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Chromatographic resolution of synthetically useful chiral glycine derivatives by high-performance liquid chromatography

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Abstract

The preparation of one oxo-oxazolidine and two dihydro-imidazole derivatives, useful chiral building blocks for amino acid syntheses, in racemic form is described. The racemic mixtures were separated on an analytical and preparative scale using high-performance liquid chromatography on chiral stationary phases. Detailed procedures for the separations are given, the results obtained are discussed, and the enantiopure compounds are fully characterized. © 1998 Elsevier Science B.V.

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1. Introduction

The preparative separation of chiral drugs and intermediates on chiral stationary phases (CSPs) is increasingly becoming an alternative to enantioselective synthetic routes [1], mainly due to advantages with regard to time and reliability of scale-up. Advances in chromatographic techniques, such as recycling/peak shaving [2], automated repetitive injection mode [3,4] and simulated moving bed (SMB) chromatography [5–10] are further reasons. Recycling/peak shaving and SMB chromatography require less stationary phase and solvent and, therefore, offer a higher specific productivity. Inevitably, however, the determination of chromatographic parameters for recycling and especially for SMB chromatography relies on developing methods for the simulation of chromatographic behaviour under non-linear conditions [11]. With these simulation methods, it is possible to obtain the appropriate parameters using analytical methods, and within a short period of time.

Because of the advantages, mentioned above, of preparative chromatography on CSPs for the resolution of enantiomers and as a result of our previous

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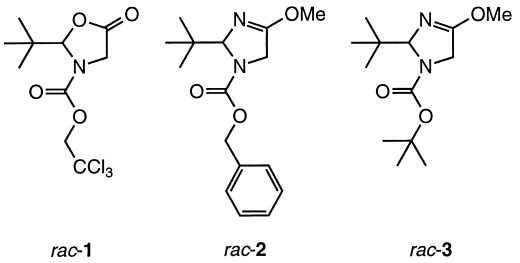


Fig. 1. Structures of chiral building blocks **1**–**3**, which were investigated using HPLC on CSPs.

successful work in this field [3,12–15], we applied this technique to the resolution of the racemic chiral building blocks **1**–**3** (Fig. 1).

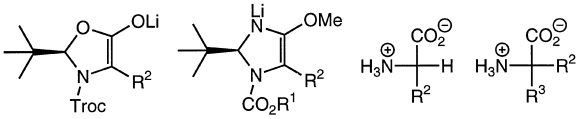
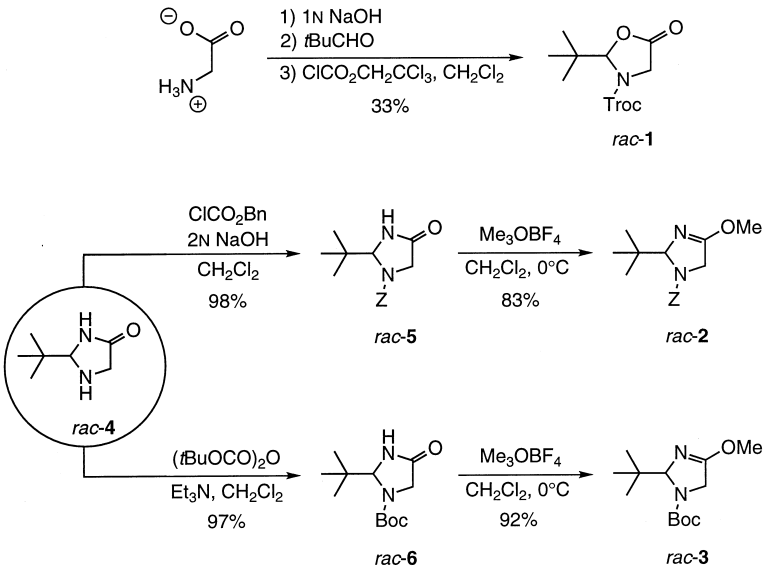


Fig. 2. Li derivatives of the heterocycles **1**–**3** (only one enantiomer shown), which are used for single and double alkylations, with subsequent hydrolysis to (non-proteinogenic and proteinogenic) amino acids and to α-branched amino acids (Troc=$CO_2CH_2CCl_3$, Bn=$CH_2C_6H_5$).

Compounds **1**–**3**, the Li derivatives of which are shown in Fig. 2, are the most recent examples of useful precursors that we use for the synthesis of enantiopure α-mono- and α,α-disubstituted α-amino acids. Recently, we published a detailed review article covering our contributions to this field of organic synthesis [16,17].

The chiral building blocks **1**–**3** have been synthesized in racemic form as outlined in Scheme 1. Detailed procedures for the synthesis of *rac*-**1**, *rac*-**2** and *rac*-**5** can be found in Section 2, whereas methods for the preparation of *rac*-**3**, *rac*-**4** and *rac*-**6** have already been published elsewhere [18]. As can be seen from Scheme 1, the dihydro-imidazoles **2** and **3** can be obtained from the corresponding racemic imidazolidinone **4** through the oxo-imidazolidines **5** or **6**. So far, the resolution of *rac*-**4** has been accomplished by diastereoisomeric salt formation [19]. We now report on the analytical separation of the enantiomers of oxo-imidazolidines **5** and **6** as well as the analytical and preparative resolution of the dihydro-imidazoles **2** and **3** and of the oxo-oxazolidine **1**. For the assignment of absolute configurations, as given in the legend to Scheme 1, see Refs. [18,20–22] and Section 3 of this publication.



Scheme 1. Preparation of oxo-oxazolidine **1**, dihydro-imidazoles **2** and **3** and oxo-imidazolidines **5** and **6** in racemic form (Z=$CO_2CH_2C_6H_5$, Boc=CO_2tBu). According to the assignment presented in Section 3 of this publication, the enantiopure compounds **1**–**3** are of (*R*)-configuration and levorotatory, while (*R*)-**5** and (*R*)-**6** are dextrorotatory.

2. Experimental

2.1. Chemicals

Pivalaldehyde was generously donated to us by BASF (Ludwigshafen, Germany). Sodium hydroxide and triethylamine were purchased from Siegfried (Zofingen, Switzerland). Glycine, methylene chloride, 2,2,2-trichloroethyl-chloroformate, benzyl-chloroformate, di-*tert*.-butyl-dicarbonate, trimethyloxonium-tetrafluoroborate, 1,3,5-tri-*tert*.-butyl-benzene (for the determination of void volumes) and silica gel for flash chromatography (Art. No. 60752) were purchased from Fluka (Buchs, Switzerland). The solvents used for the preparation of the mobile phases were of Lichrosolv grade from Merck (Darmstadt, Germany).

2.2. Preparation of rac-2′,2′,2′-trichloroethyl 2-tert.-butyl-5-oxo-oxazolidine-3-carboxylate (rac-**1**)

According to the procedure reported in [3,23], the sodium salt of glycine pivalimine (27.8 g, 0.17 mol) was suspended in CH_2Cl_2 (240 ml) and cooled to −10°C. 2,2,2-Trichloroethyl chloroformate (38.8 g, 0.183 mol) was slowly added over 2 h. The suspension was stirred for 24 h, allowing it to warm up to room temperature. $NaHCO_3$ solution (200 ml) was added to the reaction mixture and stirring was continued for 30 min. The organic phase was washed again with $NaHCO_3$ solution (200 ml) and dried over $MgSO_4$. Removal of the solvent and recrystallization of the crude product from ethyl acetate–hexane (1:1, v/v; 80 ml) led to colorless crystals of *rac*-**1** (18.0 g, 33%). M.p. 103.1–104.7°C. IR (KBr): 2973*s*, 2873*w*, 1785*s*, 1725*s*, 1477*m*, 1453*m*, 1399*s*, 1365*s*, 1356*m*, 1337*m*, 1311*s*, 1272*m*, 1235*s*, 1198*s*, 1175*s*, 1133*s*, 1066*m*, 1040*s*, 1018*s*, 987*m*, 919*s*, 880*m*, 870*m*, 810*m*, 780*m*, 770*s*, 753*m*, 725*s*, 706*m*, 628*m*. ^{1}H NMR (400 MHz, $CDCl_3$): 5.69 (*s*, 1 H); 4.81 (*m*, 2 H); 4.42 (*d*, *J*=17.6, 1 H); 3.90 (*b*, 1 H); 1.02 (*s*, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.7; 153.0; 96.7; 94.7; 74.8; 46.3; 38.5; 24.3. EI–MS: 264 (22), 262 (69), 260 (75), 236 (58), 234 (48), 232 (50), 208 (29), 206 (92), 204 (100), 170 (33), 168 (18), 133 (27), 131 (31), 130 (14), 115 (10), 113 (17), 98 (17), 97 (18), 96 (22), 95 (26), 87 (11), 85 (11), 74 (68), 71 (17), 61 (13), 57 (69), 56 (52). Anal. calc. for $C_{10}H_{14}NO_4Cl_3$ (318.58): C 37.70, H 4.43, N 4.40; found: C 37.60, H 4.14, N 4.43.

2.3. Preparation of rac-benzyl 2-tert.-butyl-4-oxo-imidazolidine-1-carboxylate (rac-**5**)

A mixture of *rac*-2-*tert*.-butyl-imidazolidin-4-one (*rac*-**4**, synthesized according to the procedure published in [18]; 2.88 g, 20 mmol), of benzyl chloroformate (4.3 ml, 30 mmol) and of 2 *M* NaOH (15 ml) in CH_2Cl_2 (90 ml) was stirred at room temperature for 3 h. After separation of the two layers, the aqueous phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic phases were washed with saturated $NaHCO_3$ solution (100 ml) and dried over $MgSO_4$. Removal of the solvent and recrystallization of the crude product from hexane–ethyl acetate (2:1, v/v; 180 ml) led to colorless crystals of *rac*-**5** (5.48 g, 98%). M.p. 131.8–133.2°C. IR ($CHCl_3$): 3440*w*, 3200*b*, 3020*w*, 3000*w*, 2960*m*, 1710*s*, 1450*m*, 1400*s*, 1370*m*, 1350*m*, 1300*s*, 1270*m*, 1160*m*, 960*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (*b*, 1 H); 7.50–7.40 (*m*, 5 H); 5.20–5.00 (*m*, 3 H); 4.20 (*b*, 1 H); 3.77 (*d*, *J*=16, 1 H); 0.94 (*s*, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.7; 155.4; 135.8; 128.6; 128.4; 128.1; 78.0; 67.7; 49.5; 38.4; 24.7. EI–MS: 219 (29), 175 (10), 91 (100), 57 (6), 41 (5). Anal. calc. for $C_{15}H_{20}N_2O_3$ (276.34): C 65.20, H 7.30, N 10.14; found: C 65.23, H 7.24, N 10.08.

2.4. Preparation of rac-benzyl 2-tert.-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylate (rac-**2**)

A mixture of *rac*-**5** (10.00 g, 36 mmol) and Me_3OBF_4 (Meerwein's salt) (5.35 g, 36 mmol) in CH_2Cl_2 (250 ml) was stirred at 0°C for 24 h. The reaction mixture was washed with saturated $NaHCO_3$ solution (200 ml) and the aqueous phase was extracted with CH_2Cl_2 (3×300 ml). The combined organic phases were dried over $MgSO_4$. Removal of the solvent and purification of the crude product by flash chromatography (pentane–ether, 4:1, v/v) led to colorless crystals of *rac*-**2** (8.68 g, 83%). M.p. 37.1–38.2°C (from pentane–ether, 4:1, v/v). IR ($CHCl_3$): 3000*w*, 2950*w*, 1690*s*, 1660*s*, 1480*w*, 1450*w*, 1440*m*, 1400*m*, 1370*s*, 1350*s*, 1330*s*, 1290*m*, 1260*w*, 1170*w*, 1100*m*, 1070*w*, 990*w*, 950*w*. ^{1}H

NMR (300 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 H); 5.34 (*b*, 1 H); 5.17 (*d*, J=13, 1 H); 5.11 (*d*, J=13, 1 H); 4.30 (*b*, 1 H); 3.86 (*dxd*, J_1=16, J_2=3, 1 H); 3.87 (*s*, 3 H); 0.92 (*s*, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) (only eleven of the twelve expected signals are seen): 168.0; 158.0; 136.3; 128.5; 128.1; 90.7; 67.3; 55.5; 50.8; 38.2; 25.6. EI–MS: 233 (46), 189 (33), 91 (100), 65 (6), 57 (6), 41 (8). Anal. calc. for $C_{16}H_{22}N_2O_3$ (304.39): C 66.18, H 7.64, N 9.65; found: C 66.23, H 7.78, N 9.61.

2.5. Liquid chromatography

A Merck–Hitachi D-6200 intelligent pump was used together with a Merck–Hitachi D-4000 UV–Vis detector, a Merck–Hitachi D-2500 chromato-integrator and a Rheodyne 7161 injection system for the analytical chromatography of oxo-oxazolidine *rac*-**1**. The preparative resolution of building block **1**, employing peak shaving recycling chromatography, was performed using a Shimadzu LC-8A pump in connection with a Merck–Hitachi D-4000 UV–Vis detector, a Rheodyne 3725i injection system, a Merck–Hitachi D-2500 chromato-integrator and a Merck Recyclomat. For the preparative SMB chromatography, a Licosep Lab from Novasep (Vandeouvre-lès-Nancy, France) was used.

The chromatographic system for the analytical chromatography of dihydro-imidazoles *rac*-**2** and *rac*-**3** and oxo-imidazolidines *rac*-**5** and *rac*-**6** consisted of a Kontron high-performance liquid chromatography (HPLC) pump (model 420) and a Kontron variable-wavelength UV detector (model 450). The semi-preparative separation of the enantiomers of *rac*-**2** was performed on a semi-preparative Chiralcel-OD column [178 g CSP, 200×40 mm I.D., purchased from Daicel (Tokyo, Japan)].

Chiralcel-OD-R (250×4.6 mm I.D.), Chiralcel-OD (250×4.6 mm I.D.), Chiralcel-OJ (250×4.6 mm I.D.) and Chiralpak-AD (250×4.6 mm I.D.) were purchased from Daicel. Ultron-OVM (150×4.6 mm I.D.) was purchased from Rockland Technology (Rockland, ID, USA).

Dead times (t_0) were estimated by injection of 1,3,5-tri-*tert*.-butyl-benzene. Capacity factors (k') were calculated according to the equation $k'=(t_r-t_0)/t_0$ and enantioselectivities (α) according to $\alpha=k'_2/k'_1$.

3. Results and discussion

3.1. Resolution of oxo-oxazolidine rac-*1*

In order to test the feasibility of a preparative resolution of *rac*-**1**, we first investigated the separation of its enantiomers on an analytical L-Chiraspher column. As can be seen from Table 1, entry 1, the obtained separation factor, α=1.87, indicated that an efficient separation on a preparative scale would be possible.

Thus, we separated 9 g of racemate **1** using peak shaving recycling chromatography on a D-Chiraspher column over four days. A typical chromatogram is shown in Fig. 3, chromatogram A. Using this methodology, we obtained 3.3 g of (*S*)-**1**, with an enantiomer ratio (e.r.) of 92.5:7.5 and 3.1 g of (*R*)-**1**, with e.r.>99.5:0.5.

Since we needed larger quantities of both enantiomers of chiral building block **1**, we were looking for

Table 1
Retention times (t), capacity factors (k') and enantioselectivities (α) for the resolution of oxo-oxazolidine *rac*-**1**, dihydro-imidazoles *rac*-**2** and *rac*-**3** and oxo-imidazolidines *rac*-**5** and *rac*-**6**

Entry	Heterocycle	t_0	t_1	t_2	$k'(1)$	$k'(2)$	α
1	*rac*-**1**	2.76	6.85	10.42	1.48	2.77	1.87
2	*rac*-**2**	5.80	13.95	17.94	1.41	2.09	1.48
3	*rac*-**3** (Chiralpak-AD)	6.02	7.98	9.21	0.33	0.53	1.63
4	*rac*-**3** (Ultron-OVM)	4.00	7.25	10.90	0.81	1.73	2.14
5	*rac*-**5**	6.10	13.54	18.33	1.22	2.00	1.64
6	*rac*-**6**	6.10	9.59	11.51	0.57	0.89	1.56

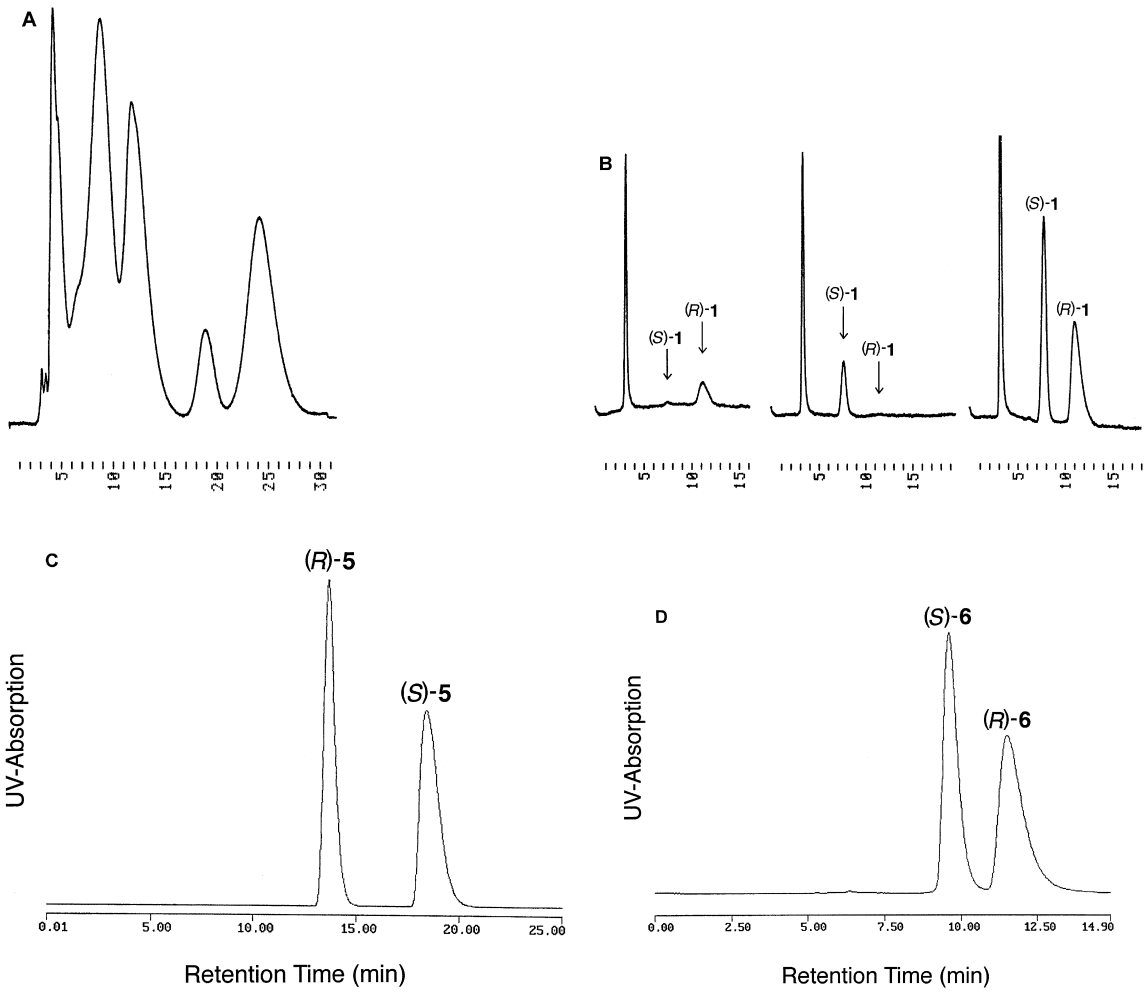
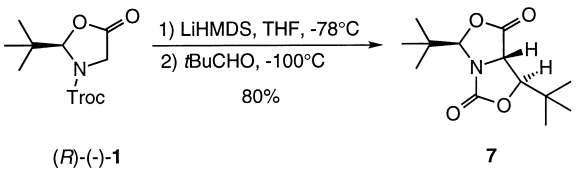


Fig. 3. Chromatograms of the preparative resolution of oxo-oxazolidine *rac*-**1** (A) and of the analytical resolution of oxo-oxazolidine *rac*-**1** (B), oxo-imidazolidines *rac*-**5** (C) and *rac*-**6** (D). A: Preparative resolution of *rac*-2′,2′,2′-trichloroethyl 2-*tert*.-butyl-5-oxo-oxazolidin-3-carboxylate (*rac*-**1**) using recycling chromatography on D-Chiraspher. Column size, 250×50 mm I.D.; mobile phase, isooctane–2-propanol (99:1, v:v); injected volume, 1 ml; sample concentration, 500 mg ml^{-1}. B: Determination of the enantiopurity of 2′,2′,2′-trichloroethyl 2-*tert*.-butyl-5-oxo-oxazolidin-3-carboxylate (**1**) on L-Chiraspher. Column size, 250×4 mm I.D.; mobile phase, hexane–2-propanol (100:1, v:v); flow-rate, 1 ml min^{-1}; room temperature; injected volume, 20 μl; sample concentration, 5 mg ml^{-1}; detection wavelength, 217 nm. C: Analytical resolution of *rac*-benzyl 2-*tert*.-butyl-4-oxo-imidazolidin-1-carboxylate (*rac*-**5**) on Chiralcel-OD-R. Column size, 250×4 mm I.D.; mobile phase, MeOH–0.5 *M* $HClO_4$ (adjusted to pH 2.0 using NaOH) (80:20, v:v); flow-rate, 0.5 ml min^{-1}; room temperature; injected volume, 20 μl; sample concentration, 1 mg ml^{-1}; detection wavelength, 205 nm. D: Analytical resolution of *rac*-*tert*.-butyl 2-*tert*.-butyl-4-oxo-imidazolidin-1-carboxylate (*rac*-**6**) on Chiralcel-OJ. Column size, 250×4 mm I.D.; mobile phase, hexane–2-propanol (95:5, v:v); flow-rate, 0.5 ml min^{-1}; room temperature; injected volume, 20 μl; sample concentration, 2 mg ml^{-1}; detection wavelength, 205 nm.

a more efficient method for its resolution and developed a separation method based on SMB chromatography. Starting with 50 g of racemate **1**, we obtained, under optimized conditions and after 30 h, 24 g of (*S*)-**1**, with e.r.>99.5:0.5, and 21 g of (*R*)-**1**, with e.r.=95:5. The enantiopurity of (*R*)-**1** was further improved by recrystallization from ethyl acetate–hexane up to e.r.=99:1. Chromatogram B in Fig. 3 shows the enantiopurity of the enantiomers of **1** that was finally obtained.



Scheme 2. Determination of the absolute configuration of oxo-oxazolidine (*R*)-(−)-**1** via the bicyclic product **7** obtained after hydroxyalkylation.

We were then able to characterize the pure enantiomers as follows: (*S*)-(+)-**1**: e.r.=99.75:0.25, $[\alpha]_D^{RT}=+6.11$ ($c=1.02$, $CHCl_3$), m.p. 125.8–127.0°C; (*R*)-(−)-**1**: e.r.=99.5:0.5, $[\alpha]_D^{RT}=-5.47$ ($c=1.06$, $CHCl_3$), m.p. 126.2–127.8°C; all spectroscopic data were identical with those of *rac*-**1** given in Section 2 of this paper. In order to determine the absolute configurations of the enantiomers of **1**, the enolate of enantiopure oxo-oxazolidine **1** was allowed to react with pivalaldehyde to form the bicyclic product **7,** as shown in Scheme 2. The same product was obtained starting from the corresponding Z-protected oxo-oxazolidine of known absolute configuration [13]. Through a comparison of the signs of optical rotation of the obtained product, **7**, and based upon our previous knowledge concerning the reactivity of such compounds, the absolute configuration of **1** was assigned to be (*S*)-(+) and (*R*)-(−).

In Table 2, specific parameters of the recycling and SMB chromatography technique are compared. These results clearly show that the SMB chromatography leads to higher specific productivity, providing the desired enantiomers with better enantiomer ratios and generally requires less eluent than the recycling method.

*3.2. Resolution of oxo-imidazolidines rac-**5** and rac-**6***

From Scheme 1, it becomes evident that there are two possibilities for obtaining the chiral building blocks **2** and **3** in an enantiopure form using HPLC on CSPs: One option involves the resolution of oxo-imidazolidines *rac*-**5** and *rac*-**6** and, afterwards, a simple chemical modification in order to obtain the corresponding methylated derivatives **2** and **3** and the other consists of the direct separation of the enantiomers of the racemic dihydro-imidazoles **2** and **3**. The direct separation methodology is outlined in the Section 3.3, whereas the resolution of the oxo-imidazolidines *rac*-**5** and *rac*-**6** is presented below.

The chromatograms of the analytical separation of precursors **5** and **6** are shown in Fig. 3, chromatograms C and D, and the characteristic data are summarized in Table 1, entries 5 and 6.

In both cases, a baseline separation of the corresponding enantiomers could be achieved. The separation factors, α, indicate that a preparative res-

Table 2
Comparison between recycling and SMB chromatography used for the preparative resolution of oxo-oxazolidine *rac*-**1**

Parameter	Recycling chromatography	SMB chromatography
Mobile phase (v/v)	Isooctane–2-propanol (99:1)	heptane–CH_2Cl_2 (92:8)
Column dimensions	250×50 mm	131×26 mm
Number of columns	1	8
Amount of stationary phase	320 g	360 g
Particle size of stationary phase	25 μm	25 μm
Feed concentration (solvent)	250 mg ml^{-1} (CH_2Cl_2)	15 mg ml^{-1} (mobile phase)
Feed processed per hour	1.00 g	1.71 g
Eluent consumption per day	99.8 l	36.0 l
Enantiomer purity (*S*)-**1**	e.r.=92.5:7.5	e.r.>99.5:0.5
Enantiomer purity (*R*)-**1**	e.r.>99.5:0.5	e.r.>99.5:0.5
Yield	70%	99%
Eluent consumption per g of *rac*-**1**	4.16 l	0.9 l
Specific productivity (g enantiomer per day×kg CSP) of (*S*)-**1**	26.16	55.44
Specific productivity (g enantiomer per day×kg CSP) of (*R*)-**1**	26.16	55.44

olution of these oxo-imidazolidines should be easily achieved. Since, at that time, we already knew that the analytical separation of the enantiomers of chiral building blocks **2** and **3** was also possible, we did not further examine the scale-up of the resolution of **5** and **6** but focused on the one of **2** and **3** as described in Section 3.3.

Nevertheless, having the pure enantiomers of oxo-imidazolidines **5** and **6** at hand, we were able to characterize them as follows (the absolute configurations have been assigned previously [20–22]): (*R*)-(+)-**5**: e.r.>99.95:0.05, $[\alpha]_D^{RT}=+11.93$ ($c=0.86$, $CHCl_3$), m.p. 135.2–135.8°C; (*S*)-(−)-**5**: e.r.> 99.95:0.05, $[\alpha]_D^{RT}=-11.36$ ($c=0.94$, $CHCl_3$), m.p. 135.6–136.3°C; (*S*)-(−)-**6**: e.r.>99.95:0.05, $[\alpha]_D^{RT}=-12.36$ ($c=0.48$, $CHCl_3$), m.p. 180.0–180.5°C; (*R*)-(+)-**6**: e.r.>99.95:0.05, $[\alpha]_D^{RT}=+12.67$ ($c=0.90$, $CHCl_3$), m.p. 180.2–180.8°C; the corresponding spectroscopic data were identical with either those of *rac*-**5**, as given in the Section 2, or those of *rac*-**6**, as published in [18].

*3.3. Resolution of dihydro-imidazoles rac-**2** and rac-**3***

As already mentioned in Section 3.2., we were looking for a second, more direct route to obtain the chiral building blocks **2** and **3** in an enantiomerically pure form. We, therefore, first tested the resolution of the racemic dihydro-imidazoles *rac*-**2** and *rac*-**3** on an analytical scale. A baseline separation of compound *rac*-**2** was obtained on a cellulose-based CSP (Chiralcel-OD). The separation of the enantiomers of compound **3** was undertaken on two different columns; one amylose-based and one protein-bound.

The chromatograms of the analytical separations are shown in Fig. 4, chromatograms A–C, and the characteristic data are summarized in Table 1, entries 2–4.

The results obtained for the chiral building block **2** demonstrate that a preparative separation on Chiralcel-OD should be feasible. There was also a clear baseline separation in the resolutions of dihydro-imidazole *rac*-**3** on the amylose-based as well as on the protein-bound column. However, as far as a preparative separation on a large scale is concerned, the methodology using the amylose-based column is more efficient.

We characterized the pure enantiomers of dihydro-imidazole **2** as follows (the corresponding data for dihydro-imidazole **3** are published in [18], the absolute configurations have been assigned previously [20–22]): enantiopure **2** is an oil; (*S*)-(+)-**2**: e.r.> 99.95:0.05, $[\alpha]_D^{RT}=+13.83$ ($c=0.81$, $CHCl_3$); (*R*)-(−)-**2**: e.r.>99.95:0.05, $[\alpha]_D^{RT}=-11.98$ ($c=0.86$, $CHCl_3$); the corresponding spectroscopic data were identical with either those of *rac*-**2**, as given in Section 2, or those of *rac*-**3**, as published in [18].

The resolution of 125 mg of the dihydro-imidazole *rac*-**2** in a single run on a semi-preparative column is shown in Fig. 4, chromatogram D. There is almost a complete baseline separation of the two peaks such that, using a fully automated repetitive injection mode process, large quantities of both enantiomers of chiral building block **2** could be obtained in a reasonable period of time, starting from racemic material. The chromatographic data suggests that the preparative separation of **2** should be more efficient than that of **3**, which was carried out on a 60-g scale, as published in [18].

4. Conclusions

The results described here can be summarized as follows: We have, for the first time, reported on the preparation and on the analytical as well as the preparative separation of the enantiomers of oxo-oxazolidine *rac*-**1** using SMB chromatography on a 50-g scale. This demonstrates the versatility of a laboratory scale SMB unit allowing a fast separation of gram quantities of enantiopure compounds. An evaluation of the SMB technique for pharmaceutical process development has recently been published by Guest [24].

Furthermore, we have presented detailed experimental procedures for the synthesis of chiral building block *rac*-**2** and methods for the analytical resolution of the chiral glycine derivatives *rac*-**2** and *rac*-**3** and their precursors, *rac*-**5** and *rac*-**6**. The enantiomers of *rac*-**2** have also been separated on a semi-preparative scale and those of *rac*-**3** on a 60-g scale, as published in [18].

Looking at the chromatographic parameters of the different separations, it becomes obvious that, for every compound, a completely different approach

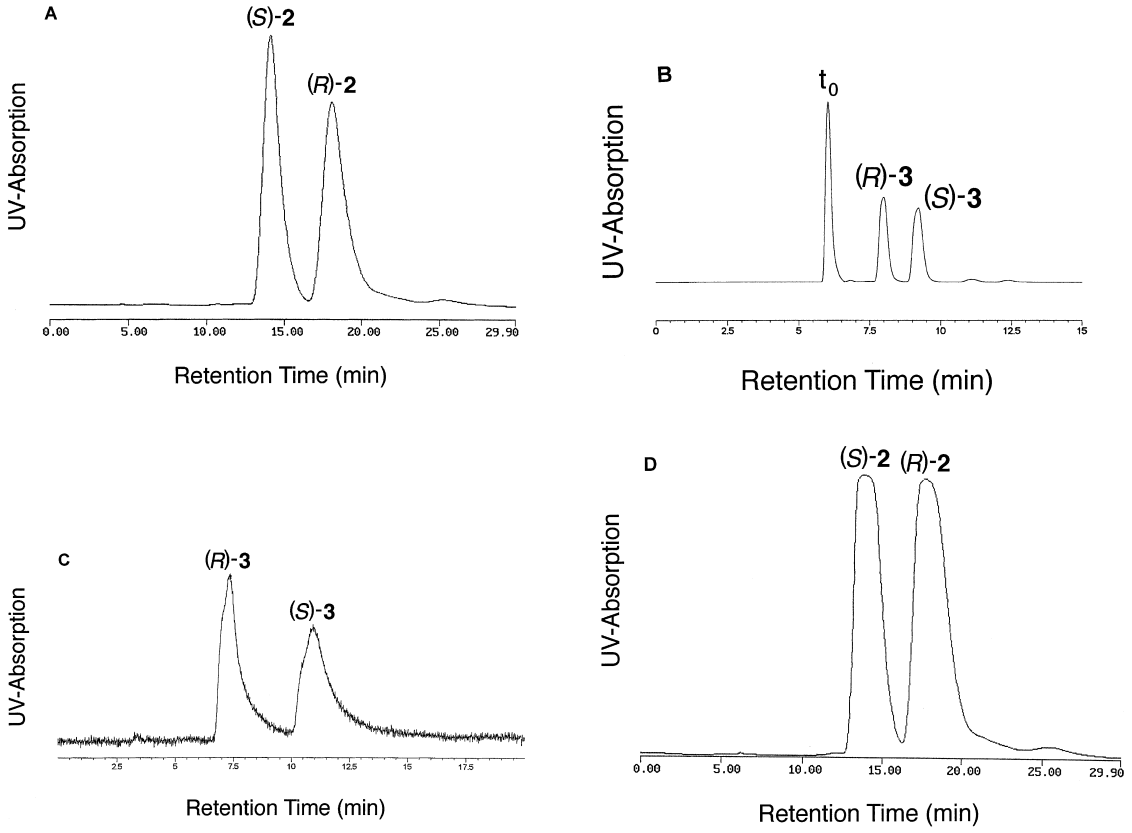


Fig. 4. Chromatograms of the analytical resolution of dihydro-imidazoles *rac*-**2** (A) and *rac*-**3** (B and C) and of the semi-preparative resolution of dihydro-imidazole *rac*-**2** (D). A: Analytical resolution of *rac*-benzyl 2-*tert*.-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylate (*rac*-**2**) on Chiralcel-OD. Column size, 250×4 mm I.D.; mobile phase, hexane–2-propanol (97.5:2.5, v:v); flow-rate, 0.5 ml min^{-1}; room temperature; injected volume, 20 μl; sample concentration, 1 mg ml^{-1}; detection wavelength, 205 nm. B: Analytical resolution of rac-*tert*.-butyl 2-*tert*.-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylate (*rac*-**3**) on Chiralpak-AD. Column size, 250×4 mm I.D.; mobile phase, hexane–2-propanol (97.5:2.5, v:v); flow-rate, 0.5 ml min^{-1}; room temperature; injected volume, 20 μl; sample concentration, 1 mg ml^{-1}; detection wavelength, 205 nm. C: Analytical resolution of *rac*-*tert*.-butyl 2-*tert*.-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylate (*rac*-**3**) on Ultron-OVM. Column size, 150×4 mm I.D.; mobile phase, 20 m*M* KH_2PO_4 (adjusted to pH 6.0)–acetonitrile (90:10, v:v); flow-rate, 0.5 ml min^{-1}; temperature, 40°C; injected volume, 5 μl; sample concentration, 0.3 mg ml^{-1}; detection wavelength, 205 nm. D: Semi-preparative resolution of *rac*-benzyl 2-*tert*.-butyl-4-methoxy-2,5-dihydro-imidazole-1-carboxylate (*rac*-**2**) on Chiralcel-OD. Column size, 230×40 mm I.D.; mobile phase, hexane–2-propanol (97.5:2.5, v:v); flow-rate, 25 ml min^{-1}; room temperature; injected volume, 2.5 ml; sample concentration, 50 mg ml^{-1}; detection wavelength, 210 nm.

towards its resolution must be developed. There is no single column that is capable of resolving all the chiral building blocks **1**–**3** and the oxo-imidazolidines **5** and **6**. The chromatographic behaviour of a compound with respect to that of a very similar compound is not predictable and the quest for a resolution method using HPLC on a CSP is therefore challenging in every case.

The use of the new building blocks for amino acid syntheses has been described in two Ph.D. theses [25,26] and will be the subject of full papers to be published shortly in J. Org. Chem. and Liebigs Ann./ Recueil.

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