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ω-Amino acids and lactams with chiral biaryl axis †

Miloš Tichý, Jana Holanová and Jiří Závada *

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague, Czech Republic

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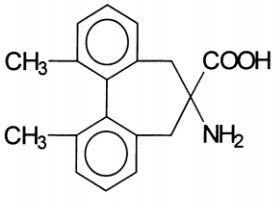
Abstract

The optically active amino acids (*R*)-**7** and (*S*)-**8** were prepared as the first representatives of ω-amino acids possessing a biaryl axis as the sole element of chirality.

1. Introduction

Many important properties and functions of amino acids depend on their chirality which usually originates from the presence of a stereogenic carbon atom. Recently, however, we have reported the first α-amino acid (**1**) whose chirality does not result from a stereogenic carbon but from a chiral biaryl axis.[1] Subsequently, Mazaleyrat with coworkers[2] have described an analogous axially chiral β-amino acid (**2**).



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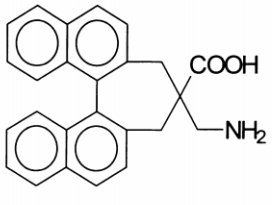

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Continuing in this endeavour, we have now examined lactams **3**–**5** and their hydrolytic cleavage into the corresponding axially chiral ω-amino acids **6**–**8** (Scheme 1). Both the lactams and the ω-amino acids may find interesting application in the design of peptidomimetics[3,4] and also in the synthesis of helical polymers.[5–7]

* Corresponding author. E-mail: zavada@uochb.cas.cz

† Dedicated to the memory of Professor Otto Wichterle.

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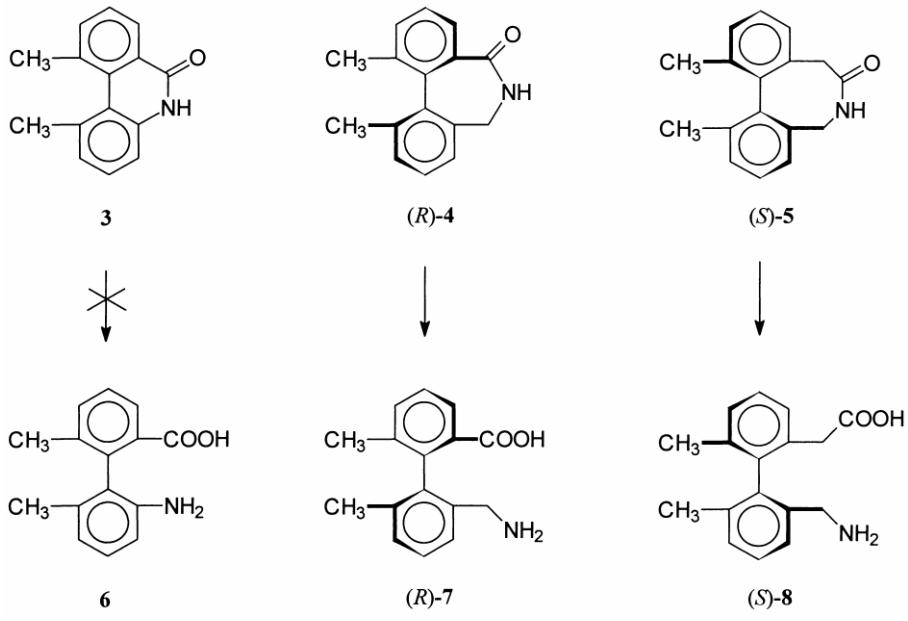


Scheme 1.

2. Results and discussion

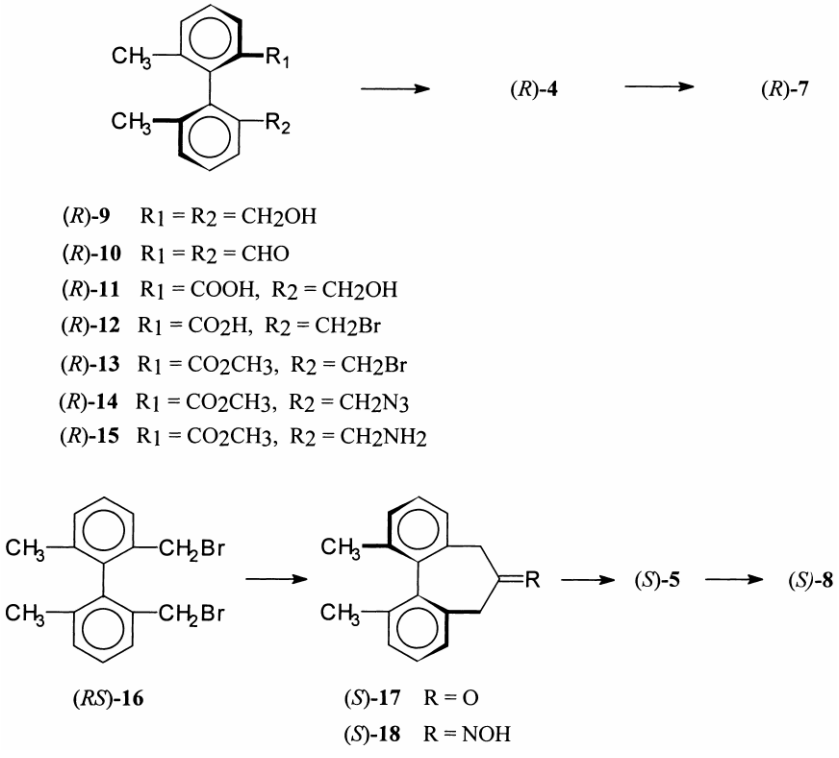
2.1. Synthesis

The lowest homologue, 1,10-dimethylphenanthridone (**3**), is already known and was prepared according to the literature.[8]

The seven-membered lactam (*RS*)-**4** was prepared starting from dialdehyde (*RS*)-**10**, which was converted by Cannizzaro reaction into the hydroxy acid (*RS*)-**11** (Scheme 2). The reaction required vigorous conditions (4 h reflux with 10M sodium hydroxide), presumably because of the steric compression of the methyls in the transition state.[9] The acid (*RS*)-**11** was treated with boiling 40% HBr to give bromo acid (*RS*)-**12** which was esterified with diazomethane and the obtained ester (*RS*)-**12** was converted into azido ester (*RS*)-**14** by reaction with sodium azide. Reduction over 10% Pd/C gave the amino ester (*RS*)-**15**, which partially cyclized on standing, and therefore was directly subjected to sodium methoxide-induced cyclization to the lactam (*RS*)-**4**. The overall yield of the whole reaction sequence (*RS*)-**10** to (*RS*)-**4** was 65%. The same route was applied to the enantiomerically pure series, starting from dialdehyde (*R*)-**10** which in turn was obtained from enantiomerically pure diol (*R*)-**9** of known absolute configuration[10] (Scheme 2). In spite of some steps performed at reflux temperature (about 100°C), the whole reaction sequence proceeded without racemization and the obtained lactam (*R*)-**4** was free from the other antipode as shown by chiral HPLC (Whelk, Merck).

The eight-membered ring lactam (*S*)-**5** was prepared by Beckmann rearrangement of the oxime (*S*)-**18** at 0°C (Scheme 2). The parent ketone (*S*)-**17** of known absolute configuration[11] was obtained by preparative HPLC resolution (triacetylcellulose) of the racemate (*RS*)-**17**, prepared in good yield by reaction of dibromide (*R,S*)-**16** with tosylmethyl isocyanide[12].

The amino acids (*R*)-**7** and (*S*)-**8** were obtained by acid hydrolysis of the corresponding lactams (*R*)-**4** and (*S*)-**5**, respectively (Scheme 1). Whereas the eight-membered lactam (*S*)-**5** was hydrolyzed smoothly on reflux with conc. hydrochloric acid for 2 h, the seven-membered one (*R*)-**4** required 15 h reflux with



Scheme 2.

a mixture of conc. hydrochloric acid and acetic acid, thus reflecting different chemical stabilities of the lactam systems. Upon heating to their melting points, both amino acids decomposed by formation of the starting lactams.

Attempted hydrolysis of the six-membered lactam **3** by prolonged boiling with conc. hydrochloric acid completely failed. Undoubtedly, mesomeric stabilization of the lactam ring is the responsible factor.[13–17]

2.2. Enantiomeric excess and stability

The enantiomeric excess of lactams (*R*)-**4** and (*S*)-**5** has been confirmed by HPLC on a chiral column (Whelk). Both the lactams were configurationally stable on heating at 120°C in toluene for 10 h. Of note is their configurational stability on sublimation. When either of them is heated under its melting point [230°C for (*S*)-**5** or 260°C for (*R*)-**4**] on a Kofler hot stage, it sublimes to the microscope cover glass without any loss of enantiomeric excess (HPLC); only after melting does it gradually racemize. Also, the amino acids (*R*)-**7** and (*S*)-**8** did not racemize on heating at 120°C (in 0.5M HCl) for 10 h and since they were prepared from the enantiomerically pure lactams, they undoubtedly are enantiomerically pure.

Unlike the configurationally highly stable and HPLC-resolvable seven- and eight-membered lactams, the lowest member of the series, lactam **3**, could not be resolved on chiral HPLC (triacetylcellulose or Whelk). Apart from the possibility of unsuitable chiral selector, one may a priori expect that the lactam **3** (in contrast to the corresponding amino acid **6**) will be configurationally labile. Pertinent information in this respect may be drawn from the available data on 4,5-dimethylphenanthrene.[18] This compound, which is non-planar (the dihedral angle between the mean phenyl planes being 27.9°), possesses a barrier to racemization of 16.1 kcal/mol and its antipodes can be separated at cryogenic temperatures. As we

have recently demonstrated in a closely similar situation, the racemization barriers of axially chiral biaryl dilactams and their carbocyclic analogues are almost identical.[19]

3. Conclusion

Novel axially chiral lactams **4** and **5** and the corresponding ω-amino acids **7** and **8** were prepared enantiomerically pure. The very high configurational stability established for these compounds constitutes an important prerequisite[20] for application in the synthesis of homochiral polyamide polymers.

4. Experimental

*4.1. (*RS*)-6,6′-Dimethyl-1,1′-biphenyl-2,2′-dicarboxaldehyde (*RS*)-**10***

A solution of diol[10c] (*RS*)-**9** (3.1 g, 12.8 mmol) in CH_2Cl_2 (60 ml) was added to a stirred suspension of pyridinium chlorochromate[21] (8.5 g, 15 mmol) in CH_2Cl_2 (50 ml) under cooling with cold water. After stirring for 2 h the mixture was diluted with ether (300 ml), stirred for 20 min, decanted from solid material and passed through a column of silica gel. Evaporation of the eluate gave pure dialdehyde (*RS*)-**10**, mp 118–119°C (reported[22] mp 114°C). Yield 2.95 g (96%).

*4.2. (*RS*)-2′-Hydroxymethyl-6,6′-dimethyl-1,1′-biphenyl-2-carboxylic acid (*RS*)-**11***

A stirred mixture of the dialdehyde (*RS*)-**10** (2.38 g, 10 mmol), NaOH (40 g, 1.0 mol), water (80 ml) and dioxane (15 ml) was refluxed for 4 h. After cooling, the mixture was diluted with water, extracted with ether, and the aqueous phase acidified with conc. hydrochloric acid. The product was taken up in ether, the extract was washed with water, dried, and the solvent was evaporated. The residue was triturated with light petroleum to give 2.19 g (86%) of hydroxy acid (*RS*)-**11**, mp 140–142°C (ether–light petroleum). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.75 (m, 6H), 4.28 (d, 1H, *J*=12 Hz); 4,19 (d, 1H, *J*=12 Hz), 1.87 (s, 3H), 1.84 (s, 3H). MS (FAB): 239 (M+1−H_2O). Anal. calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.16; H, 6.39.

*4.3. (*RS*)-2′-Bromomethyl-6,6′-dimethyl-1,1′-biphenyl-2-carboxylic acid (*RS*)-**12***

The crude hydroxy acid (*RS*)-**11** (2.19 g, 8.6 mmol) was refluxed with 40% aqueous HBr (45 ml) for 3 h. The mixture was diluted with water, the product taken up in ether and the extract washed with water. After addition of sodium sulfate and charcoal, the mixture was filtered and the solvent evaporated. The product was pure according to TLC (ether:light petroleum=1:1), mp 101–102°C (heptane). Yield 2.71 g (98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93–7.16 (m, 6H), 4.08 (s, 2H), 1.98 (s, 3H), 1.88 (s, 3H). MS (EI): 318, 320 (M^+, 19), 239 (61), 195 (100), 179 (49), 165 (31). Anal. calcd for $C_{16}H_{15}BrO_2$: Br, 25.04. Found: Br, 24.87.

*4.4. (*RS*)-1,11-Dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (*RS*)-**4***

The bromo acid (*RS*)-**12** (2.71 g, 8.5 mmol) was esterified with ethereal diazomethane and the solvent was evaporated. The obtained bromo ester (*RS*)-**13** was stirred with sodium azide (3.2 g, 50 mmol) in

DMF (30 ml) at rt for 3 h. The mixture was partitioned between water and ether and the ethereal extract was thoroughly washed with water and dried. Evaporation of the solvent gave 2.34 g (93%) of the azido ester (*RS*)-**14** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.85 (m, 6H, H-arom.), 3.91 (s, 2H, CH_2), 3.58 (s, 3H, OCH_3), 1.93 (s, 3H, CH_3), 1.92 (s, 3H, CH_3). The crude azido ester (*RS*)-**14** (2.34 g, 7.9 mmol) was hydrogenated in methanol (100 ml) over 10% Pd/C (500 mg) in a stream of hydrogen. After the reduction was over (1 h, TLC), the catalyst was filtered off and the solvent evaporated to afford oily amino ester (*RS*)-**15** (2.09 g, 98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.8–7.1 (m, 6H, H-arom.), 3.91 (s, 2H, CH_2), 3.58 (s, 3H, OCH_3), 1.93 (s, 3H, CH_3), 1.88 (s, 3H, CH_3).

The crude amino ester (*RS*)-**15** (2.09 g, 8.7 mmol) was dissolved in 0.1M methanolic sodium methoxide (6 ml, 0.6 mmol) and set aside at rt overnight. The deposited crystals were collected and washed with cold methanol to give 1.49 g (84%) of lactam (*RS*)-**4**, mp 293–295°C (ethanol). The overall yield starting from the dialdehyde (*RS*)-**10** was thus 65%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80–7.10 (m, 6H, H-arom.), 6.88 (t, 1H, NH), 4.12 (dd, 1H, $J_{(gem)}$=6.4 Hz, $J_{(CH,NH)}$=14.3 Hz, CH_2), 3.82 (dd, 1H, $J_{(gem)}$=6.4 Hz, $J_{(CH,NH)}$=14.3 Hz, CH_2), 2.22 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). MS (FAB): 238 (M+1). Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.89; H, 6.48; N, 6.05.

4.5. (R)-6,6′-Dimethyl-1,1′-biphenyl-2,2′-dicarboxaldehyde (R)-10

The optically active compound, mp 116–117°C (ether), $[\alpha]_D^{22}$ +88.2 (*c* 0.5; ethanol), was obtained in 92% yield from 3.0 g of the optically active diol[10c] (*R*)-**9** ($[\alpha]_D^{22}$ +105.7 (*c* 0.5; benzene)), using the same procedure as described for the racemic compound (*RS*)-**10**.

4.6. (R)-1,11-Dimethyl-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (R)-4

The optically active lactam, mp 315–316°C, $[\alpha]_D^{22}$ +39.2 (*c* 0.2; chloroform), was prepared from the dextrorotatory dialdehyde (*R*)-**10** (2.70 g, 11.3 mmol) in 54% overall yield in exactly the same manner as described for the racemic series, except that no crystallization was involved along the synthetic path. The intermediate compounds (*R*)-**11** ($[\alpha]_D^{22}$ +8.6 (*c* 0.5; methanol)), (*R*)-**12** ($[\alpha]_D^{22}$ −70.6 (*c* 0.5; methanol)), (*R*)-**13**, (*R*)-**14** and (*R*)-**15** had identical ^{1}H NMR spectra with those of the racemic ones.

4.7. (R)-2′-Aminomethyl-6,6′-dimethyl-1,1′-biphenyl-2-carboxylic acid (R)-7

Lactam (*R*)-**4** (200 mg, 0.84 mmol) was refluxed with a mixture of conc. hydrochloric acid (7 ml) and acetic acid (4 ml). After 8 h, another portion of hydrochloric acid (1 ml) was added and the reflux was continued for further 8 h. The volatiles were evaporated in vacuo, the residue was dissolved in water (20 ml) and the insoluble material was removed by filtration. The filtrate was reduced in vacuo and the residue was coevaporated with water. The dry hydrochloride was dissolved in water and passed through a column of Dowex 50X. Elution with 3% ammonium hydroxide, evaporation and crystallization from water gave free acid (*R*)-**7** (100 mg, 46%), mp 300–302°C (decomp.) with transition at 255–260°C, $[\alpha]_D^{22}$ +155.0 (*c* 0.5; methanol). Anal. calcd for $C_{16}H_{17}NO_2 \cdot 0.5H_2O$: C, 72.79; H, 6.86; N, 5.31. Found: C, 72.60; H, 6.67; N, 5.25. ^{1}H NMR (200 MHz, CD_3OD): δ 7.70–7.45 (m, 6H, H arom.), 4.02 (d, 1H, $J_{(gem)}$=12.5 Hz, CH_2), 3.70 (d, 1H, $J_{(gem)}$=12.5 Hz, CH_2), 2.16 and 2.03 (2×s, 2×3H (2×CH_3).

4.8. (R)- and (S)-5,7-Dihydro-1,11-dimethyl-6H-dibenzo[a,c]cyclohepten-5-one (R)-**17** and (S)-**17**

A solution of NaOH (3.8 g, 95 mmol in 5 ml water) was added at 0°C to a mixture of dibromide[10c] (*RS*)-**16** (7.0 g, 19 mmol), tosylmethyl isocyanide (4.1 g, 21 mmol), tetrabutylammonium iodide (0.35 g, 1.0 mmol) and dichloromethane (50 ml). After stirring at rt overnight, the organic layer was separated, dried and the solvent was evaporated. The residue (10.0 g) was mixed with dichloromethane (15 ml) and ether (40 ml) and stirred with conc. HCl (6 ml) for 4 h. The reaction mixture was partitioned between water and ether, the ether layer was washed with water and $NaHCO_3$, dried and the solvent was evaporated. The residue was extracted with light petroleum (50 ml), the extract was mixed with charcoal, filtered and concentrated. Chromatography of the residue (4.6 g) on silica gel in ether:light petroleum (1:5) afforded ketone (*RS*)-**17** (3.5 g, 78%), mp 72–74°C (reported[11] mp 61–63°C). The racemic ketone (2.0 g) was separated into enantiomers by chromatography on a 4×80 cm column of triacetylcellulose (TAC) in ethanol (five 400 mg/5 ml injections, flow rate 3 ml/min). The chromatography gave 754 mg (38%) of (*S*)-**17**, mp 60–62°C, $[\alpha]_D^{22}$ −610.8 (*c* 1; benzene) (reported[11b] mp 61–63°C, $[\alpha]_D^{28}$ −628 (*c* 1; benzene)) and 702 mg (35%) of (*R*)-**17**, mp 60–62°C, $[\alpha]_D^{22}$ +597 (*c* 1; benzene) (reported[11b] mp 61.5–63°C, $[\alpha]_D^{23}$ +617 (*c* 1.6; benzene)). According to analytical HPLC on TAC, both antipodes were enantiomerically pure.

4.9. (S)-5,7-Dihydro-1,11-dimethyl-6H-dibenzo[a,c]cyclohepten-6-one oxime (S)-**18**

The compound was prepared by oximation of ketone (*S*)-**17** in 94% yield, mp 186–188°C (toluene:light petroleum), $[\alpha]_D^{22}$ −439 (*c* 0.5; ethanol), enantiomerically pure according to HPLC (triacetylcellulose, ethanol). Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N,5.57. Found: C, 81.51; H, 6.77; N, 5.65. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.2–7.05 (m, 6H, H arom.), 4.15 (d, 1H, C*H*H), 3.24 (s, 2H, CH_2), 2.96 (d, 1H, C*H*H), 2.16 and 2.14 (2×s, 2×3H, 2×CH_3).

4.10. (S)-7-Aza-5,7-dihydro-1,11-dimethyl-6H-dibenzo[a,c]cycloocten-6-one (S)-**5**

To a stirred ice-cold solution of the oxime (*S*)-**18** (627 mg, 2.5 mmol) in acetone (15 ml) was added 2M NaOH (2 ml, 4 mmol) followed by a solution of benzenesulfonyl chloride (700 mg, 4 mmol) in acetone (10 ml). After cooling for 30 min, the ice bath was removed and the mixture was stirred at rt for 4 h and then set aside overnight. The solvent was evaporated in vacuo and the dry residue was partitioned between dichloromethane and a solution of $NaHCO_3$. The organic layer was dried and evaporated. Crystallization of the residue from toluene afforded 408 mg (76%) of the product, mp 242–243°C, $[\alpha]_D^{22}$ −315 (*c* 0.5; ethanol). Pure according to chiral HPLC (Whelk, Merck, 15% i-PrOH in heptane). Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.21; H, 6.84; N, 5.37.

4.11. (S)-2′-Aminomethyl-6,6′-dimethyl-1,1′-biphenyl-2-acetic acid (S)-**8**

Lactam (*S*)-**5** (90 mg, 0.36 mmol) was refluxed with hydrochloric acid (1:1, 4 ml) for 2 h. The resulting solution was evaporated and the residue co-evaporated with water (2×) and the free amino acid was liberated on Dowex 50X by the usual procedure. Yield 93 mg (96%) of amino acid (*S*)-**8**, mp 233–235°C (decomp.) (water), $[\alpha]_D^{22}$ −233 (*c* 0.5; methanol). Anal. calcd for $C_{17}H_{19}NO_2 \cdot 0.5H_2O$: C, 73.36; H, 7.24; N, 5.03. Found: C, 73.24; H, 6.99; N, 4.86. ^{1}H NMR (200 MHz, CD_3OD): δ 7.6–7.4 (m, 6H, H arom.), 4.00 and 3.61 (2×d, 2×1H, $J_{(gem)}$=12.8 Hz, CH_2N), 3.50 and 3.10 (2×d, 2×1H, $J_{(gem)}$=14.2 Hz, CH_2CO), 2.07 and 2.04 (2×s, 2×3H, 2×CH_3).

4.12. Attempted hydrolysis of 1,10-dimethylphenanthridone **3**

1,10-Dimethylphenanthridone[8] (**3**) (44 mg) in concentrated hydrochloric acid (4 ml) was refluxed for 20 h with addition of further acid (2 ml) after 8 and 15 h. The reaction mixture was evaporated in vacuo, the residue was dissolved in water (10 ml) and filtered. The filtrate on evaporation gave no discernible residue.

4.13. Racemization experiments

4.13.1. Lactams

Lactam (*R*)-**4** or (*S*)-**5** (3 mg) was dissolved in hot toluene (5 ml) and the solution was heated in a glass autoclave at 120°C for 10 h. The solvent was evaporated and the residue analyzed on a Whelk-*R*,*R* column (Merck), elution with 15% 2-propanol in heptane (flow rate 1.0 ml/min). In both cases the chromatography did not detect the presence of the second antipode (less than 0.5%).

4.13.2. Acids

A solution of acid (*R*)-**7** or (*S*)-**8** in 0.5M HCl ($c \approx 0.5$) was heated in a sealed ampoule at 120°C for 10 h. After cooling to room temperature, the optical rotation of the solution was compared with that measured before the heating. No significant differences were observed.

4.13.3. Sublimation

Optically active lactam (*R*)-**4** or (*S*)-**5** was placed on a microscope glass in a Kofler hot stage. A 2 mm high metal ring was put on the glass and another microscope glass was placed on the top of the ring. Heating at the appropriate temperature [230°C for (*S*)-**5** or 260°C for (*R*)-**4**] resulted in relatively rapid sublimation to the upper glass from which the sublimate was scratched off and analyzed by HPLC (Whelk).

4.13.4. Melting experiments

Optically active amino acid (*R*)-**7** or (*S*)-**8** was heated in a Kofler hot stage apparatus until it melted. The microscope glass with the melt was then taken out, cooled and the solid analyzed by HPLC on a Whelk column. The obtained lactams contained the other antipode in quantities which depended on how rapidly the material was removed from the stage. The same melting procedure performed with enantiomerically pure lactams (*R*)-**4** or (*S*)-**5** gave lactams whose enantiomeric excess depended on the time for which the compound remained in the molten state.

Acknowledgements

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References

1. Ridvan, L.; Abdallah, N.; Holakovský, R.; Tichý, M. *Tetrahedron: Asymmetry* **1996**, *7*, 231–236.
2. Gaucher, A.; Bintein, F.; Wakselman, M.; Mazaleyrat, J.-P. *Tetrahedron Lett*. **1998**, *39*, 575–578.

3. The parent (nonmethylated) homologue of **7**, 2′-(aminomethyl)biphenyl-2-carboxylic acid, which is conformationally mobile and thus optically unresolvable, has been already investigated as a β-sheet surrogate.[4]
4. (a) Brandmeier, V.; Sauer, W. H. B.; Feigel, M. *Helv. Chim. Acta* **1994**, *77*, 70–85. (b) Brandmeier, V.; Feigel, V. *Tetrahedron* **1989**, *45*, 1367–1376.
5. Inherently dissymmetric polyamides from axially chiral biaryl diacids and achiral diamines as well as from axially chiral diamines and achiral diacids have already been prepared;[6] synthesis and stereochemistry of helical polymers has repeatedly been reviewed.[7]
6. (a) Overberger, C. G.; Yoshimura, T.; Ohnishi, A.; Gomes, A. S. *J. Polym. Sci. A* **1970**, *8*, 2275–2291. (b) Schulz, R. C.; Jung, R. H. *Makromolekulare Chemie* **1968**, *116*, 190–202.
7. (a) Okamoto, Y.; Nakano, T. *Chem. Rev*. **1994**, *94*, 349–372. (b) Wulff, G. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 21–37.
8. Keene, B. R. T.; Tissington, P. *J. Chem. Soc*. **1965**, 3032–3037.
9. Abbaszadeh, M. R.; Bowden, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2081–2089.
10. (a) Siegel, M.; Mislow, K. *J. Am. Chem. Soc*. **1958**, *80*, 473–476. (b) McGinn, F. A.; Lazarus, A. K.; Siegel, M.; Ricci, J. E.; Mislow, K. *J. Am. Chem. Soc*. **1958**, *80*, 476–480. (c) Wittig, G.; Zimmermann, H. *Chem. Ber*. **1953**, 629–640.
11. (a) Mislow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl Jr., G. H. *J. Am. Chem. Soc*. **1964**, *86*, 1710–1733. (b) Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, K. *J. Am. Chem. Soc*. **1962**, *84*, 1455–1478.
12. Possel, O.; van Leusen, A. M. *Tetrahedron Lett*. **1977**, *48*, 4229–4232.
13. This behaviour is also in accordance with the observation that the 'parent' (unsubstituted) phenanthridone is not hydrolyzed by strong alkali.[14] The corresponding amino acid is not known.[15]
14. Graebe, C.; Wander, C. A. *Liebigs Ann*. **276**, 245–253.
15. Although the 'parent' amino acid of this series, 2′-amino-1,1′-biphenyl-2-carboxylic acid, is reported in the Beilstein database, both the two references given are not relevant. In actual fact, one[16] reference concerns 2-(2-aminophenylthio)benzoic acid whereas the other[17] relates to 4′-amino-1,1′-biphenyl-2-carboxylic acid. Thus, to the best of our knowledge, there is hitherto no report on this elusive compound in the literature.
16. Pelz, K.; Hradil, F.; Protiva, M. *Collect. Czech. Chem. Commun*. **1968**, *33*, 1873–1879.
17. Migachev, G. L. *Zh. Org. Khim*. **1979**, *15*, 567–572.
18. Armstrong, R. N.; Ammon, H. L.; Darnow, J. N. *J. Am. Chem. Soc*. **1987**, *109*, 2077–2082.
19. Tichý, M.; Ridvan, L.; Holý, P.; Závada, J.; Císařová, I.; Podlaha, J. *Tetrahedron: Asymmetry* **1998**, *9*, 227–234.
20. Meyer, R.-V. In *Houben-Weyl: Methoden der Organische Chemie*, **E20**, 4. Aufl., G. Thieme Verlag: Stuttgart, 1987; pp. 1504–1518.
21. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett*. **1975**, 2647–2650.
22. Bacon, R. G. R.; Lindsay, W. S. *J. Chem. Soc*. **1958**, 1375–1381.