(±)-*cis*-**3**, n = 2

(1*R*,2*S*)-**2**, n = 1
(1*R*,2*S*)-**4**, n = 2

(1*S*,2*R*)-**1**, n = 1
(1*S*,2*R*)-**3**, n = 2

In a first approach to the resolution of (±)-*cis*-2-aminocyclopentanol, the lipase from *Pseudomonas cepacia* (PSL) was chosen as a biocatalyst, because of its great efficiency in the enantioselective acylation of racemic *trans*-2-aminocyclopentanol and *trans*-2-aminocyclohexanol. Vinyl acetate was used as an acylation reagent and 1,4-dioxane as the solvent at 30°C. Under these reaction conditions, PSL exhibited high enantioselectivity towards the substrate, yielding the *O*-acetyl derivative (1*R*,2*S*)-**2** with an enantiomeric excess of >99% ($[\alpha]_D$=−53.6, c=1.03, EtOH) and the 2-hydroxycarbamate (1*S*,2*R*)-**1** was recovered in 99% ee ($[\alpha]_D$=+34.31, c=0.95, EtOH). These data were in accordance with the conversion (50%) and enantiomeric ratio (E >200) of the reaction (Table 1, entry 2). The absolute configuration of (1*S*,2*R*)-**1** was assigned by deprotection and subsequent transformation into the hydrochloride. The sign of the specific rotation of this compound was compared with that given in the literature.[11]

The same methodology was applied to the Cbz derivative of (±)-*cis*-2-aminocyclohexanol. The results obtained at 30°C, however, were disappointing (Table 1, entry 3). The acylated product (1*R*,2*S*)-**4** was obtained in a high enantiomeric excess (>99%) and the substrate (1*S*,2*R*)-**3** was recovered practically as the racemate (4% ee) with a conversion of 4%. Even though the enzyme exhibited a marked enantioselectivity (ee >200), the reaction rate was low. These results prompted us to increase the temperature to 60°C with the aim of accelerating the acetylation, but the results were still unsatisfactory.

This result is somewhat surprising when the behaviour of (±)-*trans*-2-aminocyclohexanol in the same enzymatic process is considered. It is to be expected that in both isomers the largest substituent (*N*-Cbz) will be in the equatorial position,[12] and thus the hydroxy group will be locked in the axial position for the *cis* isomer and in the equatorial one for the *trans* derivative. This geometrical difference could be the reason for the lower reactivity of the *cis* isomer.

In order to improve the rate of the acylation, we tried isopropenyl acetate as the acyl donor and PSL in *tert*-butyl methyl ether at 40°C (Table 2, entry 3), but the results were again unsatisfactory. The reaction rate was increased when lipase from *Candida antarctica* (CAL) was used as a biocatalyst, with vinyl ester as the acylating agent in *tert*-butyl methyl ether (Table 2, entry 6). Finally, the acylation of **3** gave enantiopure (1*R*,2*S*)-**4** in very good yield.

Table 2

Entry	Enzyme	t, d	product (1*R*,2*S*)-**4**		remaining substrate (1 *S*,2*R*)-**3**		conv.[c] (%)	*E*[c]
			yield[a] (%)	ee[b] (%)	yield.[a] (%)	ee[b] (%)		
4	PSL	8	98	99	87	7	7	>200
5[d]	CAL	7	95	99	95	70	41	>200
6[e]	CAL	7	86	96	86	96	50	193

[a] After flash chromatography. [b] determined by HPLC analysis of the Cbz-derivatives on Chiralcel-OD.
[c] See ref.10. [d]isopropenyl acetate. [e]vinyl acetate.

In summary, this paper describes a simple and efficient procedure for resolution of the important compounds (±)-*cis*-1,2-aminocyclopentanol and (±)-*cis*-1,2-aminocyclohexanol. There is a noteworthy influence of the ring size on the efficiency of conversion.

2. Experimental section

2.1. General

Candida antarctica lipase (CAL), SP 435, was a gift from Novo Nordisk Co. *Pseudomonas cepacia* lipase (PSL) was purchased from Amano Pharmaceutical Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an appropriate desiccant and stored under nitrogen. Precoated TLC plates of silica gel 60 F254 from Merck were used, while for column chromatography, Merck silica gel 60/230–400 mesh was applied. Mps were measured with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer Mattson 3000 infrared Fourier transform spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75 MHz) spectrometer. Mass spectra were recorded on a Hewlett–Packard 5897 A spectrometer. HPLC analyses were carried out on a Shimadzu LC liquid chromatograph.

The (±)-*cis*-2-aminocyclopentanol and (±)-*cis*-2-aminocyclohexanol hydrochlorides were prepared from the corresponding racemic *trans* counterparts,[13] by using a recently described inversion procedure.[11] (±)-*cis*-2-Aminocyclopentanol hydrochloride: mp 180–183°C. Lit.[13] mp 181–183°C. (±)-*cis*-2-Aminocyclohexanol hydrochloride: mp 189–191°C. Lit.[13] mp 190–191°C.

2.2. Preparation of racemic benzyl N-(2-hydroxycycloalkane)carbamates *1* and *3*

To a solution of amino alcohol (2 mmol) and sodium carbonate (0.254 g, 2.4 mmol) in water (3.4 ml), benzyl chloroformate (2.4 mmol) was added dropwise over a 0.5 h period at 0–5°C. The reaction mixture was stirred for an additional 6 h at room temperature and extracted with dichloromethane. The organic layer was dried and evaporated to dryness, to give the desired product in 85–100% yield.

2.3. (±)-Benzyl N-(2-hydroxycyclopentyl)carbamate *1*

The racemic 2-hydroxycarbamate **1** was purified by flash chromatography using ethyl acetate:hexane as eluent; this was a white solid, mp 73–75°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.98 (m, 6H), 2.65 (br s, 1H, OH), 3.85 (br s, 1H, C*H*-NH), 4.13 (br s, 1H, C*H*-OH), 5.09 (s, 2H, O-CH_2-Ph), 5.38–5.42

(m, 1H, N*H*), 7.34 (m, 5Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (CH_2), 28.9 (CH_2), 32.4 (CH_2), 55.7 (CH-NH), 66.7 (O-CH_2-Ph), 72.4 (CH-OH), 128.1 (CHarm), 128.2 (CHarm), 128.5 (CHarm), 136.4 (Carm), 156.4 (CO); IR (KBr) 3327, 1674 cm^{-1}. MS (EI) m/z: 235 ($C_{13}H_{17}NO_3$+2%), 91(C_7H_7+100%).

2.4. (±)-Benzyl N-(2-hydroxycyclohexyl)carbamate **3**

The compound (±)-**3** was a white solid, mp 75–77 °C (from ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.71 (m, 8H), 2.60 (br s, 1H, OH), 3.65 (br s, 1H, C*H*-NH), 3.92 (br s, 1H, C*H*-OH), 5.08 (s, 2H, O-CH_2-Ph), 5.37–5.41 (m, 1H, N*H*), 7.26–7.36 (m, 5Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6 (CH_2), 23.8 (CH_2), 27.5 (CH_2), 31.7 (CH_2), 52.6 (CH-NH), 66.9 (O-CH_2-Ph), 69.2 (CH-OH), 127.9 (CHarm), 128.3 (CHarm), 136.2 (Carm), 156.0 (CO); IR (KBr) 3327, 1674 cm^{-1}. MS (EI) m/z: 249 ($C_{14}H_{19}NO_3$+3%), 91 (C_7H_7+100%).

2.5. General procedure for the syntheses of benzyl carbamates **2** and **4**

Vinyl acetate (10 mmol) and carbamate (±)-*cis*-**1** or (±)-*cis*-**3** (1 mmol) were added to a suspension of PSL (320 mg) in 1,4-dioxane (9 ml) under nitrogen. The mixture was shaken at 30°C and 250 rpm for 2 days and 13 days, respectively. The enzyme was then filtered off and washed with dichloromethane (2×10 ml) and the organic solvents were evaporated off. The crude residue was subjected to column chromatography with ethyl acetate:hexane, 1:2 as eluent.

Isopropenyl acetate (5 mmol) or vinyl acetate (10 mmol) and carbamate (±)-*cis*-**3** (1 mmol) were added to a suspension of CAL (200 mg) in *tert*-butyl methyl ether (2 ml) under nitrogen. The mixture was shaken at 40°C and 250 rpm for 7 days. The enzyme was then filtered off and washed with dichloromethane (2×10 ml) and the organic solvents were evaporated off. The crude residue was subjected to column chromatography with ethyl acetate:hexane, 1:2 as eluent.

2.6. Benzyl (1R,2S)-N-(2-acetoxycyclopentyl)carbamate **2**

The above procedure gave 100% of (1*R*,2*S*)-**2** as a white solid, mp 58–60°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–2.05 (m, 9H), 4.05–4.11 (m, 1H, C*H*-NH), 4.90–5.1 (m, 4H), 7.37 (s, 5Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.98 (CH_2), 21.18 (CH_3), 29.58 (CH_2), 30.19 (CH_2), 54.02 (CH-NH), 66.84 (O-CH_2-Ph), 75.75 (CH-COMe), 127.23 (CHarm), 128.52 (CHarm), 136.3 (Carm), 155.77 (CO carbamate), 170.29 (CO ester); IR (KBr) 3378, 1728, 1594 cm^{-1}. MS (EI) m/z: 277 ($C_{15}H_{19}NO_4$+17%), 91 (C_7H_7+100%). Ee for (1*R*,2*S*)-**2** 99% determined by chiral HPLC, using hexane:propan-2-ol, 95:5 as eluent, 0.6 ml/min; t_R 29.44 min. For *rac*-benzyl carbamate, two peaks: t_R 27.68 and 29.57 min; *R*s, 1.18; $[\alpha]_D^{23}$=−60.8 (*c* 1.0 in EtOH). For the unreacted enantiomer $[\alpha]_D^{23}$=+34.3 (*c* 0.95 in EtOH) (100%), 99% ee was obtained, determined from its methyl ester derivative by chiral HPLC under the same conditions as described earlier, t_R 27.36 min.

2.7. Benzyl (1R,2S)-N-(2-acetoxycyclohexyl)carbamate **4**

The previously described procedure gave 91% of (1*R*,2*S*)-**4** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–2.06 (m, 11H), 3.81 (m, 1H, C*H*-NH), 4.90–5.09 (m, 4H), 7.38 (s, 5Harm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.85 (CH_2), 20.95 (CH_3), 23.37 (CH_2), 27.84 (CH_2), 28.34 (CH_2), 50.46 (CH-NH), 66.51 (O-CH_2-Ph), 71.94 (CH-COMe), 127.90 (CHarm), 128.27 (CHarm), 136.22 (Carm), 155.39 (CO carbamate), 170.19 (CO ester); IR (KBr) 3337, 1712, 1592 cm^{-1}. MS (EI) m/z: 291 ($C_{16}H_{21}NO_4$+2%),

91 (C_7H_7+100%). Determination of ee for (1*R*,2*S*)-**4**: 96% by chiral HPLC with hexane:propan-2-ol, 90:10 as eluent, 0.8 ml/min; t_R 10.58 and 12.23 min; $[\alpha]_D^{23}$=−55.14 (*c* 1.03 in EtOH). For *rac*-benzyl carbamate, two peaks: t_R 10.74 and 12.55 min; *R*s, 2.47. For the unreacted enantiomer $[\alpha]_D^{23}$=+29.26 (*c* 0.95 in EtOH) (86%), 96% ee was obtained, determined from its methyl ester derivative by chiral HPLC under the same conditions as described above, t_R 10.49 and 12.3 min.

Acknowledgements

Financial support of this work by CICYT (Project BIO-95-0687) is gratefully acknowledged. A.L. thanks CONACYT in México for a predoctoral scholarship. The authors also thank Novo Nordisk Co. for the generous gift of CAL.

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