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Application of a new chiral stationary phase containing the glycopeptide antibiotic A-40,926 in the direct chromatographic resolution of β-amino acids

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Abstract

A new enantioselective HPLC procedure for the direct resolution of β-amino acids is described, based on the use of a new chiral stationary phase (CSP) containing the macrocyclic glycopeptide antibiotic A-40,926, structurally related to teicoplanin, covalently bonded to silica gel microparticles. The new CSP shows higher enantioselectivity and broader applicability in this field compared to the parent teicoplanin phase. The potential for semi-preparative separations on the A-40,926-CSP is demonstrated for a selected cyclic β-amino acid. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The past decade has seen a growing interest in β-amino acids[1–3] which are relevant intermediates for the synthesis of compounds of pharmaceutical interest[4–6] and are main constituents of natural products such as alkaloids, peptides[7,8] and β-lactam antibiotics.[9–16] More recently,[17] a novel class of β-peptide analogues adopting predictable and reproducible folding patterns is being evaluated as a potential source of new drugs and catalysts.

Although several methods have been described in the literature for the synthesis of racemic β-amino acids, only a few deal with their preparation in enantiopure form. New enantioselective procedures include: (a) transformation of chiral pool material,[18–20] (b) Michael addition of

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homochiral lithium amides to α,β-unsaturated carboxylic acid equivalents,[21–24] (c) addition of homochiral enolates to imines,[25,26] and (d) enantioselective hydrogenation of prochiral 3-amino-acrylic acid derivatives in the presence of a chiral catalyst.[20] The biocatalytic approach has also been exploited.[27] Some of us found[28–30] that enantiopure β-enamino esters derived either from (*R*)- or (*S*)-1-phenylethylamine can be easily reduced with good diastereo- and enantioselectivity to the corresponding β-amino esters, which in turn yield enantiopure products after hydrogenolysis of the auxiliary group. A simple and practical method for large-scale preparation of enantiomerically pure ethyl 2-aminocyclohexanecarboxylate was also recently developed.[31]

Studies on synthetic or natural β-amino acids can be considerably facilitated by versatile and robust methods for determining the enantiomeric purity of starting materials and products; high performance liquid chromatography (HPLC) using chiral stationary phases offers some attractive features in this respect, such as precision, speed of analysis, and small amount of sample required. Moreover, the same stationary phase can be conveniently used to collect discrete amounts of pure enantiomers from racemic samples.

A few papers and reviews have been published on the development of enantioselective HPLC techniques for the separations of alicyclic β-amino acids, and they are based either on chiral stationary phases (containing a chiral crown ether or teicoplanin)[32,33] or on achiral stationary phases and pre-column derivatisation with enantiopure reagents.[34–36]

Recently, glycopeptide antibiotics have been successfully used as chiral selectors to resolve the enantiomers of a variety of racemic compounds by means of chromatographic (TLC and HPLC) and electrophoretic (HPCE) techniques.[37] These natural compounds contain multiple stereogenic centres and a variety of functional groups. In particular, teicoplanin (TE) has a macrocyclic heptapeptide aglycone with three attached sugar units. The aglycone consists of four fused rings forming a 'semi-rigid basket' that incorporates biaryl and biaryl ether units, two of which are chlorosubstituted. The three sugar units are: α-D-mannose, β-D-*N*-acetyl-glucosamine, β-D-*N*-acyl-glucosamine (acyl = 8-methyl-nonanoyl). Five main components of TE have been identified, differing from each other only in the nature of the hydrocarbon chain of the *N*-acyl-glucosamine moiety. Fig. 1 (left) shows the chemical structure of the prevalent component of TE glycopeptide complex (A_2-2, $>85\%$).

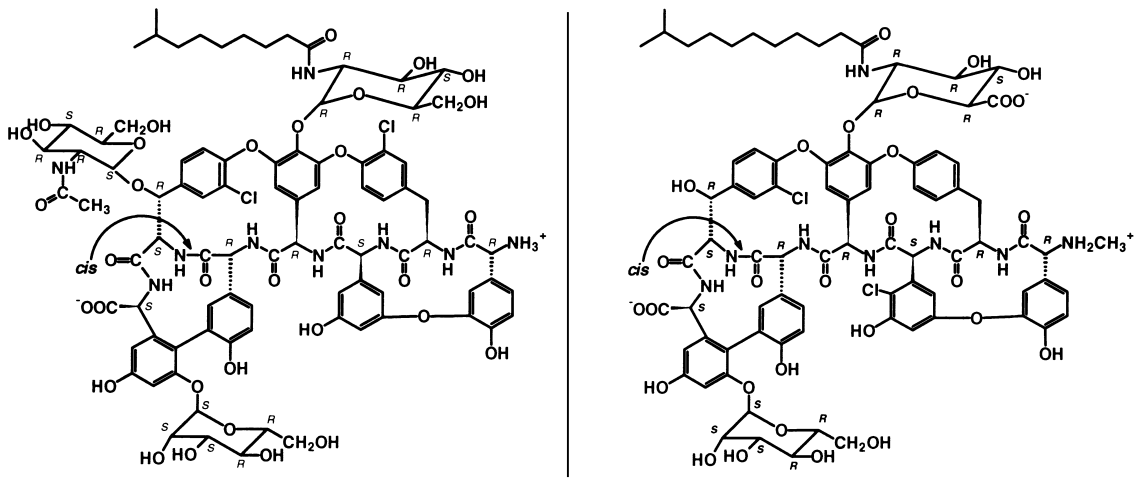


Figure 1. Chemical structure of the prevalent teicoplanin component (A_2-2, left) and of the prevalent A-40,926 component (factor B, right)

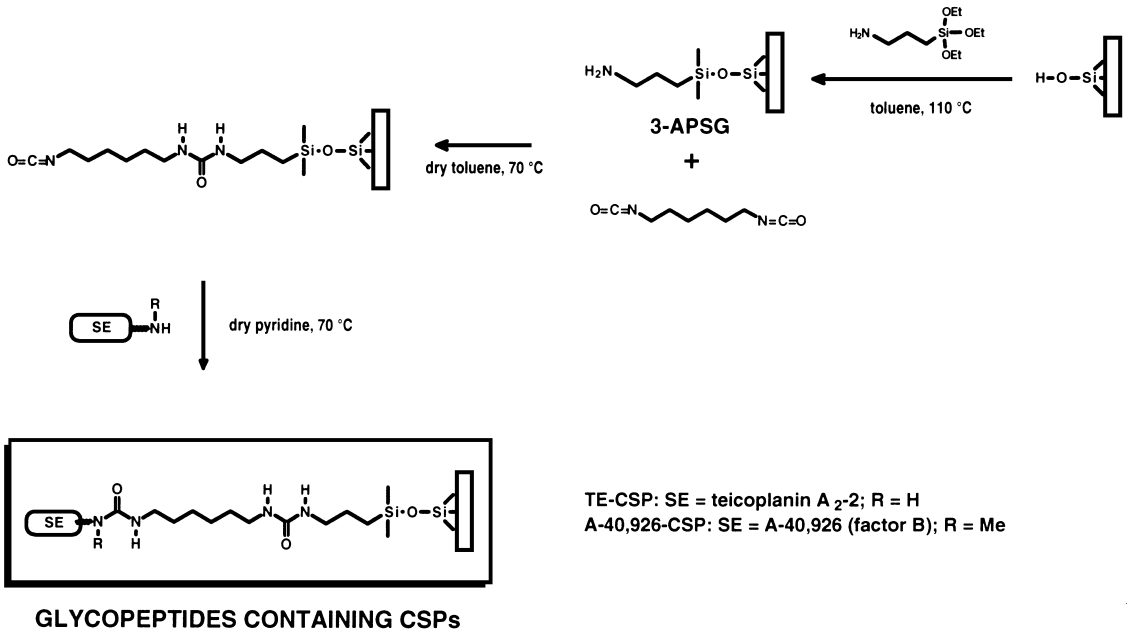
A-40,926 is a natural complex of glycopeptides produced by the *Actinomadura* strain ATCC 39726, from which factors A and B are the major recoverable species.[38–41] The chemical structure of the prevalent component of A-40,926 glycopeptide complex (factor B, >70%) is reported in Fig. 1 (right). It differs from TE for the presence of an additional carboxylic group on the β-D-*N*-acyl-glucosamine, for the lack of the β-D-*N*-acetyl-glucosamine, for the different position of a chlorine atom on phenyl rings, for the presence of an *N*-methyl group on the primary amine in the aglycone portion and finally for having a different acyl group on the β-D-*N*-acyl-glucosamine residue (acyl = 10-methyl-undecanoyl).

In this paper we describe an easy, fast and convenient procedure for the direct separation of the enantiomers of linear and cyclic β-amino acids by enantioselective HPLC on a new laboratory-made chiral stationary phase, containing covalently bonded A-40,926 as selector[42] (A-40,926-CSP). The results are compared with those obtained on the parent teicoplanin stationary phase (TE-CSP).[43]

2. Results and discussion

Teicoplanin and related glycopeptides can be immobilized on solid chromatographic supports, yielding efficient and versatile chiral stationary phases for HPLC applications.

The two phases described in this work are prepared by using the same binding process (Scheme 1), whereby the glycopeptides are covalently grafted to the silica surface via a bifunctional aliphatic isocyanate, following a novel and efficient synthetic strategy.[43] The surface densities of bound glycopeptide on the two prepared CSPs are around 0.5 μmol/m^2 (see Experimental). Thirteen different β-amino acids (see Fig. 2) were used to investigate enantioselective retention on the TE-CSP and A-40,926-CSP. Chromatographic data collected under identical conditions are gathered in Table 1. Overall, the two phases have similar affinities for the examined compounds, as judged by



Scheme 1. Synthetic pathway to glycopeptides containing chiral stationary phases (SE = Selector)

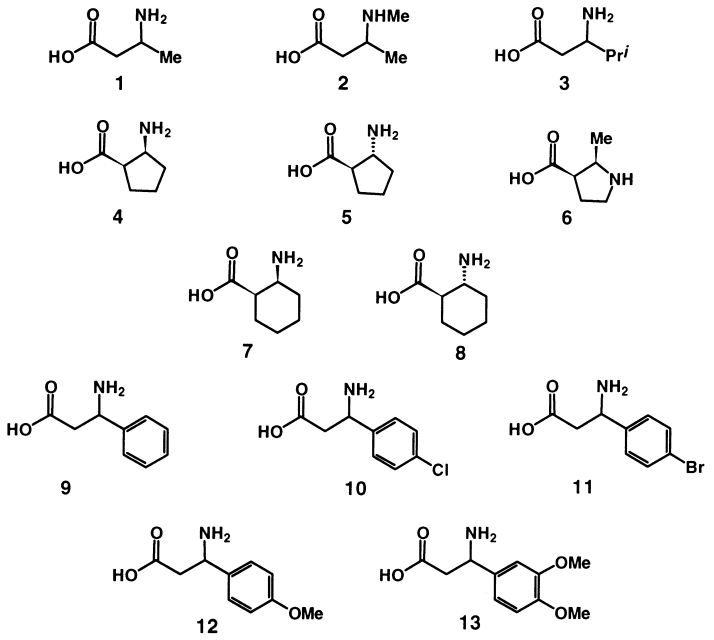


Figure 2. Structures of the 13 β-amino acids resolved on our glycopeptides containing CSPs

Table 1
Chromatographic data for the resolution of β-amino acids on A-40,926 CSP and TE-CSP

compound	k'_1 [a]		α [b]		R_s [c]		eluent	polarimetric detection [e]	absolute configuration [f]
	A-40,926 CSP	TE CSP	A-40,926 CSP	TE CSP	A-40,926 CSP	TE CSP			
1	1.45	1.32	1.20	1.12	1.66	0.70[d]	A	(-)	(*R*)
2	1.66	1.51	1.18	1.10	1.55	1.06	A	(-)	
3	0.98	0.87	1.26	1.15	1.80	1.07	A	(-)	(*S*)
4	0.73	0.73	1.36	1.22	1.76	1.52	B	(+)	(1*S*,2*R*)
5	0.77	0.60	1.24	1.00	1.14	-	B	(+)	(*S*,*S*)
6	1.50	1.42	1.31	1.00	1.25	-	C	(+)	(*S*,*S*)
7	0.50	0.69	1.76	1.00	3.06	-	B	(-)	(1*R*,2*S*)
8	1.22	1.01	1.00	1.24	-	2.06	C	(+)	(*S*,*S*)
9	0.71	0.73	1.33	1.32	2.03	2.05	C	(-)	
10	1.19	1.04	1.22	1.08	1.52	0.34[d]	C	(-)	
11	1.52	1.15	1.33	1.06	2.28	0.13[d]	C	(-)	
12	1.42	1.04	1.35	1.00	2.46	-	C	(-)	
13	1.24	1.25	1.25	1.00	1.80	-	A	(-)	

[a] Retention factor of the first eluted enantiomer. [b] Enantioselectivity factor. [c] Resolution factor. [d] Kaiser separation factor.[44]
[e] Sign of the first eluted enantiomer. [f] Absolute configuration of the first eluted enantiomer.
Eluent A = MeOH:H_2O 95:5 (v:v) + NH_4OAc 0.025 M; Eluent B = MeOH:H_2O 80:20 (v:v) + NH_4OAc 0.025 M; Eluent C = MeOH:H_2O 90:10 (v:v) + NH_4OAc 0.025 M
Flow rate: 1 mL/min; temperature: 35 °C; detection: evaporative light scattering; T = 80 °C; air flow = 6.0 L/min.

the close retention values observed for the first eluted enantiomer (k'_1 in Table 1). However, the A-40,926-CSP shows greater discrimination ability than the parent TE-CSP. Indeed, all the examined compounds (with the exception of compound **8**) can be resolved on the former, with enantioselectivity factors (α in Table 1) in the 1.18–1.76 range. On the other hand, five out of the thirteen analysed compounds (**5**, **6**, **7**, **12** and **13**) are not resolved on the TE-CSP (see Fig. 3 for typical chromatograms).

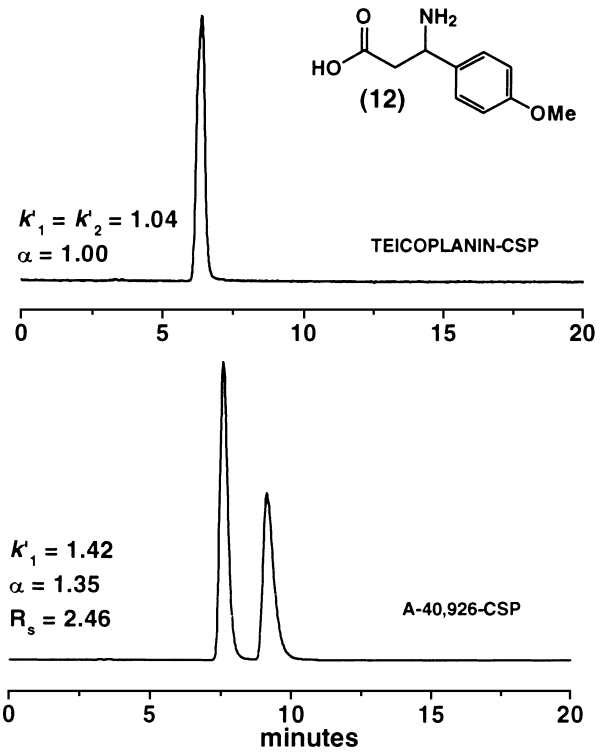


Figure 3. Chromatograms of 3-amino-3-(4-methoxyphenyl)-propanoic acid (**12**) on TE-CSP (top) and A-40,926-CSP (bottom). Columns: 250×4.5 mm ID. Eluent: MeOH:H_2O 90:10 (v:v)+NH_4OAc 0.025 M. Flow rate: 1 mL/min. Temperature: 35°C. Detection: ELSD; T = 80°C; air flow = 6.0 L/min

For those compounds that are resolved on both phases, enantioselectivity is always larger on the A-40,926-CSP.

Compared to the TE-CSP, the latter tolerates broader structural variations in the solute structure. All the considered compounds have an amino group on a stereogenic carbon. For linear compounds **1**–**3** and **9**–**13** this is the only stereogenic centre present in the structure, while cyclic compounds **4**–**8** have a second stereogenic carbon bearing the carboxylic group. In compound **2**, the β-amino group is methylated, while in compound **6** it is included in a five-membered ring.

On the A-40,926-CSP, *N*-methylation, branching at the γ position, or the presence of aromatic substituents at the β position leave enantioselectivity unaffected. Also, the electronic nature of the aryl substituents has little effect on enantioselectivity. The enantiomers of five-membered cyclic amino acids are easily discriminated, irrespective of the *cis* (compounds **4** and **6**) or *trans* (compound

5) geometry of the substituents at the stereogenic centres. Surprisingly, while (*cis*)-2-aminocyclohexanecarboxylic acid (compound **7**) is easily resolved (the largest α recorded), the corresponding *trans* isomer (compound **8**) shows no enantioselectivity at all. The situation is reversed on the TE-CSP, where enantioselectivity is observed for the *trans* and not for the *cis* isomers.

The large separation observed for the enantiomers of **7** on the A-40,926-CSP ($\alpha = 1.76$; $R_s = 3.06$) prompted us to investigate the potential application of our new chiral packing for preparative isolation of pure enantiomers. About 12 g of A-40,926-CSP were packed in a 250×10 mm ID stainless-steel column, and increasing amounts of racemic **7** (from 15 to 30 mg) were processed on the semi-preparative column (see Fig. 4). Notably, the column gives easy access to both enantiomers in almost pure form in very short times. At the extreme loadings, we obtained the second eluted enantiomer with e.e. = 99.8% and e.e. = 98.6% [15 and 30 mg of (±)-**7** injected, respectively] and a recovery of 95%. The first band collected always has an e.e. >99.9% (Fig. 5); $[\alpha]_D^{20} = -1.0$; $c = 0.93$; methanol, after conversion to the corresponding hydrochloride salt [lit.[24] $[\alpha]_D^{25} = -1.0$; $c = 0.59$; methanol]. Production rates in the two loading situations are 30 mg/hour and 60 mg/hour of each enantiomer.

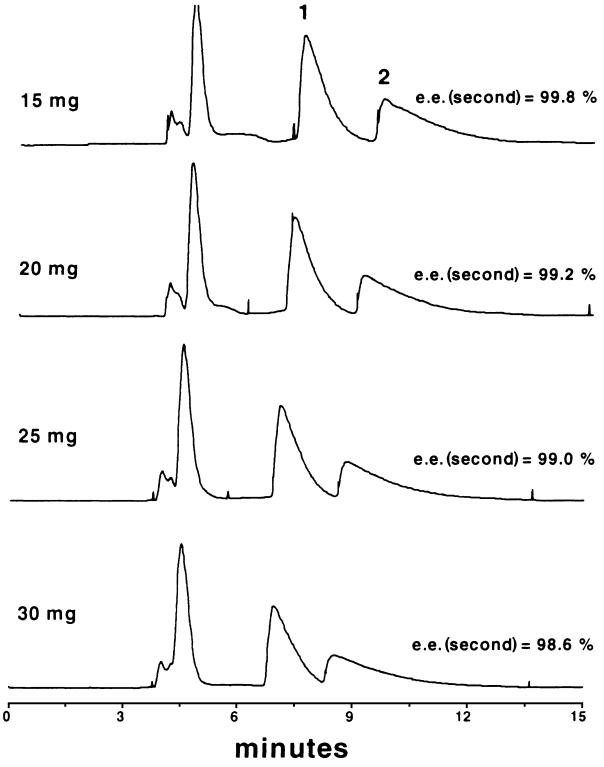


Figure 4. Semi-preparative resolutions of racemic *cis*-2-aminocyclohexanecarboxylic acid (**7**) on a 250×10 mm ID column packed with A-40,926-CSP. Eluent: MeOH:H_2O 95:5 (v:v). Flow rate: 4.0 mL/min. Temperature: 20°C. Detection: RI, at room temperature

Thus, for the first time, the application field of glycopeptides containing chiral stationary phases is practically and successfully extended from the analytical to the semi-preparative level, thanks to the easily removable mobile phases used and to the very short time analyses.

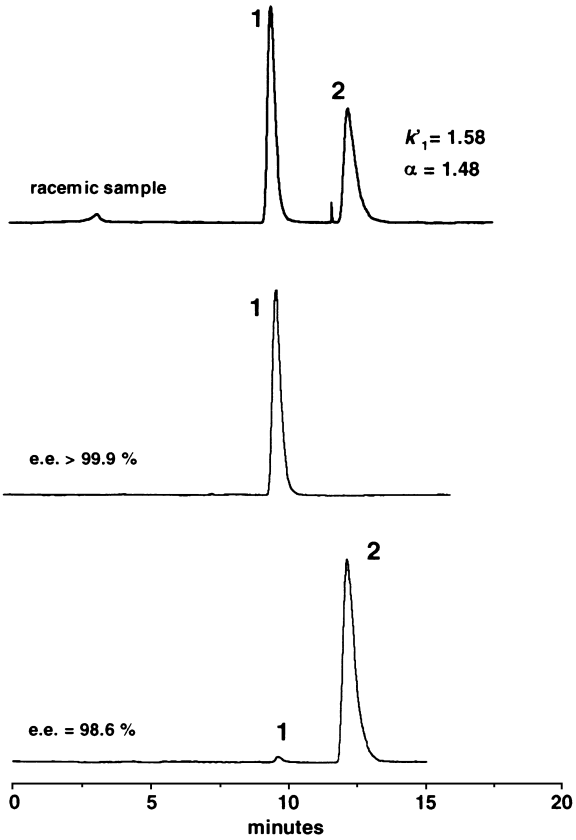


Figure 5. Analytical resolutions on A-40,926-CSP of racemic **7** (top) and control of the fractions collected in the semi-preparative separations (bottom). Eluent: MeOH:H_2O 90:10 (v:v). Flow rate: 0.60 mL/min. Temperature: 20°C. Detection: ELSD; T = 80°C; air flow = 6.0 L/min

In addition to evaporative light scattering detection (ELSD), polarimetric detection can be used to circumvent the low UV detectability of the analysed samples. Multi-wavelength polarimetric detection (230–900 nm range) resulted in good S/N values (Fig. 6). While sensitivity of the polarimetric detector was not sufficient to perform enantiomeric trace analysis, the stereochemical information contained in the bisignate polarimetric response was useful in establishing elution order for those compounds not available as single enantiomers of known configuration.

3. Conclusions

A-40,926, a natural glycopeptide strictly related to TE, has been immobilised on silica microparticles and used as HPLC chiral stationary phase in the enantiomeric resolution of β-amino acids. The new CSP shows higher enantioselectivities than the parent TE-CSP, for a set of structurally diverse β-amino acids.

Semi-preparative separations in the 15–30 mg range are feasible on a 10 mm ID column packed with the new glycopeptide containing CSP. Further studies in this direction are currently in progress

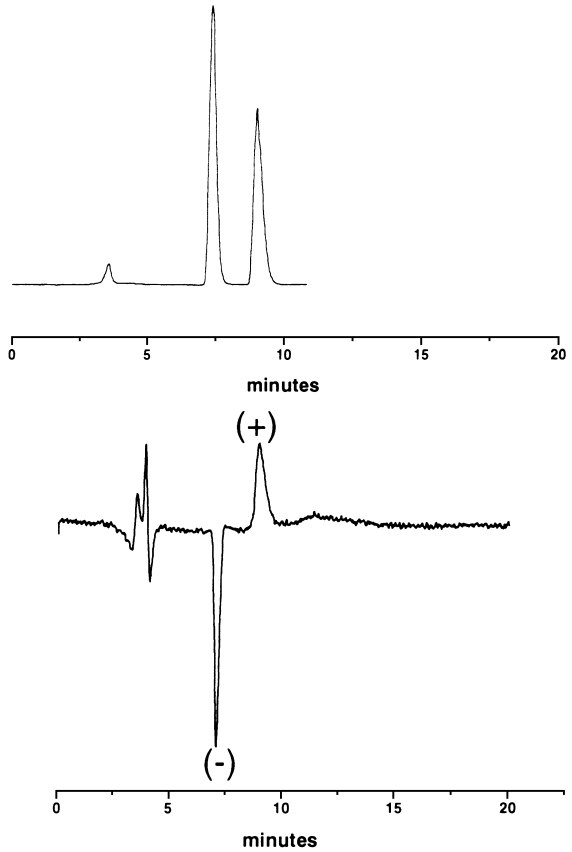


Figure 6. Example of the combined use of ELS and OR detectors in the analytical resolution of **7** on A-40,926-CSP. Eluent: MeOH:H_2O 90:10 (v:v). Flow rate: 1 mL/min. Temperature: 20°C. Detection: (top) ELSD; T = 80°C; air flow = 6.0 L/min; (bottom) multi-wavelength polarimetric detection; response = standard; λ range = 230–900 nm

in our research groups to evaluate the range of applicability and the detailed mechanism of enantioselective binding of this new selector.

4. Experimental

4.1. Apparatus

Analytical liquid chromatography was performed as previously described.[43] Semi-preparative separations were carried out on a Waters Delta Prep 3000 chromatographic system (Waters Chromatography, Milford, MA, USA), equipped with a Rheodyne Model 7010 5 mL loop injector and a Knauer differential refractive index (RI) detector.

4.2. Chemicals and reagents

LiChrosorb Si 100 silica gel (5 μm particle size, 300 m^2/g) and HPLC-grade solvents were purchased from Merck (Darmstadt, Germany); (3-aminopropyl)triethoxysilane, dry toluene, dry

pyridine, 1,6-diisocyanatohexane and water for HPLC were from Fluka (Sigma-Aldrich Company, Buchs, Switzerland); ammonium acetate was purchased from J. T. Baker (Division of Mallinckrodt Baker, Inc., Phillipsburg, NJ, USA); teicoplanin and A-40,926 were provided by the Lepetit Research Centre (Gerenzano, Italy).

β-Amino acids **1**–**9** were prepared by stereoselective reduction of β-enamino benzylesters and successive hydrogenolysis of the benzylic group,[28–30] while β-amino acids **10**–**13** were prepared by condensation of malonic acid, with ammonium acetate and appropriate derivatives of benzaldehyde.[45,46]

4.3. Preparation of the chiral stationary phases

All reactions were carried out in a laboratory-modified Rotavapor-M rotary-evaporator apparatus (Büchi, Labortecnik, Flawil, Switzerland), in which the reaction flask is fitted with a solvent condenser, a solvent collector and an argon inlet and allows syringe addition of reactant solutions and isolation of the CSP by filtration under an inert atmosphere. Stirring was obtained by spinning the flask around its axis. The preparation of the teicoplanin containing chiral stationary phase (TE-CSP) used in the present work was realised according to a synthetic procedure already described.[43] Here we report only the preparation of the A-40,926 containing chiral stationary phase (A-40,926-CSP). Silica gel and A-40,926 were vacuum-dried before use (0.1 mbar, 1 h, at 150 and 70°C, respectively). Chemical purity of A-40,926 samples was checked by HPLC on a 250×4.5 mm ID ODS Hypersil column (mobile phase, A: 0.1 M ammonium acetate; B: 0.1 M ammonium acetate:acetonitrile 20:80; linear gradient from 10% B to 50% B in 20 min, to 75% B in 15 min, to 100% B in 5 min. Flow rate 1 mL/min, T = 25°C, UV detection at 254 nm): the main A-40,926 peak (factor B) area was always greater than 70% of the total by relative area. All reactions were carried out under an argon atmosphere.

A slurry of 5.0 g of silica (LiChrosorb Si 100, 5 μm) in 120 mL of toluene was heated to reflux, and residual adsorbed water was azeotropically removed. After cooling to room temperature (3-aminopropyl)triethoxysilane was added (2.5 mL, 11 mmol) and the mixture was heated to reflux for 4 h. After cooling to room temperature, modified silica was isolated by filtration, washed with 50 mL portions of toluene, methanol and dichloromethane and dried at reduced pressure (90°C, 0.1 mbar, 1 h). Anal. found: C, 4.53; H, 1.29; N, 1.58, corresponding to 1320 μmol of aminopropyl groups per gram of unmodified silica (4.40 μmol/m^2) (based on nitrogen).

1,6-Diisocyanatohexane (2.5 mL, 15 mmol) was added with a syringe to an ice-bath cooled slurry of (3-aminopropyl) silica gel in dry toluene (3.0 g in 50 mL). The ice-bath was removed and the mixture was heated to 70°C for 2 h and, after cooling to room temperature, the liquid phase was removed by suction filtration through an immersion sintered Teflon filter under an argon atmosphere. The intermediate monoureidic silica was freed from excess 1,6-diisocyanatohexane by addition of 10 mL of dry toluene and removal of the liquid phase by suction filtration (twice). A suspension of A-40,926 in dry pyridine (0.9 g, 0.52 mmol in 90 mL) was added to the activated silica and the mixture was heated to 70°C for 12 h, with continuous stirring. Disappearance of the main A-40,926 peak from the reaction liquid phase was checked by HPLC, as described above. After cooling to room temperature, the A-40,926-CSP was isolated by filtration and washed with 50 mL portions of pyridine, water, methanol, acetonitrile and dichloromethane and dried under reduced pressure (70°C, 0.1 mbar, 2 h). Anal. found: C, 16.47; H, 2.66; N, 4.12, corresponding to ~147 μmol of A-40,926 per gram of silica (0.49 μmol/m^2) (based on carbon).

Stainless-steel analytical (250×4.5 mm ID) and semi-preparative (250×10 mm ID) columns were packed with the A-40,926-CSP using a slurry packing procedure.[43]

Acknowledgements

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References

1. Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bonffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
2. Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p. 25.
3. Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855.
4. Crumpler, H. R.; Dent, C. E.; Hardss, H.; Westall, R. G. *Nature* **1951**, *167*, 307.
5. Hettinger, T. P.; Craig, L. C. *Biochemistry* **1968**, 4153.
6. Kondo, S.; Shibahara, S.; Takahashi, S.; Maeda, K.; Umesawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1971**, *93*, 6305.
7. Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids*, *Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7.
8. Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383–391.
9. Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem.* **1985**, *97*, 183–205; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180–202.
10. Davies, S. G.; Dordor-Hedgecock, I. M.; Jones, R. H.; Prout, K. *Tetrahedron* **1986**, *42*, 5123–5137.
11. Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328–6343.
12. Brown, M. J. *Heterocycles* **1989**, *29*, 2225–2244.
13. Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447–1465.
14. van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503–7524.
15. Asao, N.; Tsukada, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1660–1662.
16. Wang, W. B.; Roskamp, E. J. *J. Am. Chem. Soc.* **1993**, *115*, 9417.
17. Iverson, B. L. *Nature* **1997**, *385*, 113.
18. Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396.
19. Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615.
20. Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582.
21. Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183–186.
22. Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1993**, 461–462.
23. Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455.
24. Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, *11*, 1411–1416.
25. Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem. Lett.* **1990**, 889.
26. Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.
27. Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhar, V. P.; Savchenko, M. V.; Švedas, V. K. *Tetrahedron: Asymmetry* **1995**, *6*, 1601–1610.
28. Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328–5335.
29. Bartoli, G.; Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1455–1458.
30. Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557–5563.
31. Xu, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1445–1451.
32. Török, G.; Péter, A.; Fülöp, F. *Chromatographia* **1998**, *48*, 20–26.
33. Péter, A.; Török, G.; Armstrong, D. W. *J. Chromatogr., A* **1998**, *793*, 283–296.

34. Péter, A.; Fülöp, F. *J. Chromatogr., A* **1995**, *715*, 219–226.
35. Péter, A.; Török, G.; Csomós, P.; Péter, M.; Bernáth, G.; Fülöp, F. *J. Chromatogr. A* **1997**, *761*, 103–113.
36. Török, G.; Péter, A.; Csomós, P.; Kanerva, L. T.; Fülöp, F. *J. Chromatogr., A* **1998**, *797*, 177–186.
37. Armstrong, D. W.; Liu, Y.; Ekborgott, K. H. *Chirality* **1995**, *7*, 474 and references cited therein.
38. Waltho, J. P.; Williams, D. H.; Selva, E.; Ferrari, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, *10*, 2103.
39. Goldstein, B. P.; Selva, E.; Gastaldo, C.; Berti, M.; Pallanza, R.; Ripamonti, F.; Ferrari, P.; Denaro, M.; Arioli, V.; Cassani, G. *Antimicrob. Agents Chemother.* **1987**, *31*, 1961.
40. Schäfer, M.; Pohl, E.; Schmidt-Bäse, K.; Sheldrick, G. M.; Hermann, R.; Malabarba, A.; Nebuloni, M. *Helv. Chim. Acta* **1996**, *79*, 1916.
41. Malabarba, A.; Donadio, S. *Drugs of the Future* **1999**, *24*, 839.
42. Carotti, A.; Cellamare, S.; Cimarelli, C.; D'Acquarica, I.; Gasparrini, F.; Misiti, D.; Palmieri, G.; Villani, C.; Zappia, G., originally presented at the 10th International Symposium on Chiral Discrimination, Vienna, August 30–September 2, 1998.
43. D'Acquarica, I.; Gasparrini, F.; Misiti, D.; Villani, C.; Carotti, A.; Cellamare, S.; Muck, S. *J. Chromatogr., A* **1999**, *857*, 145–155.
44. Kaiser, R. E. *Gas Chromatography*; Geest, Akademische Verlagsgesellschaft Geest & Portig: Leipzig, 1960.
45. Rodionov, V. M.; Malevinskaia, E. T. *Ber.* **1926**, *59B*, 2952–2958.
46. Rodionov, V. M.; Avramenko, V. G.; Suvorov, N. N. *Zh. Obshch. Khim.* **1958G**, *28*, 2242–2246.