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From 3-aza-2-oxobicyclo[3.1.0]hexane to enantiopure disubstituted cyclopropane: a convenient approach to *cis*-2,3-methano-GABA

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Abstract: Starting from the diastereomerically pure 4-ethenyl pyrrolidin-2-one **5**, through simple steps the mesyl derivative **8** was obtained, which underwent intramolecular alkylation to give, in good yield, the 3-aza-2-oxobicyclo[3.1.0]hexane **9**. This compound was subsequently converted into enantiomerically pure (−)-*cis*-2,3-methano-GABA, **2**.
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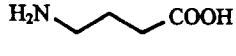
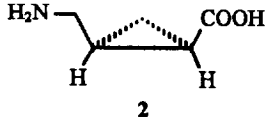
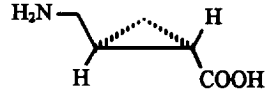
The synthesis of amino acids containing the cyclopropane ring has recently attracted much attention owing to their unique features.[1] The non-proteinogenic amino acid GABA (γ-amino butyric acid) **1** is the major inhibitory neurotransmitter in the mammalian central nervous system.[2] GABA analogs, **2** and **3**, containing a cyclopropane ring have conformationally restricted frameworks with folded or extended structures. Thus both *cis*-**2** and *trans*-**3**-isomers were prepared in the racemic and enantiomerically pure form in order to investigate the active conformers of GABA and the structural features of GABA receptors.[3]



1



2



3

As part of a program aimed at preparing non-proteinogenic amino acids with biological activity, we discovered that the 3-aza-2-oxobicyclo[3.1.0]hexane framework can be useful to synthesize **2**. In our previous work, by oxidative cyclisation mediated by Mn(III) of a methoxycarbonylacetamide, we obtained the diastereomerically pure pyrrolidin-2-one **4**, which subsequently converted to the pyrrolidin-2-one **5**.[4] In order to reach our goal, the double bond of compound **5** was cleaved by ozonolysis performed at −78°C, to give the corresponding aldehyde **6**. The subsequent reduction of **6**, performed using $NaBH_4$ in ethanol, gave the alcohol **7**. By treatment of **7** with methanesulphonyl chloride, the mesyl derivative **8** was obtained, which was then converted into the 3-aza-2-oxobicyclo[3.1.0]hexane **9**. In fact, the bicyclic framework was built on by intramolecular alkylation which readily occurred by treating **8** with Li–HMDS in THF at −10°C, and the bicyclic compound **9** was exclusively obtained in very good yield.[5] By reductive cleavage performed with Li–NH_3,[6] the phenylethyl group was easily removed to give the bicyclic amide **10**. By hydrolysis performed under acidic conditions this compound was eventually converted into the *cis*-2,3-methano-GABA **2** (Scheme 1) in the enantiomerically pure form whose spectroscopic data and specific rotation were identical with those reported in the literature.[3e,7]

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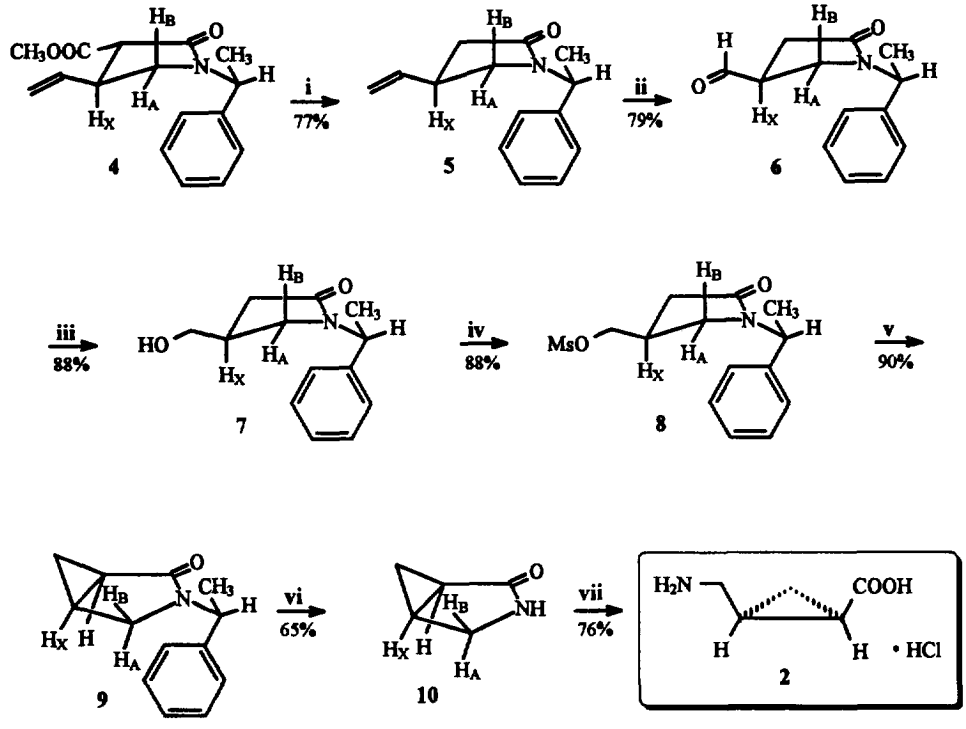

Scheme 1. *Reagents and conditions.* **i.** DMF–H_2O, NaCl, 140°C. **ii.** O_3, −78°C, CH_2Cl_2, then DMS. **iii.** $NaBH_4$, EtOH, 0°C. **iv.** MsCl, 0°C. **v.** LiHDMS, THF. **vi.** Li–NH_3, −78°C, then NH_4Cl. **vii.** 1M HCl, 70°C, 5 h.

In conclusion, we have synthesized by an intramolecular cyclisation the enantiomerically pure 3-aza-2-oxobicyclo[3.1.0]hexane **9** which resulted a good intermediate for disubstituted cyclopropanes such as **2**. The extension of this methodology to the preparation of 2,3-methanoproline and conformationally restricted aspartic acid in the enantiomerically pure form is currently in progress in our laboratory.

Experimental

General methods

Melting points were determined using an Electrothermal IA 9000 capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ as a solvent, unless otherwise stated. All chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) are measured in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Specific rotations were measured on a Perkin Elmer 241 polarimeter. GC–MS analyses were performed with a Hewlett–Packard spectrometer 5890, series II, using a HP-5 capillary column (30 m × 0.25 mm i.d.; stationary phase 5% phenyl methyl silicone). The mass spectrum of compound **2** was recorded on a Carlo Erba QMD 1000 spectrometer (EI, 70 eV). Silica gel 60 for column chromatography was purchased from ICN.

(3S,4S,1′S)-4-Ethenyl-3-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one ***4***

This compound was prepared as described in the literature.[4]

(4R,1'S)-4-Ethenyl-1-(1'-phenylethyl)pyrrolidin-2-one 5

This product was prepared starting from **4** according to the literature method.[4]

(4S,1'S)-[2-Oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]carboxaldehyde 6

A solution of the pyrrolidin-2-one **5** (4.3 g; 20 mmol) in CH_2Cl_2 (100 ml) was cooled to −78°C and ozone was bubbled through the solution until the starting material disappeared. Then methyl sulphide (5 ml) was added and after 3 h the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give the aldehyde **6** (3.4 g; 79% yield) as a colorless oil. IR ($CHCl_3$): 1715, 1665 cm^{-1}. ^1H NMR: 1.50 (d, 3H, J=7.2), 2.70 (m, 2H), 3.06 (m, 1H, H_X), 3.09 (dd, 1H, H_A, J_{AX}=8.4, J_{AB}=8.4), 3.64 (dd, 1H, H_B, J_{BX}=2.9, J_{AB}=8.4), 5.45 (q, 1H, J=7.2), 7.15–7.40 (m, 5 ArH), 9.65 (d, 1H, J=1.0). ^{13}C NMR: 16.5, 31.9, 41.7, 43.1, 49.9, 127.5, 128.0, 128.3, 129.0, 129.2, 139.9, 171.9, 199.5. $[\alpha]_D$ −73.4 (c 1, $CHCl_3$). GC–MS (EI, 70 eV): *m/z* 217 (M^+), 202, 188, 160, 146, 118, 105, 91, 77. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.81; H, 6.91; N, 6.40.

(4S,1'S)-4-Hydroxymethyl-1-(1'-phenylethyl)pyrrolidin-2-one 7

To a solution of the aldehyde **6** (3.3 g; 15 mmol) in dry ethanol (60 ml) at 0°C $NaBH_4$ (0.38 g; 10 mmol) was added and the solution was stirred at 0°C for 3 h. Then solid NH_4Cl (3.0 g) was added and the solvent was removed under reduced pressure. To the residue were added H_2O (10 ml) and ethyl acetate (60 ml) and the mixture was extracted with ethyl acetate (3×100 ml). The organic phase was dried (Na_2SO_4) and the solvent was eliminated in vacuo. The residue was chromatographed on silica gel (ethyl acetate) to give the alcohol **9** (2.9 g; 88% yield) as a low melting solid. IR ($CHCl_3$): 3335, 1668 cm^{-1}. ^1H NMR: 1.51 (d, 3H, J=7.1), 2.18–2.30 (m, 1H), 2.33–2.50 (m, 1H, H_X), 2.46 (br s, 1H, OH), 2.46–2.58 (m, 1H), 3.07 (dd, 1H, H_A, J_{AX}=7.7, J_{AB}=10.0), 3.19 (dd, 1H, H_B, J_{BX}=5.6, J_{AB}=10.0), 3.54 (dd, 1H, J=6.7, J=10.6), 3.61 (dd, 1H, J=5.6, J=10.6), 5.45 (q, 1H, J=7.1), 7.18–7.36 (m, 5 ArH). ^{13}C NMR: 16.6, 33.8, 34.9, 45.5, 49.5, 64.9, 127.5, 128.0, 129.0, 140.4, 174.2. $[\alpha]_D$ −152.4 (c 1, $CHCl_3$). GC–MS (EI, 70 eV): *m/z* 219 (M^+), 204, 160, 146, 132, 128, 105, 91, 77. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.16; H, 7.76; N, 6.35.

(4S,1'S)-4-Methanesulphonyloxymethyl-1-(1'-phenylethyl)pyrrolidin-2-one 8

To a solution of compound **7** (4.4 g; 20 mmol) in ethyl acetate (70 ml) were added triethylamine (3.9 ml; 27 mmol) and *N,N*-dimethylaminopyridine (DMAP) (100 mg). The mixture was cooled to 0°C and then a solution of methanesulphonyl chloride (2.1 ml; 27 mmol) in ethyl acetate (10 ml) was slowly added. The reaction was stirred for 3 h at 0°C. and then poured in H_2O/ice and extracted with ethyl acetate (3×100 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate) to give the methanesulphonate **8** as a colorless oil (5.2 g; 88% yield). IR ($CHCl_3$): 1668 cm^{-1}. ^1H NMR: 1.53 (d, 3H, J=7.0), 2.26 (m, 1H), 2.52–2.81 (m, 2H), 3.02 (s, 3H), 3.12 (dd, 1H, H_A, J_{AX}=7.2, J_{AB}=10.3), 3.21 (dd, 1H, H_B, J_{BX}=5.7, J_{AB}=10.3), 4.14 (dd, 1H, J=7.0, J=9.9), 4.20 (dd, 1H, J=5.7, J=9.9), 5.49 (q, 1H, J=7.0), 7.20–7.39 (m, 5 ArH). ^{13}C NMR: 16.5, 31.4, 34.4, 38.0, 45.1, 70.7, 127.6, 128.2, 129.1, 140.1, 172.5. $[\alpha]_D$ −92.2 (c 1, $CHCl_3$). GC–MS (EI, 70 eV): *m/z* 297 (M^+), 282, 220, 206, 186, 160, 146, 132, 118, 105, 96, 91, 77. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.48; H, 6.40; N, 4.66.

(1R,5S,1'S)-3-Aza-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane 9

To a solution containing the methanesulphonate **8** (4.5 g; 15 mmol) in dry THF (50 ml) at −15°C Li–hexamethyldisilazide (1M solution in THF–hexane; 15 ml) was added and the solution was stirred at −15°C for 1 h. The mixture was poured into H_2O–ice and extracted with ethyl acetate (3×100 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 30:70) to give **9**

(2.7 g; 90% yield) as a colorless oil which crystallized on standing. M.p. 49–50°C. IR ($CHCl_3$): 1665 cm^{-1}. ^1H NMR: 0.53 (ddd, 1H, J=4.0, J=4.4, J=4.4), 1.07 (ddd. 1H, J=4.4, J=4.7, J=7.8), 1.38 (d, 3H, J=7.1), 1.67–1.78 (m, 1H), 1.86–1.96 (m, 1H), 3.02 (dd, 1H, H_A, J_{AX}=5.8, J_{AB}=10.3), 3.18 (dd, 1H, H_B, J_{BX}=1.5, J_{AB}=10.3), 5.36 (q, 1H, J=7.1), 7.20–7.39 (m, 5 ArH). ^{13}C NMR: 12.1, 13.1, 17.0, 20.9, 44.8, 48.9, 127.8, 127.9, 129.0, 140.3, 175.0. $[\alpha]_D$ −160.8 (c 1, $CHCl_3$). GC–MS (EI, 70 eV): *m/z* 201 (M^+), 186, 160, 159, 146, 132, 120, 105, 91, 77. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.52; H, 7.46; N, 6.94.

(1R,5S)-3-Aza-2-oxobicyclo[3.1.0]hexane ***10***

In a flask under inert atmosphere NH_3 (about 100 ml) was condensed at −78°C and then Li (490 mg; 70 mmol) was added. When the metal dissolved in NH_3, a solution containing **9** (3.0 g; 15 mmol) in THF–*t*-BuOH 9:1 (40 ml) was quickly added. After 15 min solid NH_4Cl (5 g) was added and then the mixture was stirred for 15 min. After removal of NH_3, H_2O (50 ml) was added and the mixture was extracted with ethyl acetate (3×150 ml). The organic layer was dried (Na_2SO_4) and, after evaporation under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate) to give **10** (0.95 g; 65% yield) as a white solid. M.p. 106–109°C. IR ($CHCl_3$): 3305, 1667 cm^{-1}. ^1H NMR: 0.64 (ddd, 1H, J=4.4, J=3.3, J=3.3), 1.08 (ddd, 1H, J=4.8, J=7.9, J=8.2), 1.76–1.82 (m, 1H), 1.83–1.98 (m, 1H), 3.18 (d, 1H, H_B, J_{AB}=10.9), 3.50 (dd, 1H, H_A, J_{AX}=5.9, J_{AB}=10.9), 6.18 (br s, 1H, NH). ^{13}C NMR: 12.7, 15.2, 19.9, 44.7, 179.5. $[\alpha]_D$ +49.2 (c 1, $CHCl_3$). GC–MS (EI, 70 eV): *m/z* 97 (M^+), 69, 68, 55, 54. Anal. Calcd for C_5H_7NO: C, 61.84; H, 7.27; N, 14.42. Found: C. 61.80; H, 7.23; N, 14.39.

(1S,2R)-1-Aminomethyl-2-carboxycyclopropane hydrochloride ***2*** *[(−)-*cis*-2,3-methano-GABA]*

A solution of compound **10** (0.7 g; 7.2 mmol) in 1M HCl (40 ml) was stirred at 70°C for 6 h. After removal of H_2O under reduced pressure, the residue was recrystallized (diethyl ether–ethanol) to give **2** as white crystals (0.96 g; 88% yield). M.p. 240–241°C. (lit.[3e] 239–241°C). ^1H NMR (D_2O): 1.10 (ddd, 1H, J=7.0, J=5.7, J=5.0), 1.36 (ddd, 1H, J=8.4, J=8.4, J=5.0), 1.56–1.79 (m, 1H), 1.99 (ddd, 1H, J=8.4, J=8.3, J=5.7), 3.29 (dd, 1H, J=7.5, J=13.5), 3.35 (dd, 1H, J=7.5, J=13.5). ^{13}C NMR (D_2O): 15.7, 20.4, 20.7, 40.9, 179.4. $[\alpha]_D$ −38.1 (c 1, 1M HCl) [lit.[3e] −38.5 (c 0.99, 1M HCl)]. MS (EI, 70 eV) *m/z* 116 (MH^+), 98, 97, 78, 68. Anal. Calcd for $C_5H_{10}NO_2Cl$: C, 39.62; H, 6.65; N, 9.24. Found: C, 39.55; H, 6.59; N, 9.17.

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7. It is noteworthy that, starting from the enantiomer of the 4-ethenylpyrrolidin-2-one **5**, which can be prepared by using (*R*)-phenylethylamine as chiral auxiliary, the enantiomer of **2** can be obtained, following the same synthetic pathway.

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