Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 231-236, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00440-8

6-Amino-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic Acid: The First Chiral α-Amino Acid without Asymmetric Carbon Atom

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Abstract: The title compound **4**, possessing a biaryl axis as the sole source of chirality, has been prepared in the enantiomerically pure (*R*) as well as racemic form by two alternative procedures starting from dibromide **1**.

Many important properties and functions of amino acids depend on their chirality. In all natural and unnatural α-amino acids reported so far, chirality depends exclusively on the presence of an asymmetric carbon.[1-3]

Now we have designed and synthesized amino acid **4**, the first α-amino acid whose chirality results from another type of molecular asymmetry, a biaryl axis. It is expected that this unusual stereochemical feature may open interesting application possibilities for this acid as well as its congeners.

Synthesis

Amino acid (*RS*)-**4** was prepared starting from dibromide (*RS*)-**1**[4] by two alternative routes (Scheme 1). In the first, compound (*RS*)-**1** reacted with ethyl acetoacetate under phase-transfer catalysis to give the cyclic keto ester (*RS*)-**2** which was then converted into the acetamido ester (*RS*)-**3** by Schmidt reaction.[5] Subsequent hydrolysis gave the desired acid (*RS*)-**4**. In the second path, diphenylmethyleneglycinenitrile[6] was alkylated with the dibromide (*RS*)-**1**, again under phase transfer catalysis. The obtained cyclic derivative (*RS*)-**5** was then hydrolyzed in two steps to give the amino acid (*RS*)-**4**. The optically active amino acid (*R*)-**4** was prepared from (*R*)-**1**[4,7] by both the routes

according to the same protocols as for the racemic series.

The latter route (**1** - **5** - **6** - **4**) proved to be better than the former (**1** - **2** - **3** - **4**), not only for the somewhat higher overall yield but also for its reproducibility: the yields of the Schmidt reaction varied considerably and in some cases a large excess of sodium azide was necessary for bringing the reaction to completion. The enantiomeric purity of acid (*R*)-**4** was checked in the following way. The acid was converted into the acetamido methyl ester (*R*)-**8** by acetylation followed by esterification with diazomethane. HPLC analysis of (*R*)-**8** on a chiral stationary phase based on 6,6'-bis(3,5-dinitrobenzamido)biphenyl-2,2'-dicarboxylic acid[8] has shown that this compound (and therefore also the amino acid (*R*)-**4**) was enantiomerically pure. Also compound (*R*)-**3** has been found optically pure on the same chiral HPLC column. These findings show that the system is thermally very stable (no racemization on refluxing with concentrated HCl for several hours).

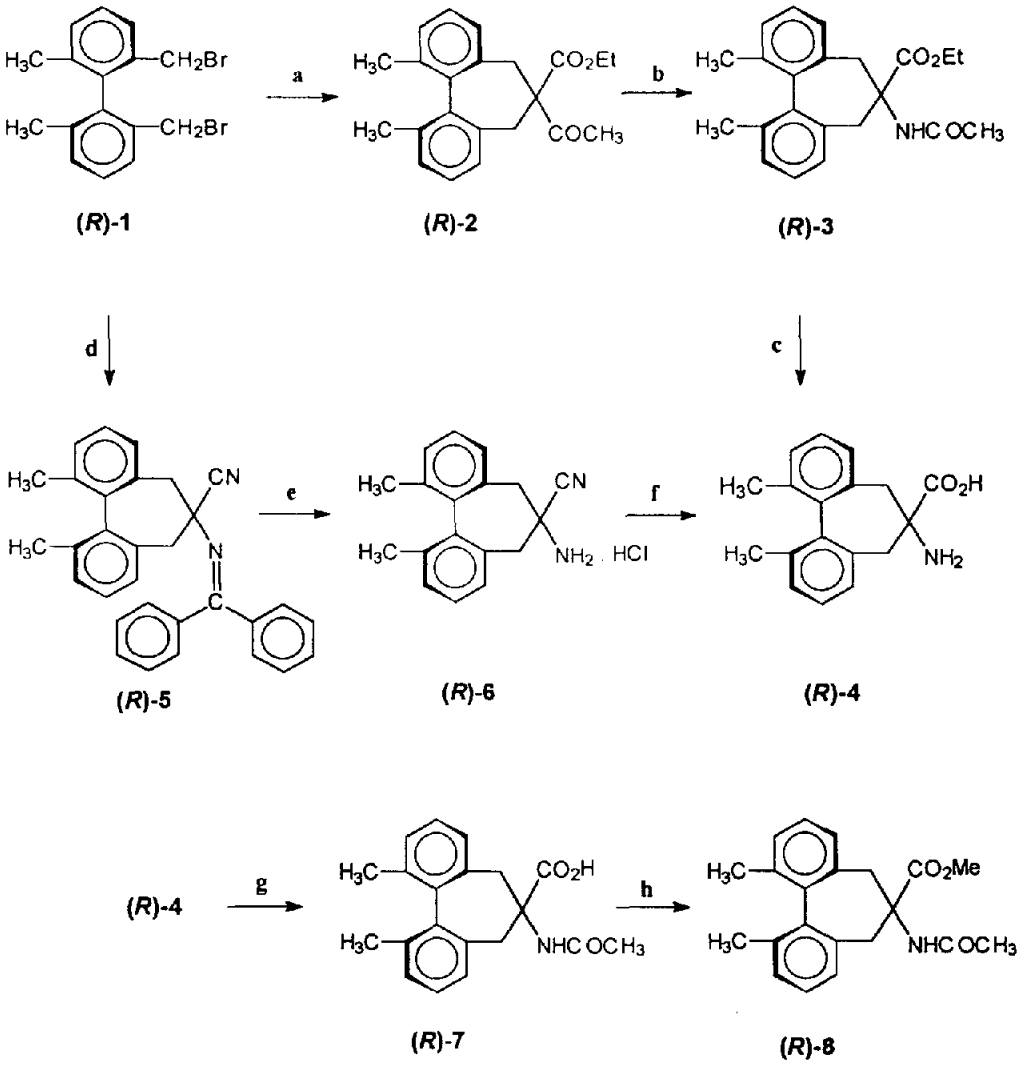
The design of new synthetic amino acids of specific properties has emerged as a challenging endeavour in connection with the expanding role of peptidomimetics in medicine.[9,10] A generally applicable method for development of peptidomimetics involves formation of conformationally restricted analogues. At the local level, this can be achieved by a modification of the individual amino acids by sterically demanding groups or incorporation of rigid structural elements. In the acid **4**, which may mimic phenylalanine, the atropoisomerism imposed by the biaryl axis provides a new and versatile tool for such a conformational restriction. In this way, it offers a promising target for further investigation since several successful modifications of phenylalanine have already been reported.[11-13]

Another prospective application of axially chiral biaryl amino acids such as **4** is expected to emerge in enantioselective transition metal catalysis. Reports concerning application of natural α-amino acids and their derivatives in the catalysis are surprisingly meagre,[14] a possible reason being easy racemization of the optically active ligands due to the enolizable α-carbon atom.[15] Such complications cannot arise with the axially chiral amino acid **4** since it lacks any enolizable α-protons. This, together with the known supreme efficiency of the C_2 biaryl grouping in chiral recognition,[17,18] makes derivatives of **4** worth of further systematic study.

Experimental

(*RS*)-6-Acetyl-1,11-dimethyl-6-ethoxycarbonyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene ((*RS*)-2). Tetra-n-butylammonium hydrogen sulfate (2.72 g; 8 mmol) was neutralized with 4 M aqueous NaOH (2 mL; 8 mmol) and a solution of (*RS*)-**1**[4] (1.47 g; 4 mmol) and ethyl acetoacetate (0.52 g; 4.0 mmol) in CH_2Cl_2 (6 mL) was added. Aqueous 4 M NaOH (2.1 mL; 8.4 mmol) was then added dropwise under vigorous stirring during 0.5 h and the stirred mixture was refluxed for 3 h. After

Scheme 1[a]



[a]Conditions: (a) $MeCOCH_2COOEt$, 4 M NaOH, $Bu_4N^+SO_4Na$, CH_2Cl_2, 60 °C, 3 h; (b) $MeSO_3H$, NaN_3, $CHCl_3$, reflux, 8 h; (c) concd HCl, dioxane, reflux, 4 h; (d) $Ph_2CH{=}NCH_2CN$, $BnEt_3N^+Cl^-$, 50% NaOH, PhMe, rt, 24 h; (e) HCl(1:10), dioxane, rt, 3 h; (f) concd HCl, reflux, 12 h; (g) $(MeCO)_2O$, dioxane-water, pH 9.5, rt, 2 h; (h) CH_2N_2, MeOH.

cooling, the mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was washed twice with ether. The combined organic phases were concentrated, the residue dissolved in ether (30 mL) and washed successively with water, 0.1 M H_2SO_4, and water. Evaporation of the solvent and crystallization from hexane gave 0.91 g (68%) of product **(*RS*)-2**, mp 131-133 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96-7.26 (m, 6H), 4.22 (q, 2H), 2.78 (d, 1H, J=13.4 Hz), 3.04 (d, 1H, J=13.4 Hz), 2.78 (d, 1H, J=14.3 Hz), 3.05 (d, 1H, J=14.3 Hz), 2.22 (s, 3H), 2.16 (s, 6H), 1.30 (t, 3H). MS(EI), m/z(%): 336 (M^+)(72), 290 (50), 247 (100), 219 (61), 193 (52). Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.59; H, 7.27.

Optically active **(*R*)-2** was prepared in 69% yield in the same way from **(*R*)-1**[4], mp 79-81 °C (hexane), $[\alpha]_D$ +87.6 (c 0.5, acetone). Its ^{1}H NMR spectrum was identical with that of the racemic compound.

(*RS*)-6-Acetylamino-1,11-dimethyl-6-ethoxycarbonyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene ((*RS*)-3). Methanesulfonic acid (2.43 mL; 37.5 mmol) was added dropwise at 0 °C to a solution of **8** (0.84 g; 2.5 mmol) in $CHCl_3$ (30 mL). Freshly activated[19] NaN_3 (0.82 g; 13 mmol) was added in portions under vigorous stirring. The stirred mixture was then refluxed for 8 h, cooled, poured into cold water, neutralized with ammonia, separated, and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with water, dried and the solvent was evaporated. Crystallization from toluene afforded 0.56 g (64%) of **(*RS*)-3**, mp 196-198 °C. ^{1}H NMR(200 MHz, $CDCl_3$) δ 6.98-7.28 (m, 6H), 5.49 (s, 1H), 4.18 (q, 2H), 2.15 (d, 1H, J=12.8 Hz), 3.12 (d, 1H, J=12.8 Hz), 2.85 (d, 1H, J=13.7 Hz), 2.97 (d, 1H, J=13.7 Hz), 2.15 (s, 3H), 2.16 (s, 3H), 1.97 (s, 3H), 1.23 (t, 3H). MS(FAB), m/z: 352 $(M+1)^+$. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 75.14; H, 7.29; N, 3.95.

Optically active **(*R*)-3** was prepared from **(*R*)-2** (0.84 g) as described for **(*RS*)-3** in 60% yield, mp 194-196 °C (toluene), $[\alpha]^{20}_D$ +165.4 (c 0.5, acetone). CD (MeOH, $\lambda_{ext}/\Delta\varepsilon$): 198 nm (end) (-68.0), 205 (-89.5), 220 (+68.8), 241 (+33.5), 270 (-2.0). Its ^{1}H NMR and MS spectra were identical with those of the racemate.

(*RS*)-6-(N-Diphenylmethylene)amino-6-cyano-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene ((*RS*)-5). A solution of dibromide **(*RS*)-1**[4] (1.84 g; 5 mmol) in toluene (1.5 mL) was added at 0° to a vigorously stirred mixture of diphenylmethyleneglycinenitrile (1.1 g; 5 mmol), benzyltriethylammonium chloride (0.14 g, 0.6 mmol), and 50% NaOH (1 mL). After stirring for 24 h at rt, the mixture was partitioned between water and toluene, the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent, followed by crystallization from ethanol, gave 1.47 g (69%) of **(*RS*)-5**, mp 192-194 °C. ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 16H), 3.10 (d, 1H, J=12.8 Hz), 2.84 (d, 1H, J=12.8 Hz), 2.79 (d, 1H, J=13.1 Hz), 2.69 (d, 1H, J=13.1 Hz), 2.21 (s, 3H), 2.20 (s, 3H). MS(FAB), m/z: 427 (M+H). Anal. Calcd for $C_{31}H_{26}N_2$: C, 87.28; H, 6.14; N, 6.57. Found: C, 87.20; H, 6.15; N, 6.73.

Optically active **(*R*)-5** was prepared in the same way from **(*R*)-1**[4] ($[\alpha]_D$ -52.0 (c 0.5, benzene); 660 mg; 1.8 mmol), in the yield of 67%, mp 161-164 °C (ethanol), $[\alpha]_D$ +101.7 (c 0.5, $CHCl_3$). Its ^{1}H NMR spectrum was identical with that of **(*RS*)-5**.

(*RS*)-6-Amino-6-cyano-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene hydrochloride ((*RS*)-6). A solution of **(*RS*)-5** (750 mg; 1.76 mmol) in dioxane (15 mL) was stirred at rt with dilute (1:10) hydrochloric acid (15 mL) for 3 h (monitored by TLC on silica gel in ether-light petroleum 5:1). The solvent was evaporated in vacuo and the solid residue was triturated with ether (3 x 10 mL) to remove benzophenone. Crystallization from aqueous ethanol gave 450 mg (83%) of product **(*RS*)-6**, mp 161-164 °C. Anal. Calcd for $C_{18}H_{19}ClN_2.0.5H_2O$: C, 70.24; H, 6.56; N, 9.10. Found: C, 70.53; H, 6.53; N, 9.11. A sample of the free aminonitrile was obtained from the hydrochloride by treatment

with ammonia. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15 (m, 6H), 2.86 (d, 1H, J=13.1 Hz), 2.75 (d, 1H, J=13.4 Hz), 2.61 (d, 1H, J=13.4 Hz), 2.29 (d, 1H, J=13.1 Hz), 2.16 (s, 6H). MS (FAB): 263 (M+H).

Optically active (*R*)-**6** was obtained from (*R*)-**5** as described for the racemate, yield 71%, mp 173-175 °C, $[\alpha]_D$ +41.4 (c 0.5, $CHCl_3$). The free base had the same ^{1}H NMR spectrum as the racemate.

(*RS*)-6-Amino-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid ((*RS*)-4). *Procedure A.* A stirred mixture of (*RS*)-**3** (673 mg, 2 mmol), dioxane (8 mL) and concd HCl (8 mL) was refluxed for 4 h. After evaporation, the dry residue was dissolved in water, treated with charcoal, filtered and made alkaline with ammonia. Evaporation of the solvent and crystallization from aqueous ethanol afforded (*RS*)-**4**, mp 226-228 °C (decomp.). Yield 526 mg (85%). ^{1}H NMR (200 MHz, CD_3OD) δ 97.02-7.32 (m, 6H), 2.31 (d, 1H, J=12.8 Hz), 2.91 (d, 1H, J=12.8 Hz), 2.55 (d, 1H, J=14.5 Hz), 3.14 (d, 1H, J=14.5 Hz), 2.07 (s, 3H), 2.11 (s, 3H). MS(FAB), m/z: 282 (M+1). Anal. Calcd for $C_{18}H_{19}NO_2.H_2O$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.37; H, 6.97; N, 4.62.

Procedure B. A mixture of compound (*RS*)-**6** (290 mg; 0.97 mmol) and concd HCl (10 mL) was refluxed for 12 h. After 3 and 6 h, another portion (10 mL) of conc. hydrochloric acid was added. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The solid on the filter and the residue were combined, dissolved in a small amount of water, and the solution was made alkaline with ammonia. The solution was evaporated and the dry residue was crystallized from water, yield 225 mg (77%), mp 227-228 °C (decomp.), identical (mp, NMR) with the product obtained by procedure A.

Optically active (*R*)-**4** was prepared by both the procedures A and B described above from (*R*)-**3** (yield 74%) and (*R*)-**6** (yield 71%), respectively. Both the routes gave identical products, mp 225-227 °C (decomp.) (aq. ethanol), $[\alpha]_D$ -23.3, $[\alpha]_{578}$ -23.7, $[\alpha]_{546}$ -22.9, $[\alpha]_{436}$ +8.1, $[\alpha]_{365}$ +147.0 (c 0.5, methanol). ^{1}H NMR spectrum was identical with that of (*RS*)-**4**. CD ($\lambda_{ext}/\Delta\varepsilon$, methanol): 195 nm (end) (-85.3), 205 sh (-57.2), 221 (+23.5), 243 (+25.5), 271 (-2.2). Anal. Calcd for $C_{18}H_{20}NO_2.H_2O$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.37; H, 6.97; N, 4.62.

(*RS*)-6-Acetylamino-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid ((*RS*)-7). Acetic anhydride (41 mg; 0.4 mmol) in dioxane (1 mL) was added to a stirred suspension of (*RS*)-**4** (56 mg; 0.2 mmol) in dioxane (1 mL) and water (1 mL) that had been adjusted to pH 9.5 with 4 M aqueous NaOH. The mixture was stirred at rt for 2 h, the pH being held at 9-10 by addition of 4 M NaOH. The solvent was evaporated, the residue dissolved in water and extracted with ether. Acidification with 4 M HCl and repeated extraction with ethyl acetate gave 61 mg (94%) of (*RS*)-**7**, mp 236-238 °C.

Optically active (*R*)-**7** was obtained from (*R*)-**4** as described for the racemate, mp 241-243 °C, yield 87%. In the preparation of (*R*)-**8** the compound was used without purification.

(*RS*)-6-Acetyl-1,11-dimethyl-6-methoxycarbonyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene ((*RS*)-8). Prepared from (*RS*)-**7** (49 mg; 0.15 mmol) in methanol (1 mL) by treatment with diazomethane. Yield 50 mg (98%), mp 254-256 °C (methanol). ^{1}H NMR(200 MHz, $CDCl_3$) δ 6.96-7.30 (m, 6H), 5.51 (s, 1H), 3.71 (s, 3H), 2.15 (d, 1H, J=12.8 Hz), 3.12 d, 2H, J=12.8 Hz), 2.85 (d, 1H, J=13.7 Hz), 2.97 (d, 1H, J=13.7), 2.15 (s, 3H), 2.16 (s, 3H), 1.97 (s, 3H). MS(FAB), m/z: 265 (M+H). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.51; H, 6.94; N, 4.14.

Optically active (*R*)-**8** was obtained as described for the racemate (*RS*)-**8** ; yield 98%, mp 202-204 °C, $[\alpha]_D$ +168.7 (c 0.5, acetone). The HPLC determination of enantiomeric purity was done with the crude (uncrystallized) product. The ^{1}H NMR spectrum was identical with that of (*R,S*)-**8**. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.97; H, 6.93; N, 4.16.

Acknowledgement. This work was supported by the Grant Agency of the Academy of Sciences of the Czech Republic (Grant No. A4055501).

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† On leave of absence from National Research Centre, Dokki, Cairo, Egypt.

1. Beyond the category of α-amino acids, we have traced down a few amino acid structures in the literature which contain elements of chirality other than asymmetric carbon atom, including 1,11-diamino-6,6'-dicarbethoxydibenzo[a,c]-1,3-cycloheptadiene[2] and 6-aminomethylspiro[3,3]heptane-2-carboxylic acid[3].
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(*Received in UK* 25 *October* 1995)