Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3527–3534

TETRAHEDRON: *ASYMMETRY*

Chiral selectors based on C_2-symmetric dicarboxylic acids

Stig Allenmark,* Urban Skogsberg and Linda Thunberg

Department of Chemistry, Göteborg University, SE-41296 Göteborg, Sweden

Received 12 June 2000; accepted 22 August 2000

Abstract

Bis-allylamides of rigid C_2-symmetric dicarboxylic acids, useful as precursors in the synthesis of liquid chromatographic chiral stationary phases via hydrosilylation reactions, have been prepared by two different approaches. One involved resolution of the dicarboxylic acid followed by reaction with allylamine via the acid chloride or by a carbodiimide-assisted condensation. The other route involved acetalization of *N*,*N*′-diallyl-L-tartardiamide (DATD) with aromatic aldehydes. Moreover, transformation of the enantiopure dicarboxylic acid used in the first route into the corresponding diamine permitted the synthesis of selectors possessing a reversed amide functionality. The enantiomer-discriminating properties of some of these selectors were studied by NMR.

1. Introduction

In the search for readily obtainable chiral synthons useful for transformation into selectors for liquid chromatographic separation of enantiomers or catalytic asymmetric reactions, derivatives of C_2-symmetric dicarboxylic acids are of interest since they can often be prepared on a large scale from easily available starting materials. The numerous routes from L-tartaric acid illustrate this point well.[1] Moreover, many chiral *trans*-1,2-dicarboxylic acids can be obtained via Diels–Alder reactions with fumaric acid as dienophile and from metallation/carbonation reactions involving suitable double bonds.

We have previously found that *N*,*N*′-diallyl-L-tartardiamide forms an excellent starting point for the preparation of chiral stationary phases which are obtained via acylation and hydrosilylation with concomitant crosslinking and immobilization to vinyl-silica.[2,3] Columns packed with chiral sorbents based on this principle are commercially available and their use for enantiomer separation has been well documented.[4] In order to try to expand the scope of the general concept, selectors with a conformationally rigid central part were designed in two different ways, one from cyclocondensation of L-DATD with aromatic aldehydes to give acetals, the other from resolution of cyclic or bicyclic 1,2-dicarboxylic acids, followed by condensation with allylamine.

* Corresponding author. Tel: +46 31 7723841; fax: +46 31 7723840; e-mail: stig.allenmark@oc.chalmers.se

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00331-1

The relationship between the two selector types is shown in Fig. 1. In this paper we describe the synthesis and properties of these selectors, except for compound **1b** which has recently been reported elsewhere,[5] and for **2b** which has not yet been prepared but should be readily available in analogy with **2a**. The enantiomer-discriminating ability of the compounds, as displayed by induced chemical shift differences in the NMR,[6] is also described.

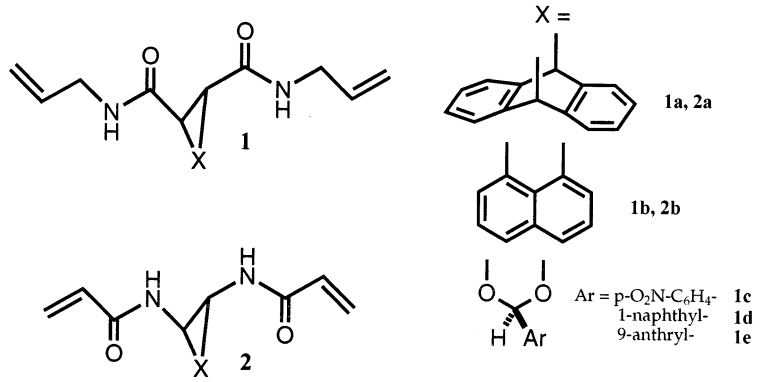


Figure 1. Structural relationship of the selectors **1** and **2**

2. Results and discussion

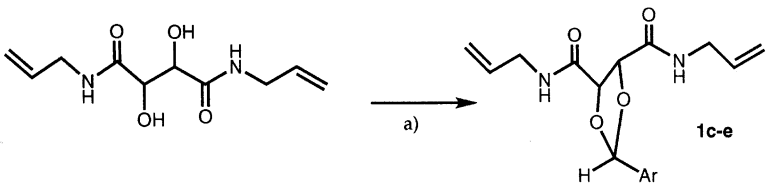
2.1. Synthesis

The synthetic routes to compounds **1** and **2**, respectively, are shown in Fig. 2. From an HPLC analysis it was concluded that the transformation of L-DATD into **1c–e** had occurred without any observable racemization, in agreement with earlier findings from similar reactions.[7] The resolution of *rac*-**1a**′, achieved with brucine,[8] took place with extreme ease, since only one recrystallization was needed to yield a >99% e.e. of the (−)-enantiomer.

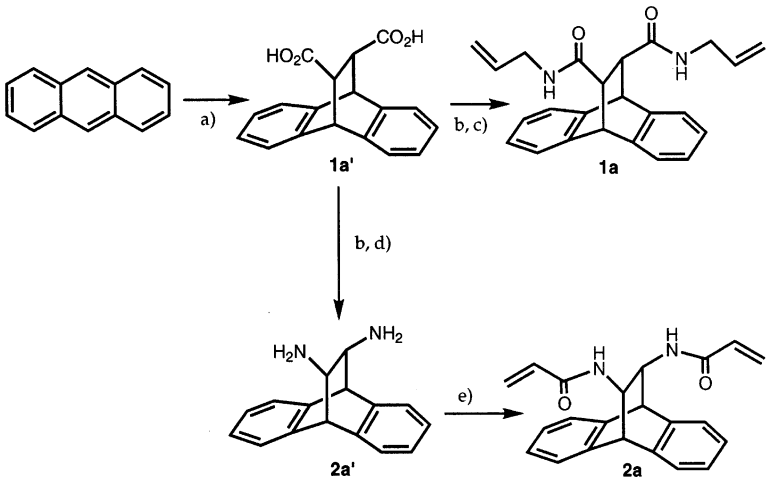
(−)-(*S*,*S*)-**1a**′ was readily transformed into (+)-(*S*,*S*)-**1a** by diisopropyl carbodiimide (DIPC)-assisted condensation with allylamine in the presence of 1-hydroxybenzotriazole (HOBT) to suppress possible racemization.[9]

2.2. NMR studies of selector–selectand equilibria

In order to estimate the enantiomer-discriminating ability of the new selectors, we used a mixture of (+)- and (−)-dibenzoyltartaric acid (DBTA) as a probe in a series of NMR experiments. Without any added chiral selector the methine protons in DBTA give a sharp singlet at 6.05 ppm at 0°C in $CDCl_3$. Upon the addition of the selector this singlet splits into two resonance lines and the chemical shift difference, expressed in $\Delta\nu$ (Hz), between the DBTA methine protons caused by the diastereomeric complexes formed from (+)- and (−)-DBTA can be determined. Since the exchange between free and bound DBTA is fast on the NMR time scale, the chemical shift values represent the equilibrium situations.



a) **1c**: p-Nitrobenzaldehyde, p-TsOH, $CHCl_3$, reflux; **1d**: 1-Naphthaldehyde, p-TsOH, $CHCl_3$, reflux; **1e**: 9-Anthraldehyde, p-TsOH, $CHCl_3$, reflux



a) Fumaric acid, dioxane, reflux; b) resolution (brucine, 36% ethanol); c) allylamine, DIPC, HOBT, $CHCl_3$/DMF; d) (i) $SOCl_2$, (ii) NaN_3, Δ, (iii) hydrolysis, e) acryloyl chloride, C_5H_5N, $CHCl_3$.

Figure 2. Synthetic pathways used

The effect of increasing selector concentrations on the chemical shift differences at −30°C is shown in Table 1.

The failure of selector **1a** to cause any observable $\Delta\nu$ is most likely due to an unfavourable equilibrium in the solvent used. On the other hand, at a constant selector concentration, **1b** gave the largest $\Delta\nu$ in the series, of opposite sign to those generated by TBB (*O*,*O*′-bis-(*p*-*tert*-butylbenzoyl)-*N*,*N*′-diallyl-L-tartardiamide) and DMB (*O*,*O*′-bis-(3,5-dimethylbenzoyl)-*N*,*N*′-diallyl-L-tartardiamide), respectively. The configurational relationship between the compounds studied is given in Fig. 3. Since the substituent arrangement at the stereogenic centres are opposite in the (*R*,*R*)-DATD-based selectors (DMB, TBB) as compared to (*R*,*R*)-**1b**, the negative $\Delta\nu$ in the latter case is consistent with the other data found.

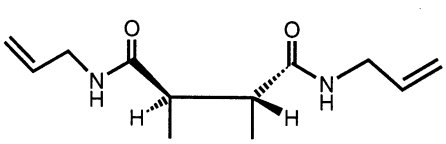
As expected, the $\Delta\nu$ values increased with decreasing temperature. Fig. 4 shows the temperature effect on TBB and **1b**, respectively.

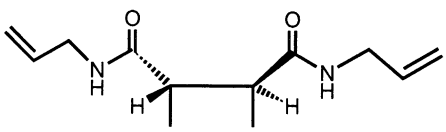
NOE data were used to identify the various protons in compounds **1c**–**e**. Fig. 5 shows the structure and ^{1}H NMR spectrum of **1d**, illustrating the non-equivalence of the two allylamido chains. The proton assignment based on the NOE data was in agreement with the result obtained from molecular modelling, which showed a global energy minimum for a conformation in which the naphthyl ring should give an anisotropy effect on the *syn*-located allyl group shifting all its protons upfield. This conformation also agrees fairly well with the observed NOE's, since the calculated 19↔31, 19↔20, 16↔31 and 16↔20 proton distances were found to be 2.40, 3.53, 3.34 and 4.30 Å, respectively.

Table 1
Chemical shift differences (at 500 MHz) induced by various selectors at different concentrations

Selector	Selector conc. (mM)	Δv (Hz)[a]
TBB	3.78	15.3
TBB	44.64	27.2
DMB	0.69	5.2
DMB	4.54	13.4
DMB	28.48	18.3
1a	1.57	0
1a	4.68	0
1a	34.56	0
1b	0.67	−6.6
1b	2.58	−18.6
1c	7.38	1.7
1c	43.56	5.0

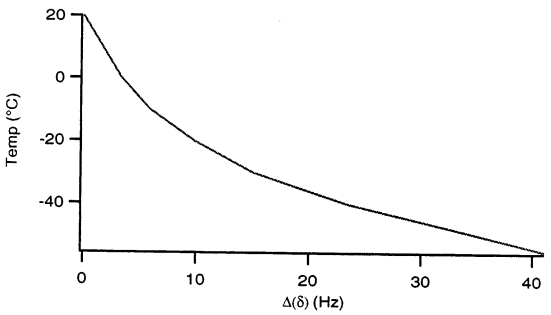
[a] Δv is defined as $v_{(R,R\text{-DBTA})} - v_{(S,S\text{-DBTA})}$ which is negative in the case of **1b** as selector.



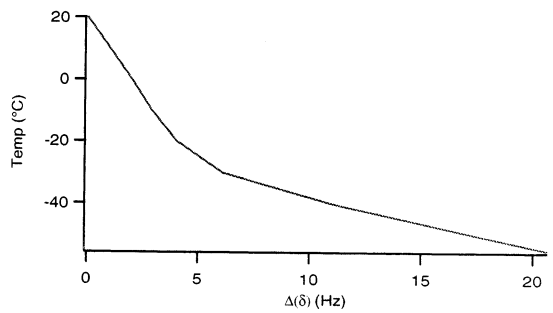


Compound	Configuration
DMB	(*R*,*R*)-
TBB	(*R*,*R*)-
1c-e	(*R*,*R*)-
1a	(*S*,*S*)-
1b	(*R*,*R*)-
2a	(*S*,*S*)-
2b	(*R*,*R*)-

Figure 3. Illustration of the stereochemical relationship

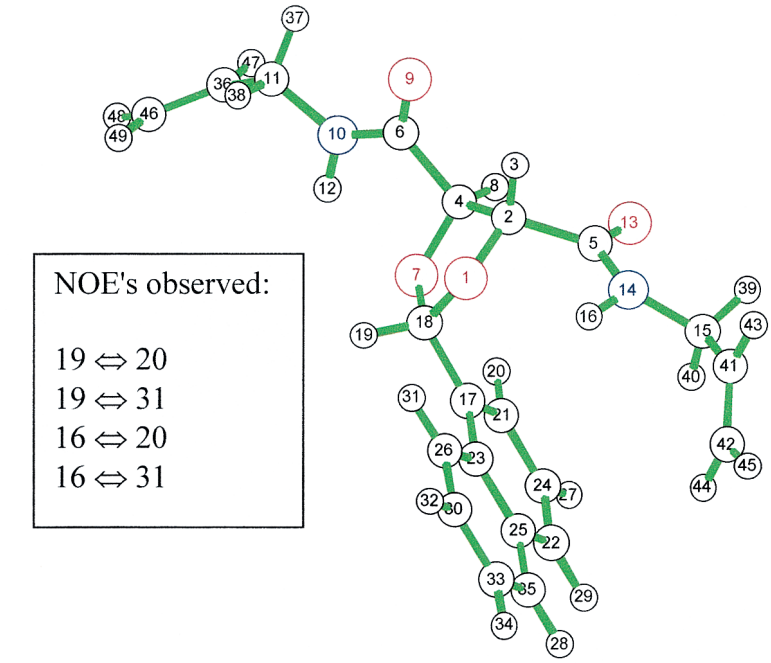


a)



b)

Figure 4. Δv as a function of temperature; selector used: (a) TBB (3.8 mM); (b) **1b** (0.67 mM). DBTA concentration: 0.36 mM



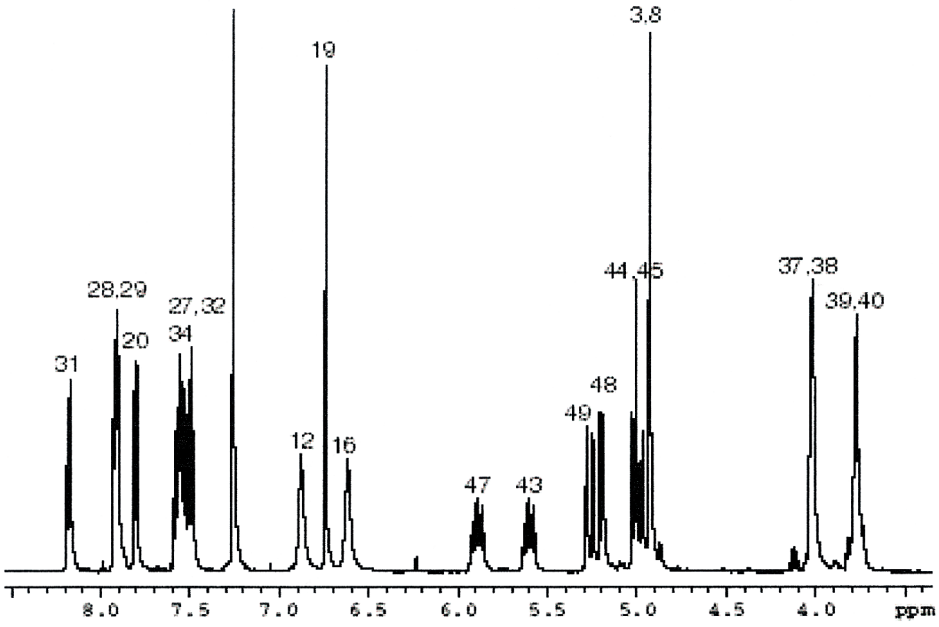


Figure 5. Structure and NMR proton shift assignment of **1d**

3. Experimental

3.1. Instrumentation and methodology

Routine ^{1}H NMR spectra were obtained with a 400 MHz Varian VXR-400 spectrometer. Variable temperature 1-D and 2-D ^{1}H NMR spectra were recorded at 500 MHz with $CDCl_3$ as solvent on a Varian Unity 500 NMR spectrometer.

A stock solution of DBTA (6.71 mM) was made from (±)-DBTA dissolved in $CDCl_3$ containing a small amount of TMS as internal reference. Assignment of the signals was made via subsequent addition of a small amount of (*R*,*R*)-DBTA. To each NMR tube was first added a 40 μl aliquot of the stock solution, which was then diluted with 700 μl of the respective solution of the selector in $CDCl_3$. Thus, the total concentration of DBTA in the tubes was 0.36 mM throughout the series.

The NMR tubes were thermostatted for at least 10 min before each spectrum was recorded. The temperature was varied from 20 to −55°C in steps of 10°C.

Phase sensitive $^1H\{^1H\}$ NOESY spectra were recorded on compound **1d** dissolved in $CDCl_3$ (5 mM) with a Varian Unity spectrometer operating at 500 MHz. The number of increments was 256, with 16 transients in each increment. A mixing time of 0.70 s was used and the spectra were recorded at ambient temperature.

Analytical chiral liquid chromatography for e.e. determination was performed with the use of equipment composed of a Varian mod. 9012Q solvent delivery pump and mod. 9050 variable wavelength UV detector. Samples were introduced via a Rheodyne injector equipped with a 20 μl loop onto a 4.6×250 mm Kromasil CHI-TBB column. Optical rotations were determined with a Perkin–Elmer mod. 341LC instrument and CD spectra were recorded with a Jasco mod. J-715 instrument.

High resolution mass spectra of **1a** and of the acetals **1c**–**e** were obtained with a VG ZabSpec high resolution mass spectrometer (Micromass) in the FAB-MS mode. The mass spectrometer was calibrated with PEG 400 and 3-nitrobenzylalcohol (Fluka) was used as a matrix.

Computer graphics and molecular modelling were performed on a Silicon Graphics Indy workstation using the Spartan ver. 5.0 program package (Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA).

3.2. Synthesis

3.2.1. (4R,5R)-2-(p-Nitrophenyl)-1,3-dioxolane-4,5-dicarboxylic acid bis-allylamide **1c**

In a 100 ml two-necked round bottomed flask with a reflux condenser and a reversed Dean–Stark water separator, a chloroform solution of (+)-*N*,*N*′-diallyl-L-tartaradiamide (1.0 g), *p*-nitrobenzaldehyde (0.83 g) and *p*-toluenesulfonic acid monohydrate (0.30 g) was refluxed for 45 h. The solution was extracted with diluted sodium carbonate (2×50 ml), water (50 ml), diluted sodium bisulfite (50 ml) and water (50 ml). The solution of the crude product was dried ($MgSO_4$) and evaporated to dryness, giving 1.50 g (84%). The product was purified by flash chromatography on silica with ethyl acetate as eluent, yielding 0.78 g (49%) of white crystals. Mp 85°C. $[\alpha]_D^{20}=+2.58$ (*c* 0.3, EtOAc). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 212, −0.400.

3.2.2. (4R,5R)-2-(1′-Naphthyl)-1,3-dioxolane-4,5 dicarboxylic acid bis-allylamide **1d**

With the equipment described above, a chloroform solution of (+)-*N*,*N*′-diallyl-L-tartaradiamide (1.0 g), 1-naphthaldehyde (0.75 ml) and *p*-toluenesulfonic acid monohydrate (0.14 g) was refluxed for 6 days. After work-up, the product was purified by flash chromatography on silica with ethyl acetate/hexane (2/1) as eluent, yielding 2.0 g (87%) of a yellow oil. $[\alpha]_D^{20}=+3.50$ (*c* 0.4, EtOAc). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 234, −0.050.

*3.2.3. (4*R,*5*R*)-2-(9′-Anthryl)-1,3-dioxolane-4,5 dicarboxylic acid bis-allylamide* ***1e***

Reflux of (+)-DATD (1.0 g) and 9-anthraldehyde (1.13 g) for three weeks using the method described, yielded, after work-up and purification as described for **1d**, 1.18 g (65%) of a crystal mass. Mp 89.5°C. $[\alpha]_D^{20}=-82.1$ (*c* 0.095, EtOAc). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 278, −0.252.

3.3. trans-*9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid* ***1a′***

Compound **1a′** was prepared by a cycloaddition reaction of fumaric acid with anthracene,[10] giving a product of mp 253–254°C in 82% overall yield. Resolution of **1a′** was achieved with brucine in ethanol[8] yielding (−)-(*S*,*S*)-**1a′** in 95% e.e. after a single recrystallization. Mp 222–224°C, (Ref. 11: mp 220.5°C). $[\alpha]_{546}^{20}=-15.5$ (*c* 2.03, dioxane) (Ref. 8: $[\alpha]_{578}^{25}=-15.3$ (*c* 2, dioxane), Ref. 11: $[\alpha]_{405}=-35.6$ (*c* 1.96, dioxane)). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 233, −0.629. $[\alpha]_{546}^{20}=-15.5$ (*c* 2.03, dioxane) (Ref. 8: $[\alpha]_{578}^{25}=-15.3$ (*c* 2, dioxane), Ref. 11: $[\alpha]_{405}=-35.6$ (*c* 1.96, dioxane)). LC (Kromasil CHI-TBB, 2.5% 2-propanol, 0.1% HOAc in hexane): $k_1'=7.8$, $\alpha=1.3$.

*3.3.1. (+)-(*S,S*)-*trans-*9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid bis-allylamide* ***1a***

Reaction of **1a′** (1.0 g) with diisopropyl carbodiimide (DIPC) (1.27 ml) and allylamine (1.02 ml) in the presence of 1-hydroxybenzotriazole (HOBT) (1.10 g) in chloroform/5% DMF gave after work-up 1.30 g (98%) of **1a** of mp 152°C. $[\alpha]_D^{20}=+39.4$ (*c* 0.17, EtOAc). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 234, +3.17.

1a: ^{1}H NMR ($CDCl_3$): δ values: 2.87 (s, 2H), 3.80 (m, 4H), 4.65 (s, 2H), 5.03 (d, 2H), 5.07 (d, 2H), 5.76 (m, 2H), 6.86 (s, br, 2H), 7.14 (m, 4H), 7.29 (d, 2H), 7.41 (d, 2H). HRMS found: $(M+H)^+$ 373.18890; $C_{24}H_{25}N_2O_2$ requires 373.19160.

LC (Kromasil CHI-TBB, 2.5% 2-propanol, 0.2% HOAc in hexane): $k_1'=1.68$, $\alpha=2.2$.

1c: ^{1}H NMR ($CDCl_3$) δ values: 3.92 (t, 2H), 4.00 (m, 2H), 4.78 (q, 2H), 5.20 (m, 4H), 5.84 (m, 2H), 6.17 (s, 1H), 6.84 (s (br), 2H), 7.73 (d, 2H), 8.28 (d, 2H). HRMS found: $(M+H)^+$ 362.13792; $C_{17}H_{20}N_3O_6$ requires 362.13521.

1d: ^{1}H NMR ($CDCl_3$) δ values: 3.78 (m, 2H), 4.02 (m, 2H), 4.93 (q (AB), 2H), 4.99 (dd, 1H), 5.02 (dd, 1H), 5.20 (dd, 1H), 5.27 (dd, 1H), (5.61 (m, 1H), 5.90 (m, 1H), 6.62 (s (br), 1H), 6.74 (s, 1H), 6.88 (s (br), 1H), 7.54 (m, 3H), 7.81 (d, 1H), 7.92 (m, 2H), 8.18 (d, 1H). HRMS found: $(M+H)^+$ 367.16485; $C_{21}H_{23}N_2O_4$ requires 367.16578.

1e: ^{1}H NMR ($CDCl_3$) δ values: 3.94 (m, 1H), 4.04 (m, 3H), 5.02 (q (AB), 2H), 5.18 (ddd, 2H), 5.24 (ddd, 2H), 5.88 (m, 2H), 6.90 (s (b), 1H), 6.96 (s (b), 1H), 7.40 (s, 1H) 7.52 (m, 4H), 8.04 (d, 2H), 8.48 (d, 2H), 8.58 (s, 1H). HRMS found: $(M+H)^+$ 417.17990; $C_{25}H_{25}N_2O_4$ requires 417.18143.

*3.4. (+)-(*S,S*)-11,12-Diamino-9,10-dihydro-9,10-ethanoanthracene* ***2a′***

(−)-(*S*,*S*)-**1a′** (1.43 g, 4.85 mol) was converted to the acid chloride by reaction with thionyl chloride in benzene. Reaction of the crude acid chloride with sodium azide in anhydrous DMF[11] yielded 1.20 g (86%) of the diisocyanate. A 793 mg (2.75 mmol) amount of this was dissolved in dichloromethane (10 ml) and 8 M hydrochloric acid (15 ml) was added. The two-phase system was stirred at room temperature for 21 h. The layers were separated and the aqueous layer extracted with dichloromethane (2×15 ml). The aqueous phase was made alkaline and extracted with ether (2×30 ml) and dichloromethane (3×30 ml). The combined organic phases were washed

with brine, dried ($MgSO_4$) and evaporated to dryness, giving 41.3 mg (59%) of the diamine **2a**′. $[\alpha]_D^{20} = +22.4$, $[\alpha]_D^{20} = +28.1$ (*c* 2.34, MeOH) (Ref. 11: $[\alpha]_D = +20.5$, $[\alpha]_{405} = +81.3$ (*c* 2.275, MeOH)). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 242, −0.515.

3.4.1. Bis-3,5-dinitrobenzoyl derivative[†]

Reaction of **2a**′ with 3,5-dinitrobenzoyl chloride in pyridine afforded the bis-derivative. Racemate:[12] LC (Kromasil CHI-DMB, 10% 2-propanol in hexane): $k'_1 = 20.8$, $\alpha = 1.1$. (*S*,*S*)-form: enantiomeric purity >99% (from LC determination).

*3.4.2. Bis-acryloyl derivative **2a***

(+)-(*S*,*S*)-**2a**′ (31.4 mg, 0.133 mmol) was dissolved in a mixture of chloroform (2 ml) and pyridine (0.1 ml). The solution was cooled to ca. −25°C and a solution of acryloyl chloride (25 μl, 0.295 mmol) in chloroform (1 ml) was added dropwise. The reaction mixture was stirred for 15 min and after attaining room temperature for 4 h. Washing with 1 M hydrochloric acid (3×6 ml), 0.1 M sodium hydroxide (3×6 ml) and water (2×6 ml), followed by drying ($MgSO_4$) and evaporation, yielded 16.3 mg (36%) of **2a**, mp 275–276°C.

LC (Kromasil CHI-EB,[‡] 2.5% 2-propanol in hexane): $k'_1 = 2.4$, $\alpha = 1.6$.

2a: ^1H NMR ($CDCl_3$) δ values: 4.07 (d, 2H), 4.43 (s, 2H), 5.40 (d (br), 2H), 5.62 (d, 2H), 5.95 (dd, 2H), 6.24 (d, 2H), 7.20 (t (split), 4H, 7.30 (d (split), 2H, 7.40 (d (split), 2H.

Acknowledgements

This work was supported by a grant from the Swedish Foundation for Strategic Research.

References

1. Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis*; Wiley: New York, 1999.
2. Allenmark, S.; Andersson, S.; Möller, P.; Sanchez, D. *Chirality* **1995**, *7*, 248–256.
3. Andersson, S.; Allenmark, S; Möller, P.; Persson, B.; Sanchez, D. *J. Chromatogr. A* **1996**, *741*, 23–31.
4. Kromasil Chiral Phases for HPLC, SFC and SMB; Application Guide. EKA Chemicals AB, Separation Products, SE-44580 Bohus, Sweden.
5. Allenmark, S.; Skogsberg, U. *Enantiomer* **2000**, in press.
6. See e.g.: (a) Casy, A. F. *Trends Anal. Chem.* **1993**, *12*, 185–189; (b) Uccello-Baretta, G.; Pini, D.; Rosini, C.; Salvadori, P. *J. Chromatogr. A* **1994**, *666*, 541–548; (c) Yashima, E., Yamada, M.; Yamamoto, C.; Nakashima, M.; Okamoto, Y. *Enantiomer* **1997**, *2*, 225–240.
7. (a) Tsuzuki, F.; Koyama, M.; Tanabe, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1008–1013; (b) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171–2209.
8. Brienne, M.-J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1973**, 190–197.
9. König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798.
10. Bachmann, W. E.; Scotter, L. B. *J. Am. Chem. Soc.* **1948**, *70*, 1458–1461.
11. Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.
12. Pirkle, W. H.; Liu, Y.; Welch, C. J. *Enantiomer* **1998**, *3*, 477–483.

[†] Liquid chromatographic resolution of the bis-3,5-dinitrobenzoyl derivative of *rac*-**2a**′ has been described recently (Ref. 12).

[‡] Experimental column containing a polymer made from *O*,*O*′-bis-[3,5-(pivaloyamino)-benzoyl]-*N*,*N*′-dialkyl-L-tartaradiamide as chiral stationary phase.