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High-performance liquid chromatographic enantioseparation of 2-aminomono- and dihydroxycyclopentanecarboxylic and 2-aminodihydroxycyclohexanecarboxylic acids on macrocyclic glycopeptide-based phases

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ABSTRACT

The direct separation of the enantiomers of four 2-aminomono- or dihydroxycyclopentanecarboxylic acids and four 2-aminodihydroxycyclohexanecarboxylic acids was performed on chiral stationary phases containing macrocyclic glycopeptide antibiotics such as teicoplanin (Astec Chirobiotic T and T2), teicoplanin aglycone (Chirobiotic TAG) or ristocetin A (Chirobiotic R) as chiral selectors. The effects of the nature of organic modifiers, the pH, the mobile phase composition and the structures of the analytes on the separation were investigated. Chirobiotic TAG, and in some cases Chirobiotic T, proved to be the most useful of these columns. The elution sequence was determined in most cases.

1. Introduction

β-Amino acids are key building blocks of numerous bioactive molecules [1]. These compounds are to be found in a large number of natural products, β-lactams and antibiotics, some of which, *e.g.* cispentacin, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid, exhibit antifungal activity [2–4]. They can be introduced into peptides in order to modify and increase their biological activities [5]. The hydroxy-functionalized β-amino acids play important roles in medicinal chemistry because of their occurrence in many biologically relevant compounds, such as paclitaxel (Taxol, Bristol Myers Squibb, New York, USA) and docetaxel (Taxotere, Sanofi-aventis, Paris, France), which have chemotherapeutic effects [6–8]. Some cyclic hydroxylated β-amino acid derivatives, *e.g.* oryzoxymycin have antibiotic or antifungal activities [9–12].

The enantioselective syntheses [13,14] requires analytical methods as a check on the enantiopurity of the final products. Few papers deal with the chromatographic enantioseparation of alicyclic β-amino acids. In the past decade, our group has examined the high-performance liquid chromatographic (HPLC) enantioseparations of alicyclic-β-amino acids by using either chiral derivatizing agents [15–17] or chiral stationary phases (CSPs) [18,19].

The aim of the present work was to investigate the effectiveness of different macrocyclic glycopeptide-based CSPs for the separation of 2-aminomono- or dihydroxycycloalkanecarboxylic acids. The influence of the pH, the mobile phase composition, the nature of the alcoholic modifier and the specific structural features of the

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analytes and selectors on the retention are discussed. The elution sequence was determined in most cases.

2. Experimental

2.1. Materials and methods

Racemic *cis*- and *trans*-2-amino-3-hydroxycyclopentanecarboxylic acid (**1** and **2**; Fig. 1) were prepared from ethyl *cis*- and *trans*-2-acetylaminocyclopent-3-enecarboxylate, which were transformed to ethyl (3a*R**,4*R**,6*R**,6a*R**)-6-bromo-2-methyl-4,5,6,6a-tetrahydro-3aH-cyclopentaoxazole-4-carboxylate and ethyl (3a*R**,4*S**,6a*S**)-2-methyl-4,5,6,6a-tetrahydro-3aH-cyclopentaoxazole-4-carboxylate with *N*-bromosuccinimide, and then converted by selective reduction of the halogen group and subsequent hydrolysis to the desired product [20].

Racemic (1*R**,2*R**,3*S**,4*R**)-2-amino-3,4-dihydroxycyclopentanecarboxylic acid (**3**) was synthetized by the oxidation of ethyl-

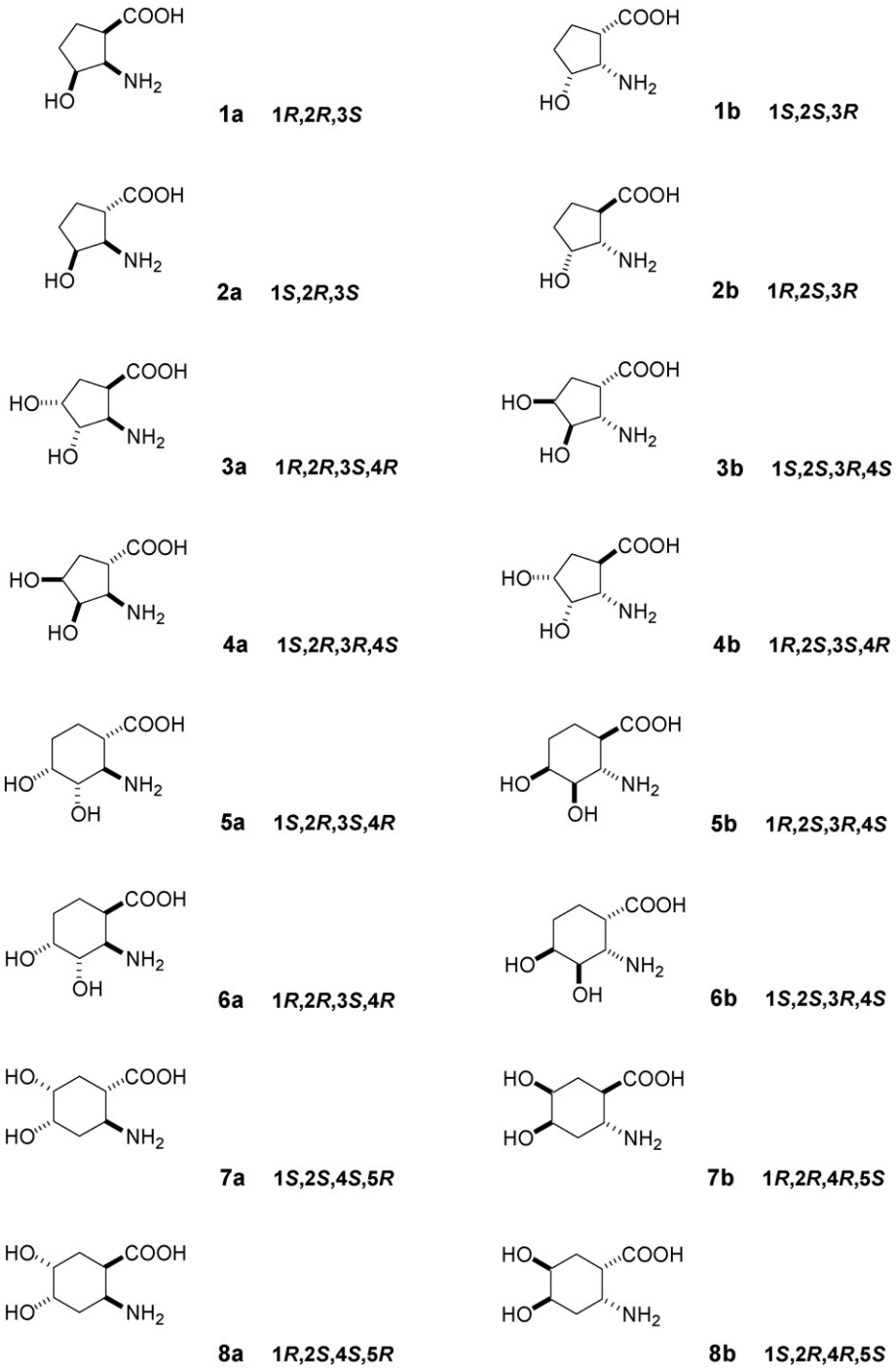

Fig. 1. Structures of analytes: **1a** (1*R*,2*R*,3*S*)- and **1b** (1*S*,2*S*,3*R*)-2-amino-3-hydroxycyclopentane carboxylic acid; **2a** (1*S*,2*R*,3*S*)- and **2b** (1*R*,2*S*,3*R*)-2-amino-3-hydroxycyclopentane carboxylic acid; **3a** (1*R*,2*R*,3*S*,4*R*)- and **3b** (1*S*,2*S*,3*R*,4*S*)-2-amino-3,4-dihydroxycyclopentane carboxylic acid; **4a** (1*S*,2*R*,3*R*,4*S*)- and **4b** (1*R*,2*S*,3*S*,4*R*)-2-amino-3,4-dihydroxycyclopentane carboxylic acid; **5a** (1*S*,2*R*,3*S*,4*R*)- and **5b** (1*R*,2*S*,3*R*,4*S*)-2-amino-3,4-dihydroxycyclohexane carboxylic acid; **6a** (1*R*,2*R*,3*S*,4*R*)- and **6b** (1*S*,2*S*,3*R*,4*S*)-2-amino-3,4-dihydroxycyclohexane carboxylic acid; **7a**, (1*S*,2*S*,4*S*,5*R*)- and **7b** (1*R*,2*R*,4*R*,5*S*)-2-amino-4,5-dihydroxycyclohexane carboxylic acid; **8a** (1*R*,2*S*,4*S*,5*R*)- and **8b** (1*R*,2*R*,4*R*,5*S*)-2-amino-4,5-dihydroxycyclohexane carboxylic acid.

cis-2-*tert*-butoxycarbonylaminocyclopent-3-enecarboxylate with a catalytic amount of OsO_4 and 4-methylmorpholine *N*-oxide as the stoichiometric co-oxidant, which selectively afforded the expected product. The other dihydroxy compounds, *e.g.* cyclopentane **4** and cyclohexane **5**–**8** derivatives, were prepared according to the method described for **3** [20]. For the enantiomers, the same synthesis route was followed as for the racemic compounds [20].

Methanol (MeOH) of HPLC grade was purchased from Scharlau (Sentmenat, Spain). Triethylamine (TEA), glacial acetic acid (AcOH), ethanol (EtOH), *n*-propanol (PrOH), 2-propanol (IPA) and other reagents of analytical reagent grade were from Sigma–Aldrich (St. Louis, MO, USA). The Milli-Q water was further purified by filtration on a 0.45-μm filter, type HV, Millipore (Molsheim, France).

Most of the separations were performed with mobile phases of 0.1% aqueous triethylammonium acetate (TEAA, pH 4.1)/MeOH = 20/80 (v/v) and 0.1% TEAA (pH 4.1)/EtOH = 20/80 (v/v) on the four different Chirobiotic columns at 25 °C using Spark Mistral column thermostat (Spark Holland, Emmen, The Netherlands).

2.2. Apparatus

The HPLC separations were carried out on a Waters HPLC system consisting of an M-600 low-pressure gradient pump, an M-996 photodiode-array detector and a Millenium^{32} Chromatography Manager data system (Waters Chromatography, Milford, MA, USA) equipped with Rheodyne Model 7125 injector (Cotati, CA, USA) with 20 μL loop.

The macrocyclic glycopeptide-based stationary phases used for analytical separation were teicoplanin-containing Chirobiotic T and T2, teicoplanin aglycone-containing Chirobiotic TAG or ristocetin A-containing Chirobiotic R columns, 250 mm × 4.6 mm I.D., 5-μm (for each column) (Astec, Whippany, NJ, USA). Chirobiotic T and T2 are both based on silica gel with a 5 μm, but the Chirobiotic T material has a 120-Å pore size and the Chirobiotic T2 material has a 200-Å pore size. Moreover, the linkage chain in Chirobiotic T2 is approximately twice as long as that in Chirobiotic T. Hence, the coverage and spacing will be different for the two. This will manifest itself mainly in the form of steric interaction differences between the two columns.

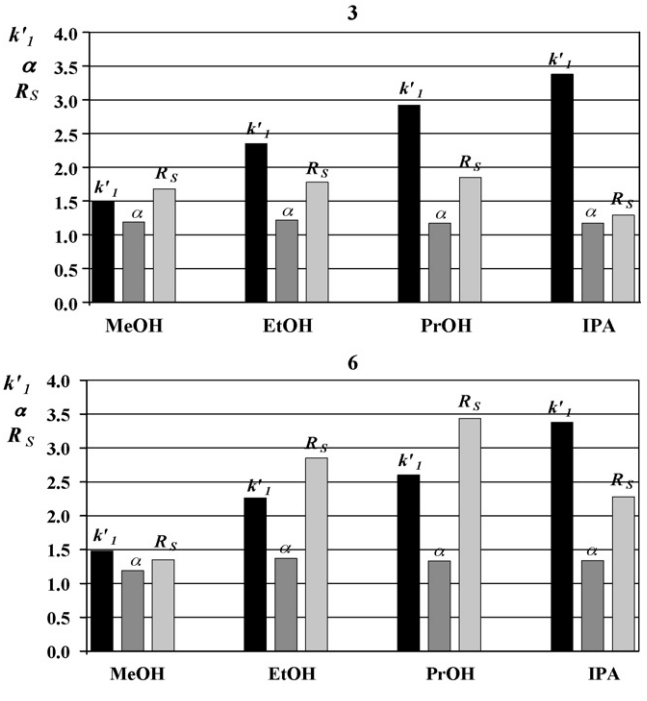

Fig. 2. Effects of the nature of the alcoholic modifier on the retention factor of the first-eluting enantiomer (k'_1), the separation factor (α) and the resolution (R_S) for analytes **3** and **6** on the Chirobiotic T2 column. Chromatographic conditions: mobile phase, 0.1% TEAA (pH 4.1)/alcoholic modifier = 20/80 (v/v); alcoholic modifiers, MeOH, EtOH, PrOH and IPA; flow rate, 0.5 mL min^{-1}; detection, 205 nm.

3. Results and discussion

The experimental conditions, including the pH of the mobile phase, the buffer type and concentration, and the nature of the organic modifier, were investigated in the course of the separation process. The analytes in this study (Fig. 1) possess either a cyclopentane or a cyclohexane skeleton. Besides carboxy and primary amino groups, analogs **1** and **2** bear one hydroxy group, while analytes **3**–**8** possess two hydroxy groups This distinction results in different steric effects and hydrogen bonding, and influences the hydrophobicity, bulkiness and rigidity of the molecules.

3.1. Effect of pH

A decrease in the pH of the 0.1% aqueous TEAA (pH 4.1)/EtOH = 20/80 (v/v) eluent system from 6.52 to 3.00 considerably increased the retention factors of analytes **3** and **6** on Chirobiotic T2, while the selectivity and resolution decreased. Similar results were obtained by Armstrong et al. [21] on a teicoplanin CSP for analytes with free carboxylic acid groups. The pH that produced the highest α also yielded the best resolution. The discontinuities in k', α and R_S at low pH are most probably due to the protonation of the teicoplanin CSP and analyte. Protonation of teicoplanin either directly affects the charge–charge or dipolar interactions between the analyte and CSP, or indirectly

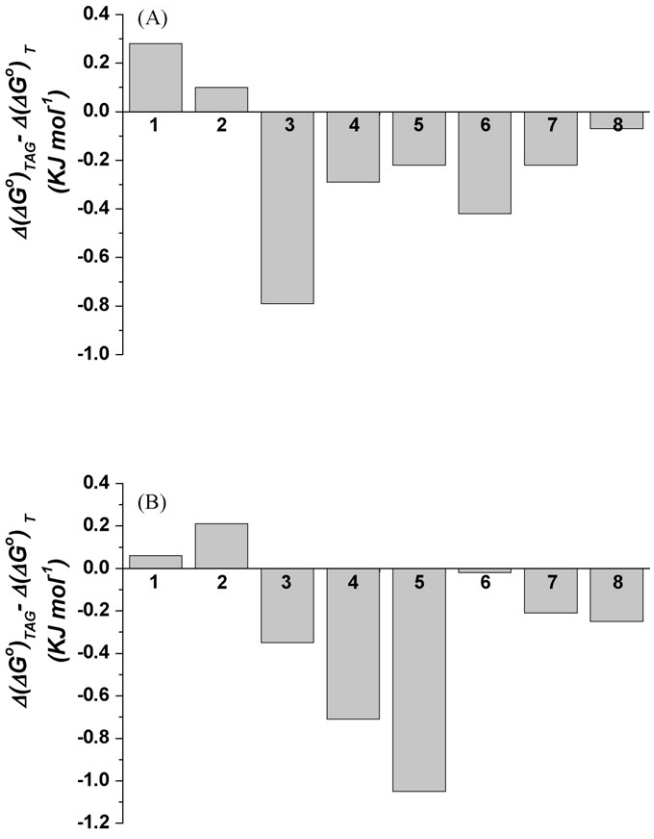

Fig. 3. Enantioselectivity free energy differences, $\Delta(\Delta G^\circ)_{TAG} - \Delta(\Delta G^\circ)_T$, between aglycone and native teicoplanin CSPs. Chromatographic conditions: mobile phase, **A**, 0.1% TEAA (pH 4.1)/MeOH = 20/80 (v/v), **B**, 0.1% TEAA (pH 4.1)/EtOH = 20/80 (v/v); flow rate, 0.5 mL min^{-1}; detection, 205 nm.

Table 1
Chromatographic data, retention factor (k'), separation factor (α) and resolution (R_S) for alicyclic mono- and dihydroxyamino acids on macrocyclic glycopeptide-based CSPs with variation of the type of the organic modifier.

Compound	Column	Mobile phase	k'_1	k'_2	α	R_S
1	T	**a**	2.73	3.21	1.18	1.65
	T	**b**	4.22	5.20	1.23	2.10
	T2	**a**	2.39	2.75	1.15	1.60
	T2	**b**	4.00	4.68	1.17	1.35
	TAG	**a**	5.11	5.38	1.05	0.40
	TAG	**b**	7.61	9.17	1.20	0.80
	R	**a**	1.92	2.11	1.10	1.40
	R	**b**	n.d.	n.d.	n.d.	n.d.
2	T	**a**	3.56	3.70	1.04	0.50
	T	**b**	3.72	4.05	1.09	1.15
	T2	**a**	2.61	2.74	1.05	0.50
	T2	**b**	3.59	3.87	1.08	0.60
	TAG	**a**	5.09	5.09	1.00	0.00
	TAG	**b**	6.95	6.95	1.00	0.00
	R	**a**	1.97	1.97	1.00	0.00
	R	**b**	3.14	3.21	1.02	0.40
3	T	**a**	2.43	2.74	1.13	1.70
	T	**b**	3.47	3.88	1.12	1.30
	T2	**a**	1.76	2.14	1.22	1.80
	T2	**b**	2.90	3.57	1.23	1.20
	TAG	**a**	3.26	5.04	1.55	3.95
	TAG	**b**	4.55	5.87	1.29	2.45
	R	**a**	1.81	1.93	1.06	0.65
	R	**b**	2.99	3.26	1.09	0.80
4	T	**a**	2.96	3.36	1.14	1.75
	T	**b**	3.89	4.81	1.24	2.50
	T2	**a**	2.76	2.98	1.08	1.05
	T2	**b**	3.77	4.53	1.20	1.70
	TAG	**a**	4.66	5.96	1.28	2.90
	TAG	**b**	5.67	9.33	1.65	2.95
	R	**a**	2.11	2.11	1.00	0.00
	R	**b**	3.60	3.60	1.00	0.00
5	T	**a**	2.13	2.48	1.17	1.90
	T	**b**	2.97	4.07	1.37	3.20
	T2	**a**	1.61	1.86	1.15	1.40
	T2	**b**	2.43	3.35	1.38	2.90
	TAG	**a**	3.02	3.86	1.28	2.75
	TAG	**b**	3.79	7.96	2.10	4.95
	R	**a**	1.75	1.75	1.00	0.00
	R	**b**	2.80	2.94	1.05	0.40
6	T	**a**	2.27	2.49	1.10	1.00
	T	**b**	3.33	4.09	1.23	2.30
	T2	**a**	1.67	2.03	1.22	1.50
	T2	**b**	2.58	3.73	1.44	2.75
	TAG	**a**	3.34	4.35	1.30	2.50
	TAG	**b**	5.66	7.03	1.24	0.80
	R	**a**	1.59	1.66	1.04	0.40
	R	**b**	2.65	2.82	1.06	0.80
7	T	**a**	2.20	2.59	1.18	2.10
	T	**b**	2.96	3.79	1.28	2.80
	T2	**a**	1.57	1.79	1.14	1.30
	T2	**b**	2.19	2.78	1.27	2.00
	TAG	**a**	2.93	3.77	1.29	2.60
	TAG	**b**	4.18	5.81	1.39	2.40
	R	**a**	1.79	2.22	1.24	2.10
	R	**b**	2.93	3.84	1.31	2.90
8	T	**a**	2.73	2.94	1.08	1.05
	T	**b**	3.90	4.41	1.13	1.55
	T2	**a**	1.80	2.18	1.21	1.83
	T2	**b**	2.92	3.78	1.29	2.15
	TAG	**a**	4.01	4.45	1.11	1.20
	TAG	**b**	7.29	9.12	1.25	1.50
	R	**a**	1.84	2.03	1.10	1.10
	R	**b**	3.07	3.48	1.13	1.40

Chromatographic condition: mobile phase, **a**, 0.1% aqueous triethylammonium acetate (TEAA, pH 4.1)/MeOH = 20/80 (v/v), **b**, 0.1% TEAA (pH 4.1)/EtOH = 20/80 (v/v); flow rate, 0.5 mL min^{-1}; detection, 205 nm; n.d., no data available.

influences the separation by changing the conformation of the selector.

3.2. Effect of organic modifier nature and content

The nature of the alcoholic modifier exerted considerable effects. Fig. 2 reveals that at constant organic modifier content the retention factors increased with increasing chain length of the alcohol, especially for alcohols with branched and bulky side-chains. The apolar character of the mobile phase increased in the sequence MeOH, EtOH, PrOH, IPA, while at a constant percentage of alcohol modifier, the molar concentrations of the longer-chain alcohols were less because of their higher molar mass. Increasing carbon number is disadvantageous for polar interactions between the mobile phase and analytes: the retention factor may increase. The lower molar concentration of propanols relative to MeOH may decrease the apolar character of the mobile phase. The overall resultant of these two effects is that the retention factor increases with increasing chain length of the alcohol (Fig. 2). This behavior was more pronounced for IPA. In this case, the steric effect probably contributes to the decreased interactions between the mobile phase and the analytes. As concerns resolution, the highest R_S values were obtained on application of EtOH or PrOH.

The effects of the organic modifier content on the separation were also investigated. On variation of the ratio of 0.1% TEAA (pH 4.1) and EtOH in the range 80/20 to 0/100 (v/v), as the EtOH content of the mobile phase was increased, the retention factor increased; this was due to the reduced solubility of the polar analytes in the EtOH-rich, more apolar mobile phase. This behavior was observed on all four CSPs. In all cases, the α values varied slightly, while the R_S values progressively increased with increasing EtOH content in the mobile phase.

Relevant separation data for all compounds are given in Table 1. As expected, EtOH exhibited larger k' values than MeOH. When the same mobile phases were used, the retention factors were smallest on ristocetin A and largest on the teicoplanin aglycone chiral selector. The native teicoplanin phases (Chirobiotic T and T2) exhibited intermediate k' values. Similar trends, with higher k' values on Chirobiotic TAG than on a Chirobiotic T column, were observed by Berthod et al. [22], D'Acquarica et al. [23] and Péter et al. [18,19,24–26] for unusual α-amino acids and cyclic β-amino acids. Comparison of the Chirobiotic T and T2 columns revealed that the retention factors on Chirobiotic T were somewhat larger (Table 1). Slightly higher k' values on Chirobiotic T2 than on Chirobiotic T were observed by Péter et al. [26] for β^3-homoamino acids.

Another obvious trend indicated by the data in Table 1 was that α and R_S were smallest on the ristocetin A selector (with the exception of analyte **7**), while larger α and R_S values were obtained on both teicoplanin and teicoplanin aglycone selectors.

3.3. Comparison of separation performances and effect of sugar units of Chirobiotic columns

The different separation ability of the Chirobiotic TAG column relative to Chirobiotic T for hydroxyamino acids with cycloalkane skeletons indicates a possible difference in the separation mechanism on the teicoplanin versus the teicoplanin aglycone CSPs. From the aspect of enantiomeric separations, the sugar moieties of the native teicoplanin may intervene in the chiral recognition process

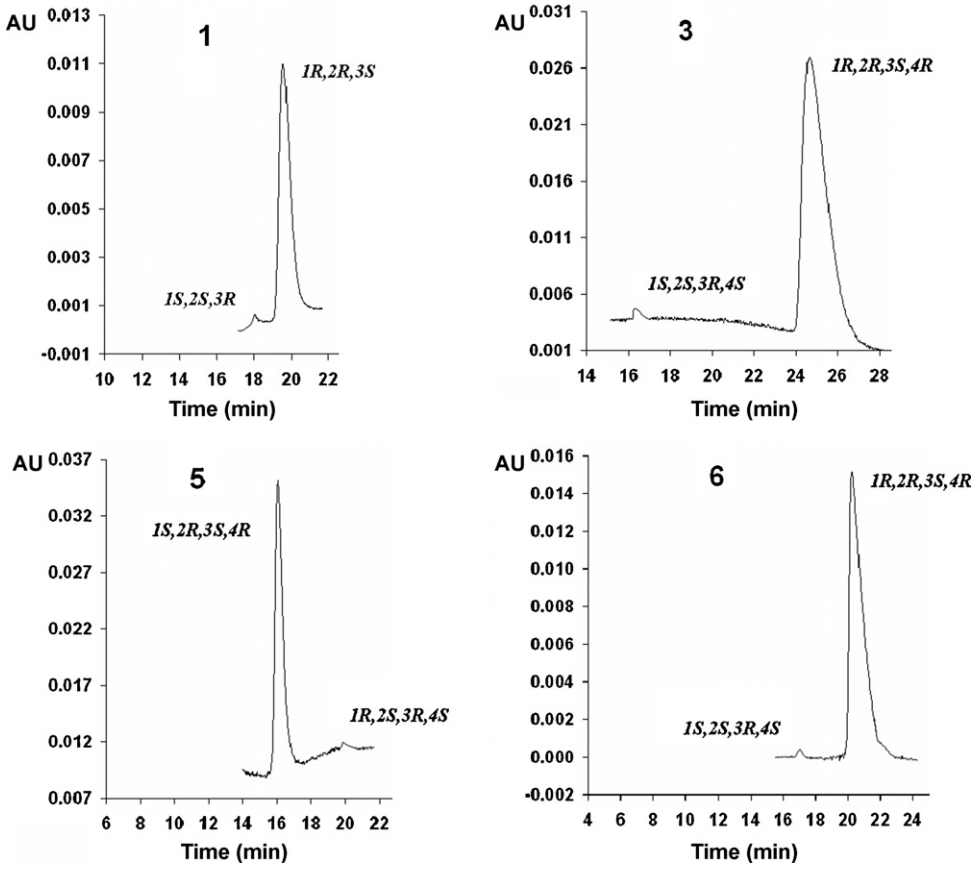

Fig. 4. Separation of minor enantiomers of **1**, **3**, **5** and **6** when it is present in an excess of the major isomer. Chromatographic conditions: column, Chirobiotic T2 for **1**, Chirobiotic TAG for **3**, and Chirobiotic T for **5** and **6**; mobile phase for **1** 0.1% TEAA (pH 6.5)/MeOH = 20/80 (v/v); for **3**, **5** and **6** 0.1% TEAA (pH 4.1)/EtOH = 20/80 (v/v), 0.5 mL min^{-1}; detection, 205 nm.

in at least three ways [22]: (i) sugar units occupy the space inside the "basket"; (ii) they block the possible interaction sites on the aglycone (phenolic hydroxy groups and an alcohol moiety); (iii) they offer competing interaction sites, since the three sugars are themselves chiral and have hydroxy, ether and amido functional groups.

To quantify the effects of the sugar units, the differences in enantioselective free energies between the two CSPs, $\Delta(\Delta G^\circ)_{TAG} - \Delta(\Delta G^\circ)_T$, were used. $\Delta(\Delta G^\circ)$ values were taken from Table 1 [$-\Delta(\Delta G^\circ) = RT\ln\alpha$]. The $\Delta(\Delta G^\circ)_{TAG} - \Delta(\Delta G^\circ)_T$, values were plotted as shown in Fig. 3. A negative number means that the stereoisomers were better separated on the aglycone CSP. A positive number means that the stereoisomers are better separated on the native teicoplanin CSP. As can be seen in Fig. 3, hydroxyamino acid enantiomers were much better separated by the aglycone CSP (exceptions were analytes **1** and **2**). The negative energy difference means that the absence of sugar units increases the amino acid enantiorecognition. It also indicates that the aglycone basket of the teicoplanin molecule is solely responsible for the enantiorecognition.

3.4. Effect of the structures of the analytes

The structures of the analytes influenced the chiral recognition. On the same column, the α values were generally lower for analytes **1** and **2**, which possess a single hydroxy group. As indicated by the positive free energy differences for analytes **1** and **2**, the contribution of the interaction of the sole hydroxy group with the basket resulted in decreased enantioselectivity (Fig. 3). However, the additional hydroxy groups in analytes **3**–**8** contributed considerably to chiral recognition by the aglycone basket (*i.e.* Chirobiotic TAG). Interestingly, it seems that the positions of the hydroxy groups on the cycloalkane skeleton (positions 3, 4 or 4.5) produced only a small effect on the selectivity factor.

β-Amino acids possessing cycloalkane skeletons exhibited much lower enantioselectivity on Chirobiotic columns [18,19]. The hydroxyl groups attached to the cycloalkane skeleton significantly contribute to the chiral recognition therefore Chirobiotic phases are much more suitable for the enantioseparation of hydroxycycloalkane β-amino acids.

The limit of detection (LOD) was determined as a peak whose area was three times the baseline noise. For the monohydroxy derivatives 5.12 nmol, while for the dihydroxy derivatives 4.23 nmol were obtained as LOD. The relative standard deviation for the LOD was 3%. Further, the determination limit for the minor isomer is less than 0.1% when it is present in an excess of the major isomer (Fig. 4).

3.5. Elution sequences of investigated analytes

On the Chirobiotic T, T2 and TAG columns for analytes **1, 3** and **6**, the elution sequence was **b** < **a** (Fig. 1), while for analytes **5** and **8** it was **a** < **b**; these retention sequences were independent of the organic modifier used (*e.g.* MeOH or EtOH). On the Chirobiotic R column for analyte **1**, **b** < **a**, while for analytes **3, 6** and **8**, the elution sequence **a** < **b** was found. Neither the configuration of the carbon atom attached to the carboxyl group nor the configuration of the carbon atom attached to the amino group determined the elution sequence, in most cases the elution sequence 1*S* < 1*R* or 2*S* < 2*R* was observed.

4. Conclusions

The enantioseparations of hydroxycycloalkane amino acid analogs were investigated by using macrocyclic glycopeptide-based CSPs, *i.e.* Chirobiotic T, T2, TAG and R columns. The separations could be accomplished in reversed-phase mode by using 0.1% TEAA (pH 4.1)/alcoholic modifier mobile phases in different compositions. Of the four Chirobiotic columns, Chirobiotic T and TAG appeared most suitable for the enantioseparation of 2-aminomono- or dihydroxycycloalkanecarboxylic acids. The elution sequence was determined in most cases, but no general rule could be established relating the elution sequence to the absolute configuration.

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