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High-performance liquid chromatographic separation of enantiomers of cyclic 1,3-amino alcohol derivatives

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Abstract

Different high-performance liquid chromatographic methods were developed for the separation and identification of enantiomers of racemic *cis*- and *trans*-2-aminocyclohexane-1-methanol and *cis*- and *trans*-2-amino-4-cyclohexene-1-methanol derivatives. Direct separation was carried out on a cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD) stationary phase, which allowed the simultaneous separation of enantiomers of alcohol and ester analogues of the amino alcohols. Derivatization of amino alcohols with 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide produced diastereomers which were separable with high resolution (R_s>5), whereas derivatives with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate coeluted. The absolute configurations and elution sequences of the enantiomers were determined by both methods. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Enantiomer separation; 2-Aminocyclohexane-1-methanol; 2-Amino-4-cyclohexene-1-methanol; Cyclic amino alcohols

1. Introduction

Cyclic 1,3-amino alcohols with two adjacent stereogenic centres (Fig. 1; 1a–4a) are important compounds from both synthetic and pharmaceutical aspects. Quaternary ammonium salts of (+)-1a and (−)-1a are used as chiral phase-transfer catalysts for enantioselective alkylation of compounds possessing an active methylene group [1]. (+)-2a is an intermediate in the stereoselective synthesis of an orally active angiotensin converting enzyme inhibitor [2] and also in the synthesis of a novel chiral super-Lewis acid catalyst [3]. *N*-Benzyl derivatives of optically active (+)-1a, (−)-1a, (+)-2a and (−)-2a are used as agents for the resolution of racemic carboxylic acids [4]. Enantiomers of 1–4 can serve as building blocks of pharmacologically active fused saturated 1,3-heterocycles [5,6]. One possible way to prepare these amino alcohols in highly enantiomerically pure form is enzymatic resolution [7].

The present paper describes different high-performance liquid chromatographic (HPLC) methods suitable for separation and identification of the enantiomers of racemic 1–4, and determination of the absolute configurations. Direct separation was carried out on a cellulose phenylcarbamate stationary

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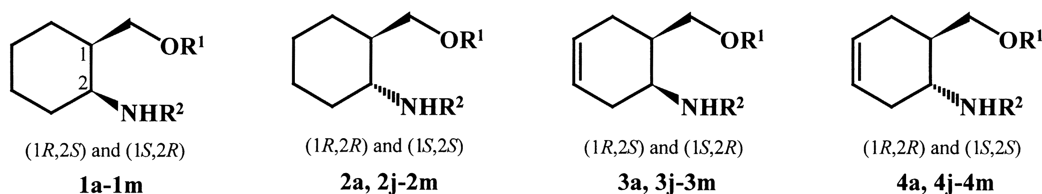

	a	b	c	d	e	f	g	h	i	j	k	m
R^1	H	H	COMe	H	COMe	COPr	H	COMe	COPr	H	COMe	COPr
R^2	H	COMe	COMe	COPr	COPr	COPr	Boc	Boc	Boc	Z	Z	Z

Boc=COO*t*Bu, Z=$COOCH_2Ph$

Fig. 1. Structures of 2-aminocyclohexane-1-methanol and 2-amino-4-cyclohexene-1-methanol derivatives. 1a–1m (1*R*,2*S*)- and (1*S*,2*R*)-2-aminocyclohexane-1-methanol derivatives, 2a, 2j–2m (1*R*,2*R*)- and (1*S*,2*S*)-2-aminocyclohexane-1-methanol derivatives, 3a, 3j–3m (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-4-cyclohexene-1-methanol derivatives, 4a, 4j–4m (1*R*,2*R*)- and (1*S*,2*S*)-2-amino-4-cyclohexene-1-methanol derivatives.

phase (Chiralcel OD), and indirect separations were performed on achiral phases after precolumn derivatization with chiral reagents: 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA, Marfey's reagent) or 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC or TAGIT). The developed methods were useful for monitoring the enzymatic resolutions of 1,3-amino alcohols.

2. Experimental

2.1. Chemicals and reagents

The racemic starting amino alcohols 1a–4a (Fig. 1) were obtained from the corresponding β-amino acid esters by reduction with $LiAlH_4$ [8,9]. Derivatives of amino alcohols were synthetized by standard methods. In order to establish the absolute configurations of enantiomers, homochiral 1,3-amino alcohols [(1*R*,2*S*)-1a, (1*S*,2*S*)-2a, (1*R*,2*S*)-3a and (1*S*,2*S*)-4a] were prepared from the corresponding homochiral β-amino acid esters [10] by $LiAlH_4$ reduction, and used as standards after appropriate derivatization [7].

FDAA and GITC were purchased from Fluka BioChemika (Buchs, Switzerland), methanol and acetonitrile of HPLC grade were from Merck (Darmstadt, Germany), *n*-hexane, dichloromethane and 2-propanol of HPLC grade were from Lab–Scan (Dublin, Ireland), and Milli-Q water was from Milli-Q Plus apparatus (Millipore Corporation, Bedford, MA, USA).

2.2. Apparatus

The HPLC system consisted of a Kontron 422 isocratic pump equipped with a Kontron 4.22 data system and a Melz LCD 312 refractive index detector (Beun De Ronde Serlabo, Anderlecht, Belgium), an M-600 low-pressure gradient pump equipped with an M-486 tunable absorbance detector (Waters Chromatography, Milford, MA, USA) and an HP 3395 integrator (Hewlett–Packard, Waldbronn, Germany). Injectors with a 10 μl loop were from Rheodyne (Cotati, USA).

The column used for direct separations was Chiralcel OD 250×4.6 mm I.D., 5 μm particle size (Daicel Chemical Industries, Ltd., Tokyo, Japan), while for achiral analyses APEX ODS 250×4.6 mm I.D., 5 μm particle size, and APEX silica 250×4.6 mm I.D., 5 μm particle size (Jones Chromatography Ltd., Hengoed, UK) columns were used.

2.3. Sample preparation and derivatization procedure

For direct separations, 5 $mg\,ml^{-1}$ solutions of amino alcohols were prepared in the eluent. For precolumn derivatizations, the corresponding derivatives were prepared with GITC for reversed-phase

analyses by the method of Nimura et al. [11], and for normal-phase analyses by the method of Olsen [12]. FDAA derivatives were made by the method of Marfey [13] and were analysed in reversed-phase mode. In the latter case, the racemic compounds were dissolved in an acetonitrile–water 1:1 mixture instead of pure water because of the poor solubility of amino alcohols in water.

3. Results and discussion

3.1. Direct separation

Direct analyses were performed on a cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD) column. Regarding the mechanism of chiral discrimination, the most important docking sites on these types of columns are considered to be the polar carbamate groups, which can interact with enantiomers via H-bonding and/or dipole–dipole interaction [14]. Nevertheless, the chiral recognition mechanism at a molecular level is still not obvious [15].

Firstly, different derivatives of racemic *cis*-2-aminocyclohexane-1-methanol (1a–1m) were tested and separated on this chiral polymer stationary phase, with 2-propanol in *n*-hexane as the mobile phase. Results are listed in Table 1. Increase of the 2-propanol concentration in the mobile phase decreased the retention (e.g. 1j), and the column behaved as a real normal-phase column. The retention factors (k) of alcohols were always higher than those of the corresponding esters (1b>1c; 1d>1e>1f; 1g>1h>1i; 1j>1k>1m), and a decrease in retention was observed when the bulk of the R^1 group was increased. As concerns the retention mechanism, in the case of alcohols, the dominating H-bond can be formed between the OH proton of the analyte and the carbonyl oxygen of the cellulose phenylcarbamate, while the carbonyl oxygen of the ester function may interact with the NH proton of the carbamate residue through H-bonding (Fig. 2) [14]. However, due to the electron-donating character of the methyl substituents on the phenyl groups of the stationary phase, the acidity of the NH proton decreases, while the electron density on the carbonyl

Table 1
Retention factors (k), separation factors (α) and resolutions (R_s) of derivatives of racemic *cis*-2-aminocyclohexane-1-methanol (1a–1m)

	R^1	R^2	Eluent[a]	k_1	k_2	α	R_s
1a	H	H	90:10	0.65	0.65	1	0
			95:5	1.41	1.41	1	0
1b	H	COMe	90:10	2.01	2.33	1.16	1.57
1c	COMe	COMe	90:10	1.64	1.86	1.13	1.24
			95:5	3.81	4.23	1.11	1.32
1d	H	COPr	90:10	1.19	1.29	1.08	0.68
			95:5	3.40	3.59	1.06	0.69
			[b]95:5	1.59	1.59	1	0
1e	COMe	COPr	95:5	2.40	2.84	1.18	2.23
			[b]95:5	1.36	1.36	1	0
1f	COPr	COPr	90:10	0.83	1.01	1.22	2.00
1g	H	Boc	95:5	0.85	0.92	1.08	0.72
			97:3	1.31	1.41	1.08	0.68
1h	COMe	Boc	97:3	0.81	0.96	1.19	1.70
1i	COPr	Boc	97:3	0.57	0.72	1.26	2.00
1j	H	Z	90:10	2.36	2.55	1.08	0.92
			93:7	3.49	3.72	1.07	0.89
			95:5	5.16	5.94	1.15	2.05
			97:3	8.58	9.97	1.16	2.24
1k	COMe	Z	95:5	2.98	4.56	1.53	6.94
1m	COPr	Z	95:5	2.06	3.86	1.87	7.65

Column, Chiralcel OD; flow-rate, 0.9 ml min^{-1}; detection, refractive index.
[a] *n*-hexane–2-propanol.
[b] *n*-hexane–ethanol.

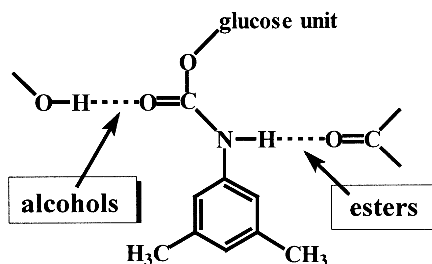

Fig. 2. Presumed interactions on cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD) stationary phase.

oxygen of the carbamates is expected to increase [16]. Accordingly, the H-bond can be weaker in its interactions with esters than in those with alcohols, and therefore the latter can be more strongly retained. Our results support these expectations; the discussed effects contributed to the observed difference in retention, i.e. the alcohols are more strongly retained, whereas the esters are less so.

The use of ethanol instead of 2-propanol as alcohol modifier in the mobile phase in the case of 1d and 1e resulted in shorter retentions and coelution of the enantiomers, which indicates the solvent-dependence of retention and resolution.

For compounds possessing the same R^1 group and different R^2 groups (R^1=H: 1a,b,d,g,j; R^1=COMe: 1c,e,h,k; R^1=COPr: 1f,i,m), the significantly higher *k* values of the Z derivatives are obvious. This shows the possible role in the retention mechanism of $\pi-\pi$ interactions between the phenyl groups on the column and the aromatic groups of the solute [16].

The results presented in Table 2 relate to different Z derivatives of the investigated amino alcohols (Fig. 1; 1j,k,m–4j,k,m). In accordance with the data obtained for racemic *cis*-2-aminocyclohexane-1-methanol derivatives (Table 1), longer retention times were observed for the alcohols (k_{III} and k_{IV}) than for the corresponding esters (k_I and k_{II} of acetates or butyrates). However, the ester analogues were consistently better resolved than the alcohols ($R_{s;I,II}>R_{s;III,IV}$). The only exception was R_s for 3k, $R_{s;I,II}$=3.33, which was very similar to R_s for the alcohol 3j, $R_{s;III,IV}$=3.67.

Racemic 1j–4j were also found to be appropriate

Table 2
Retention factors (*k*), separation factors (α) and resolutions (R_s) of derivatives of racemic *cis*- and *trans*-2-aminocyclohexane-1-methanol and *cis*- and *trans*-2-amino-4-cyclohexene-1-methanol (1j,k,m–4j,k,m; R^2=Z)

Compound	R^1	k_I	k_{II}	k_{III}	k_{IV}	$\alpha_{I,II}$	$\alpha_{II,III}$	$\alpha_{III,IV}$	$R_{s;I,II}$	$R_{s;II,III}$	$R_{s;III,IV}$
		(1*S*,2*R*)[a]	(1*R*,2*S*)[a]	(1*R*,2*S*)[b]	(1*S*,2*R*)[b]						
1j	H	–	–	5.16	5.94	–	–	1.15	–	–	2.05
1k	COMe	2.98	4.56	–	–	1.53	1.13	–	6.94	1.94	–
1m	COPr	2.06	3.86	–	–	1.87	1.34	–	7.65	3.89	–
		(1*R*,2*R*)[a]	(1*S*,2*S*)[a]	(1*R*,2*R*)[b]	(1*S*,2*S*)[b]						
2j	H	–	–	7.22	7.72	–	–	1.07	–	–	1.17
2k	COMe	3.52	6.64	–	–	1.89	1.09	–	10.37	1.48	–
2m	COPr	3.17	5.39	–	–	1.70	2.28	–	6.86	5.28	–
		(1*S*,2*R*)[a]	(1*R*,2*S*)[a]	(1*R*,2*S*)[b]	(1*S*,2*R*)[b]						
3j	H	–	–	4.09	5.11	–	–	1.25	–	–	3.67
3k	COMe	3.17	3.86	–	–	1.22	1.06	–	3.33	1.31	–
3m	COPr	2.15	2.94	–	–	1.37	1.39	–	4.47	5.32	–
		(1*R*,2*R*)[a]	(1*S*,2*S*)[a]	(1*S*,2*S*)[b]	(1*R*,2*R*)[b]						
4j	H	–	–	8.98	9.99	–	–	1.11	–	–	1.68
4k	COMe	5.11	8.72	–	–	1.71	1.03	–	7.80	0.47	–
4m	COPr	3.91	6.31	–	–	1.61	1.42	–	6.75	5.38	–

Column, Chiralcel OD; flow-rate, 0.9 ml min^{-1}; eluent, *n*-hexane–2-propanol=95:5, detection, refractive index.
[a] and [b] refers to stereogenic centres in esters or in alcohols, respectively.
k_I: retention factor of the first-eluting ester enantiomer, k_{II}: retention factor of the second ester enantiomer, k_{III}: retention factor of the first-eluting alcohol enantiomer, k_{IV}: retention factor of the second alcohol enantiomer; $\alpha_{I,II}$ and $R_{s;I,II}$: separation factor and resolution of ester enantiomers; $\alpha_{II,III}$ and $R_{s;II,III}$: separation factor and resolution of the second ester and the first alcohol enantiomers; $\alpha_{III,IV}$ and $R_{s;III,IV}$: separation factor and resolution of alcohol enantiomers.

starting substrates for enzymatic resolution with high selectivity [7]. Lipase-catalysed *O*-acylation of these Z derivatives produces four possible derivatives in the reaction mixture at the same time: two alcohol enantiomers (1j–4j) and two ester enantiomers (1m–4m or 1k–4k). Table 2 reveals that on the Chiralcel OD column these enantiomers were separable in a single chromatographic run, thus offering a very convenient method for monitoring both conversion and enantioselectivity of an enzymatic resolution at the same time.

The sequence of elution of the enantiomers is indicated on the chromatograms in Fig. 3; it was determined by the addition of standards. In spite of the stereogenic centres in the alcohols and esters having the same configurations, for the *cis* isomers the sequence of elution for 1m and 3m (1*S*,2*R*)>(1*R*,2*S*) was the reverse of that for 1j and 3j (1*R*,2*S*)>(1*S*,2*R*). For the unsaturated *trans* isomers, the elution sequence changed from (1*R*,2*R*)>(1*S*,2*S*) for the butyrate analogues (4m) to (1*S*,2*S*)>(1*R*,2*R*) for the alcohol analogues (4j). As discussed above, the H-bonds formed between the enantiomers and the stationary phase differ for the alcohols and the esters. The change in the discrimination mechanism might be responsible for a reversal of the elution sequence. However, there was no change in the elution sequence for the saturated *trans* isomers: (1*R*,2*R*)>(1*S*,2*S*) for both ester (2m) and alcohol (2j) analogues. The above elution sequences were also valid

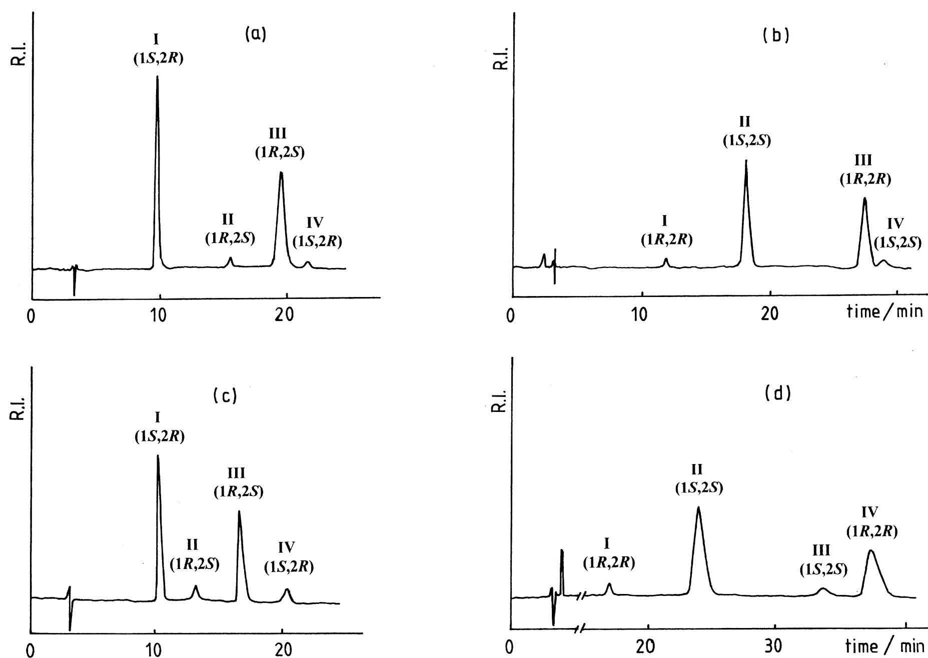

Fig. 3. Chromatograms and elution sequences of the enantiomers of the Z derivatives of racemic 2-aminocyclohexane-1-methanols, 2-amino-4-cyclohexene-1-methanols and their butyrate analogues. Column, Chiralcel OD; flow-rate, 0.9 ml min^{-1}; detection, refractive index; mobile phase, *n*-hexane–2-propanol 95:5. (a) I (1*S*,2*R*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol butyrate [(−)-1m], II (1*R*,2*S*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol butyrate [(+)-1m], III (1*R*,2*S*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol [(+)-1j], IV (1*S*,2*R*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol [(−)-1j]; (b) I (1*R*,2*R*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol butyrate [(−)-2m], II (1*S*,2*S*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol butyrate [(+)-2m], III (1*R*,2*R*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol [(−)-2j], IV (1*S*,2*S*)-2-(benzyloxycarbonylamino)cyclohexane-1-methanol [(+)-2j]; (c) I (1*S*,2*R*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol butyrate [(−)-3m], II (1*R*,2*S*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol butyrate [(+)-3m], III (1*R*,2*S*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol [(−)-3j], IV (1*S*,2*R*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol [(+)-3j]; (d) I (1*R*,2*R*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol butyrate [(−)-4m], II (1*S*,2*S*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol butyrate [(+)-4m], III (1*S*,2*S*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol [(+)-4j], IV (1*R*,2*R*)-2-(benzyloxycarbonylamino)-4-cyclohexene-1-methanol [(−)-4j].

for the acetates (1k–4k) (Table 2). These observations clearly indicate that the retention mechanism for amino alcohol derivatives on this column is complex and influenced by many factors and there appears to be no simple general rule for prediction of the elution sequence, particularly for compounds possessing more than one stereogenic centre.

3.2. Indirect separation

The enantiomers of the racemic 1,3-amino alcohols 1a–4a were additionally separated after precolumn derivatization with a chiral reagent.

With GITC as derivatizing agent, no discrimination occurred during the elution of the diastereomers formed. An attempt was made to separate GITC derivatives on a reversed-phase column and on a normal-phase column, but the result was total coelution in either aqueous (methanol, acetonitrile or tetrahydrofuran in water) or organic (dichloromethane or 2-propanol in *n*-hexane) eluent systems.

In the case of FDAA, very high resolutions ($R_s>5$) were achieved, as indicated in Table 3. These derivatives do not contain any ionizable group, and it was therefore not necessary to use buffers in the eluent: the peak shapes were adequate in water. At almost the same eluent strength, the resolution was in all cases higher in the methanol-containing system than in the acetonitrile-containing mobile phase, especially for the saturated amino alcohols. These observations are in agreement with our earlier results on unusual amino acids [17,18].

The sequence of elution of the diastereomers was determined by standard addition, and was found to be (1*R*,2*S*)>(1*S*,2*R*) for the *cis* isomers and (1*S*,2*S*)>(1*R*,2*R*) for the *trans* isomers. The amino group attached to stereogenic centre C(2) takes part in the derivatization reaction. The configuration of C(2) in the first-eluting diastereomer was 2*S* in every case. This follows the rule relating to the sequence of elution of FDAA derivatives in general [19].

4. Conclusions

High-performance liquid chromatographic methods were developed for the separation of enantiomers of racemic 1,3-amino alcohol derivatives. Direct separations were performed on a cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD) stationary phase. The column is suitable for the separation of enantiomers of 1,3-amino alcohol derivatives. The separation process permits a simple and rapid check of selectivity for enzymatic resolutions. Indirect

Table 3
Retention factors (k), separation factors (α) and resolutions (R_s) of FDAA derivatives of racemic *cis*- and *trans*-2-aminocyclohexane-1-methanol and *cis*- and *trans*-2-amino-4-cyclohexene-1-methanol 1a–4a

Compound	Eluent composition	k_1	k_2	α	R_s
		(1*R*,2*S*)[a]	(1*S*,2*R*)[a]		
	H_2O–MeOH=40:60	2.55	6.74	2.64	9.09
1a	H_2O–MeCN=60:40	2.29	4.00	1.75	7.22
	H_2O–MeCN=65:35	4.18	8.03	1.92	11.45
		(1*S*,2*S*)[a]	(1*R*,2*R*)[a]		
2a	H_2O–MeOH=40:60	2.00	5.79	2.90	10.47
	H_2O–MeCN=60:40	2.05	3.82	1.86	6.09
		(1*R*,2*S*)[a]	(1*S*,2*R*)[a]		
	H_2O–MeOH=40:60	2.21	4.58	2.07	5.54
3a	H_2O–MeCN=60:40	2.05	3.08	1.50	4.11
	H_2O–MeCN=65:35	3.68	5.97	1.62	6.82
		(1*S*,2*S*)[a]	(1*R*,2*R*)[a]		
4a	H_2O–MeOH=40:60	2.26	4.42	1.96	5.21
	H_2O–MeCN=60:40	2.24	3.32	1.48	4.56

Column, APEX ODS; flow-rate, 0.8 ml min^{-1}; detection, 340 nm.
[a]Refers to the stereogenic centres of amino alcohols 1a–4a in FDAA derivatives.

separation involving precolumn derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide permitted the differentiation of 1,3-amino alcohol enantiomers with high resolution. In combination with the addition of standards, both direct and indirect methods can be used to identify absolute configurations and hence to determine enzyme selectivity.

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