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Conformationally Constrained ACPD Analogues. Synthesis and Resolution of 3-Aminobicyclo[3,3,0]Octane-1,3-Dicarboxylic Acids

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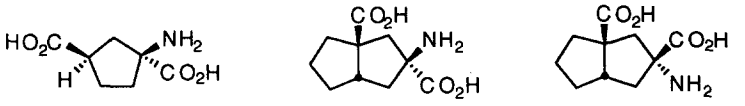
Abstract: The synthesis of racemic 3-aminobicyclo[3.3.0]octane-1,3-dicarboxylic acids (**2** and **3**) which are conformationally constrained ACPD analogues, has been achieved in seven steps starting from the readily available Weiss diketone (**4**). Partial reduction of of **4** to **5**, followed by phenyl ring oxidation with $RuCl_3/NaIO_4$, gave the bicyclic ketoacid **6** which, after Bucherer-Bergs reaction and fractional crystallization, afforded spirohydantoins **7** and **8** in a 2/1 ratio. Both isomers were hydrolyzed to amino acids **2** and **3**. Optical resolution of racemic **7** was performed by crystallization of the corresponding (-)-(*S*)-brucine diasteromeric salts and, after decomposition and hydrolysis, (+)-(1*S**, 3*R**, 5*R**) and (-)-(1*R**, 3*S**, 5*S**)-3-aminobicyclo[3,3,0]octane-1,3-dicarboxylic acids (**2a** and **2b**) were obtained to be biologically compared with (1*S*, 3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (*trans*-ACPD). Due to the solubility profile of hydantoins **7** and amino acids **2**, the enantiomeric purity was measured in the dimethyl derivative **9**, being determined by chiral-HPLC.

Excitatory amino acid (EAA) receptors are generally accepted as the main transmitter receptors mediating synaptic excitation in the mammalian Central Nervous System (CNS).[1] At present three ionotropic receptors, (NMDA, kainate and AMPA) are recognised, together with the metabotropic receptor that is selectively activated by (1*S*, 3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (*trans*-ACPD[2]) (**1**). The receptor selectivity of this latter conformationally constrained glutamic acid rests on the fixed distance between the amino and distal carboxyl groups.[3] In order to study structural steric effects on (**1**) *versus* the activity at the metabotropic receptor, we decided to prepare the 3-amino-bicyclo[3,3,0]-octan-1,3-dicarboxylic acids (**2**) and (**3**) (Figure 1) as conformationally constrained ACPD analogues.

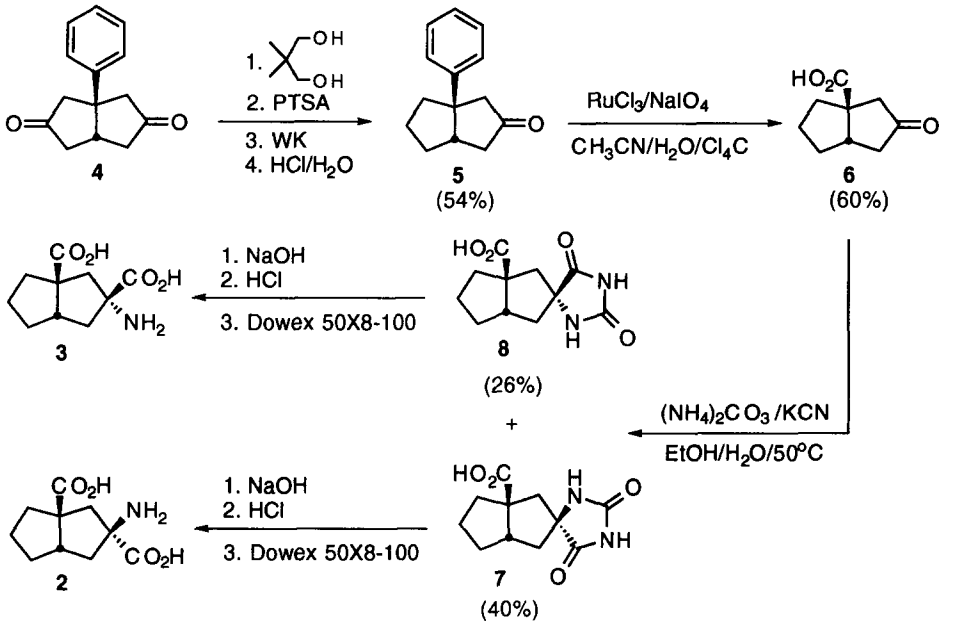


1 **2** **3**

Figure 1

The synthesis of enantiomerically pure (1*S*, 3*R*)-ACPD (**1**) has been described starting from 3-oxocyclopentanecarboxylic acid, obtained optically pure either from brucine resolution[4] or by chemoenzymatic synthesis,[5] with the ketone moiety being transformed into the α-amino acid through the corresponding hydantoin.

Our approach to **2** and **3** (Scheme 1) starts from the readily available (±)-1-phenylbicyclo[3,3,0]octan-3,7-dione (**4**), obtained from phenylglyoxal and dimethyl 3-oxoglutarate *via* Weiss reaction.[6]

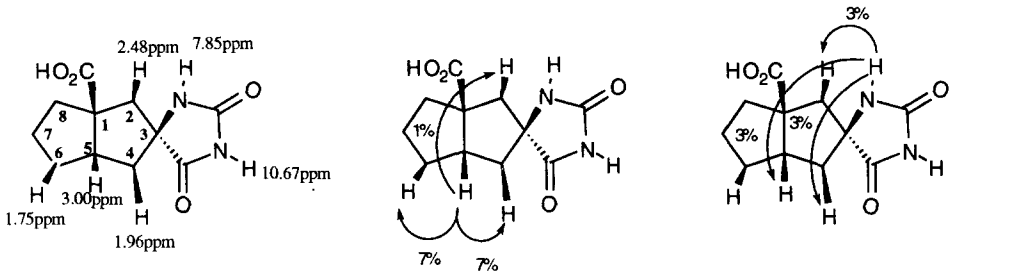


Scheme 1

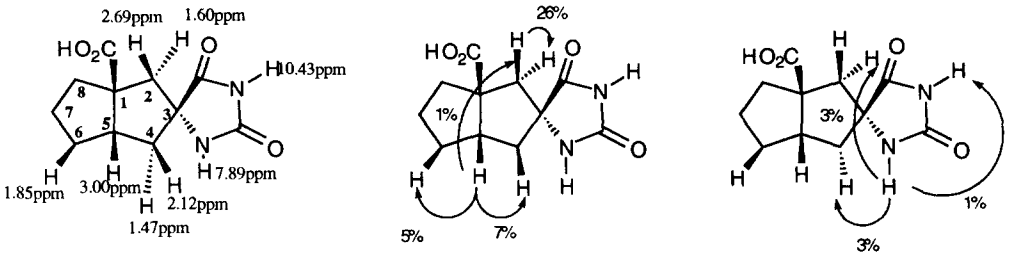
The diketone **4** was protected as diketal with 2,2-dimethylpropane-1,3-diol (98% yield) and said compound was partially hydrolyzed to the monoketal with *p*-toluenesulfonic acid in an acetone/H_2O mixture (70% yield). For our purposes this diprotection-monodeprotection protocol[7] proved to be more effective than the monoketal formation[8] of the diketone. The monoketal intermediate was reduced very efficiently under Wolff-Kishner conditions[7a] (80% yield) giving rise to ketone **5** in a 54% overall yield from **4**. The phenyl substituent at the bridge-head position of **5** was oxidized with ruthenium tetroxide,[9] yielding the oxo acid **6**[10] in 60% yield. Its treatment with ammonium carbonate and potassium cyanide in ethanol/water (Bucherer-Bergs reaction conditions[11]) delived a mixture of epimeric hydantoins **7** (40% yield) and **8** (26% yield) which could be easily separated by fractional recrystallization in water. The found diastereoisomeric ratio (2:1) is in accordance with the general stereochemical outcome of the Bucherer-Bergs reaction,[12] the thermodynamically controlled product being the one with the C-4' carbonyl group in the less hindered possition. This stereochemical result is quite similar to that previously found in the same reaction with *cis*-bicyclo[3,3,0]octan-3-one.[13] However, in contrast with the stereoselectivity found in the unsubstituted

bicyclic system, when **6** was reacted with KCN and ammoniun chloride (Strecker conditions[13]), a nearly equimolar mixture of epimeric amino nitriles was obtained. Finally hydantoins (**7**) and (**8**) were independently hydrolysed under basic conditions [14] yielding **2** and **3** which were isolated as ziwtterions after ion exchange chromatography.

The stereochemistry of hydantoins (**7**) and (**8**) were established by NMR methods. The assignment strategy was to use nOe experiments to determine whether the bridgehead proton H-5 and the NH are on the same or opposite faces of the bicyclic ring system. For hydantoin (**8**) assignment of the key H-5, CH_2-2 and CH_2-4 protons was obtained from analysis of H-H couplings observed in a double quantum filtered COSY spectrum and from a ^1H-^{13}C HMQC spectrum used to distinguish protons from CH or CH_2 groups. Then, irradiation of H-5 (3.00ppm) in an nOe difference experiment produced significant enhancements to the cis vicinal H-4 (2.12ppm) and H-6 (1.85ppm) resonances and a weak enhancement at the cis H-2 (2.69ppm) signal. Irradiation of the hydantoin NH (7.89ppm) then produced signficant enhancements to H-4 and H-2 protons resonating at lower frequency (1.47 and 1.60ppm respectively) confirming that this NH is trans with respect to H-5 (Figure 2). Similar experiments conducted on hydantoin (**7**) confirmed that in this case the NH was cis to H-5 as both these protons showed enhancements to the same H-4 proton (1.96ppm) in the nOe experiments (Figure 2).



Compound **7**

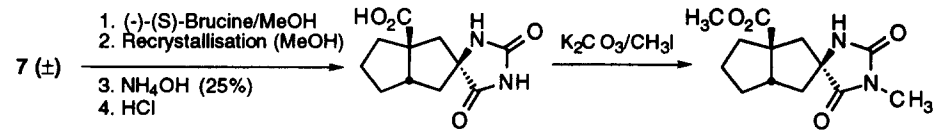


Compound **8**

Figure 2

In order to obtain **2** enantiomerically pure, several attempts were made for the resolution with (-)(*S*) brucine of keto acid **6**. Though this resolution has been successfully applied in 3-oxo-cyclopentane carboxylic acid,[4] it was ineffective in our case due to the high solubility of brucine salts. However, when the racemic hydantoin carboxylic acid **7** was treated with (-)-(*S*)- brucine, the diastereomeric salts were

separated after three recrystallizations in methanol (Scheme 2).[15] The salts were destroyed by the addition of NH_4OH (25% solution) and the free acids were precipitated by acidification with HCl.



7 (+): $[\alpha]_D$ = +28.9 (c=1, 1N NaOH) **9 (+)**: $[\alpha]_D$ = +4.3 (c=1, $CHCl_3$)
7 (-): $[\alpha]_D$ = -29.8 (c=1, 1N NaOH) **9 (-)**: $[\alpha]_D$ = -4.8 (c=1, $CHCl_3$)

Scheme 2

In order to get a better solubility profile, the resolved acids **(+)-7** and **(-)-7** were transformed into their dimethyl derivatives **(+)-9** and **(-)-9** with CH_3I/K_2CO_3 (79% yield) and the enantiomeric purity of these compounds was measured using a chiral-AGP-HPLC column (e.e.≥ 99%).

ACKNOWLEDGEMENTS. This research was supported by a **CDTI** programme (Plan concertado 94/0036) and the Spanish **FARMA III** programme (Ministerio de Industria y Ministerio de Sanidad). R. G. and L. P thank Lilly, S. A. for a fellowship. We would like to thank Ms. Alicia Rivas from the Analytical Department (Centro de Investigación Lilly, S. A.) for running the chiral HPLC..

EXPERIMENTAL SECTION

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Bruker AC-200P (200 MHz and 250 MHz). Double-quantum filtered COSY, HMQC and NOE experiments were recorded on a Bruker AC300 (operating at 300MHz for proton observation) using standard Bruker microprograms. IR spectra were obtained on Nicolet 510 P-FT (film and KBr). Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254} silica gel 60 (UV, 254 nm and Iodine). Chromatographic separations were performed by using 230-400 mesh silica gel (Merck). Enantiomeric purity was measured by using a chiral-AGP-HPLC columm (packed with α_1-acid glycoprotein. 150 x 4 mm i.d., purchased from Chromotech.). Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

(±)-(1*S, 5*R**)-1-Phenyl-3,7-bis(2,2-dimethyltrimethylenedioxy)bicyclo[3.3.0]octane (4a).**

A stirred mixture of (±)-(1*S**, 5*R**)-1-phenylbicyclo[3.3.0.]octane-3,7-dione[6] (**4**) (6.3 g, 29.4 mmol), 2,2-dimethyl-1,3-propanediol (11,9 g, 114 mmol) and *p*-toluenesulfonic acid monohydrate (191,4 mg) in benzene (282 ml) was refluxed for 2 h under a Dean-Stark water trap. The solution was cooled and washed successively with saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml), dried over $MgSO_4$ and concentrated to yield 10.8 g (95%) of the bisketal product (**4a**) as a yellow oil, which was purified by column chromatography using ethyl acetate-hexane (2:3) as eluent. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (s, 6H, CH_3); 1.01 (s, 6H, CH_3); 2.05-2.25 (m, 4H, H-4 and H-6); 2.41 and 2.55 (2d, 4H, *J* = 13.9 Hz, H-2 and H-8); 2.89-

3.05 (m, 1H, H-5); 3.33 (s, 4H, -CH_2O); 3.48 (s, 4H, -CH_2O); 7.10-7.20 (m, 1H, H-4'); 7.25-7.45 (m, 4H, aromatic protons) ppm.^{13}C-RMN ($CDCl_3$) δ: 149.7, 128.0, 126.1, 125.4, 109.2, 72.3, 71.7, 54.1, 48.9, 44.4, 40.9, 30.0, 22.6, 22.5 ppm. Analysis calc. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.86. Found: C, 74.50; H, 8.79.

(±)-(1*S, 5*R**)-1-Phenyl-7-(2,2-dimethyltrimethylenedioxy)bicyclo[3.3.0]octan-3-one (4b).**

Diketal **4a** (2.151 g, 5.565 mmol) and *p*-toluenesulfonic acid monohydrate (0.313 g, 1.64 mmol) were dissolved in 75 ml of 5% aqueous acetone. The light yellow solution was stirred at room temperature for 2h, and the reaction was quenched by the addition of 25 ml of saturated aqueous sodium bicarbonate. The acetone was evaporated under reduced pressure, and the aqueous solution extracted with ether (3 x 50 ml). The ether layers were washed with brine (30 ml), dried ($MgSO_4$) and concentrated to give 1.783 g of light oil. The mixture was separated by column chromatography using ethyl acetate-hexane (3:7) as eluent to give, despite mechanical losses, 0.61 g (28%) of recovered diketal and 1.037 g (62%) of pure monoketal (**4b**).^{1}H-NMR ($CDCl_3$) δ: 0.97 (s, 3H, CH_3); 0.99 (s, 3H, CH_3); 2.00-2.60 (m, 8H, H-4, H-6, H-7 and H-8); 2.78 (s, 2H, H-2); 3.05-3.20 (m, 1H, H-5); 3.51 (s, 4H, CH_2O); 7.20-7.40 (m, 5H, Ph) ppm. ^{13}C-NMR ($CDCl_3$) δ: 147.7, 128.7, 125.6, 126.3, 108.6, 72.1, 71.9, 52.3, 52.1, 49.5, 44.4, 44.1, 42.1, 30.1, 22.4, 22.4 ppm. (The C=O signal was not observed). IR (film): 3390; 1749 and 1150 cm^{-1}. Analysis calc. for $C_{19}H_{24}O_3$: C, 75.96; H, 8.05. Found: C, 75.58; H, 8.02.

(±)-(1*S, 5*R**)-1-Phenyl-bicyclo[3.3.0]octan-3-one (5).**

Ketoketal **4b** (1 g, 3.3 mmol), 85% hydrazine hydrate (2.03 ml, 34 mmol) and triethanolamine were heated at 130°C for 3h. Potassium hydroxide (2.2 g, 33 mmol) dissolved in hot triethanolamine (6 ml) was added to the reaction. The temperature was rapidly raised to 205°C and maintained for 6h while water and hydrazine were distilled. The cool reaction was diluted with water (27 ml), acidified with concentrated HCl (15.7 ml) and allowed to stand for two days. After extraction with CH_2Cl_2 (3 x 150 ml), the organic layers were washed with saturated aqueous sodium bicarbonate (125 ml) and saturated aqueous sodium chloride (125 ml), dried ($MgSO_4$) and concentrated, to give 1.297 g of a yellow oil. This product was chromatographied on silica gel with ethyl acetate-hexane (3:7) as eluent to give 0.463 g (70%) of pure **5.** ^{1}H-NMR ($CDCl_3$) δ: 1.53-2.23 (m, 7H); 2.55-2.75 (m, 3H, H-2 and H-4); 2.90-3.05 (m, 1H, H-5); 7.20-7.40 (m, 5H, Ph) ppm. ^{13}C-NMR ($CDCl_3$) δ: 148.1, 128.5, 126.1, 125.7, 55.0, 52.2, 45.7, 45.6, 40.9, 33.4, 24.5 ppm (the C=O is not observed). IR (film): 1750 cm^{-1}. Analysis calc. for $C_{14}H_6O$: C, 83.95; H, 8.05. Found: C, 83.58; H, 7.92.

(±)-(1*S, 5*R**)-3-Oxobicyclo[3.3.0]octane-1-carboxylic acid (6).**

To a stirred solution of 10.5 ml of carbon tetrachloride, 10.5 ml of acetonitrile, 16 ml of water, 0.754 g (2.63 mmol) of (**5**) and 7.883 g (36.85 mmol) of sodium metaperiodate, 13.16 mg (57.9 mmol) of ruthenium trichloride was added. Vigorous stirring was continued for 3 days at room temperature. Then 300 ml of diethyl ether were added in 3 portions, stirring for another 15 min. Filtration through a celite pad, gave a solution which was dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel with ethyl acetate:hexane (1:1) as eluent to give 0.267 g (60%) of **6** as a viscous oil.^{1}H-NMR ($CDCl_3$) δ: 1.50-1.90 (m, 6H, H-6, H-7 and H-8); 2.05-2.35 (m, 1H, H-2); 2.35-2.55 (m, 1H, H-4β); 2.65-2.75 (m, 1H, H-4α); 2.95-3.05 (m, 2H, H-2 and H-5) and 9.19 (s, 1H, CO_2H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 217.7, 183.2,

55.9, 47.7, 45.6, 44.2, 37.2, 34.0, 25.5 ppm. IR (film): 1735 and 1720 cm^{-1}. Analysis calc. for $C_9H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 63.84; H, 7.02.

(±)-(1*S, 3S*, 5*R**)-Bicyclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylic acid [(±)-7].**

A solution of **6** (4.8 g, 24 mmol), potassium cyanide (4.9 g, 36 mmol) and ammonium carbonate (5.6 g, 73 mmol) in ethanol (13 ml) and water (31 ml) was heated at 65-70 °C for three days in a closed vessel. After cooling to r t the solution was acidified to pH = 1 with 3% HCl. The precipitated solid was filtered and recrystallized from water to yield 2.27 g (40%) of pure **7**. Mp > 300 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.49-2.00 (m, 8H, methylene protons); 1.85-2.00 (m, 1H, H-4), 2.45-2.55 (m, 1H, H-2), 2.95-3.05 (m, 1H, H-5); 7.85 (s, 1H, H-1'); 10.67 (s, 1H, H-3') and 12.26 (s, 1H, CO_2H) ppm. ^{13}C-NMR (DMSO-d_6) δ: 178.2, 176.8, 155.8, 69.8, 58.7, 47.9, 46.3, 43.2, 38.2, 31.6, 24.3 ppm. IR (KBr): 3340; 3160, 3060, 1755, 1730 and 1720 cm^{-1}. Analysis calc. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.12; H, 5.76; N, 11.52.

(±)-(1*S, 3*R**, 5*R**)-Bicyciclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylic acid (8).**

The mother liquids of the above reaction were partially evaporated to 1/3 of their initial volume. After 24 h the formed precipitate was collected by filtration and recrystallised from methanol to yield1.19 g (21%) of **8**. Mp > 300 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.47 (m, 2H, H-2 and H-6); 1.61-1.85 (m, 6H); 2.10-2.20 (m, 1H, H-4); 2.60-2.75 (m, 1H, H-2); 2.95-3.05 (m, 1H, H-5); 7.89 (s, 1H, H-1'); 10.43 (s, 1H, H-3') and 12.00 (s, 1H, CO_2H) ppm. ^{13}C-NMR (DMSO-d_6) δ: 178.0, 177.6, 155.4, 67.7, 57.6, 45.5, 44.0, 41.61, 38.7, 32.2, 24.4 ppm. IR (KBr): 3340, 3180, 3070, 1740 cm^{-1}. Analysis calc. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11,76. Found: C, 55,32; H, 5.79; N, 11.49.

Optical resolution of 7. (+)-(1*S, 3*S**, 5*R**)- and (-)-(1*R**, 3*R**, 5*S**)-Bicyclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylic acids [(+)-7 and (-)-7].**

A stirred mixture of **7** (1.308 g, 5.49 mmol) and (-)-(*S*)-brucine dihydrate (2.363 g, 5.49 mmol) in methanol (300 ml) was refluxed overnight. The hot reaction mixture was filtered and 0.504 g (2.11 mmol) of unreacted acid was recovered (39%). After 24 h the precipitated salts were collected by filtration (1.724 g, 2.41 mmol, 44%). Three recrystallizations gave (+)-(1*S**, 3*S**, 5*R**)-bicyclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylic acid (-)-brucine salt (71.5%, calculated from the total diastereomeric salts). Mp = 191 °C. To a stirred suspension of this material (600mg, 0.84 mmol) in water (5 ml) into an ice bath, was added 0.12 ml (0.84 mmol) of NH_4OH (25%) and allowed to stand for 1 h. After extraction with CH_2Cl_2 (2 x 25 ml) to remove the free brucine, the aqueous layers were acidified with 3% HCl to give 180 mg (0.75 mmol) (90%) of **(+)-7** as a white precipitate with a specific rotation of $[\alpha]_D$ = +28.9 (c=1, 1*N* NaOH). The combined methanol solutions were evaporated to dryness *in vacuo* and the more soluble salt was isolated by recrystallization from acetone-water (0.471 g, 0.65 mmol, 12%). Three more recrystallizations in the same solvent mixture gave *t*(-)-(1*R**, 3*R**, 5*S**)-bicyclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylic acid (-)-brucine salt (19.5 %, calculated from the total diastereomeric salts). Mp = 156 °C. The salt was destroyed as above and the free acid was found to have a specific rotation of $[\alpha]_D$ = - 29.8 (c = 1, 1*N* NaOH).

Enantiomeric purity determination of (+)-7 and (-)-7. Derivatization to methyl 3'-methyl-(+)-(1*S, 3*S**, 5*R**)- (+)-9 and (-)-(1*R**, 3*R**, 5*S**)-bicyclo[3.3.0]octane-3-spiro-5'-hydantoin-1-carboxylate. (+)-9 and (-)-9.**

A suspension of **(+)-7** (0.38 mmol) in dry acetone (20 ml) was stirred with anhydrous potassium carbonate (0.112 g, 0.81 mmol) under an argon atmosphere at r t for 1 h, prior to addition of methyl iodide (1.135 g, 7.99 mmol). After being stirred for 24h, another portion of methyl iodide was added and stirred overnight. The reaction mixture was filtered and the filtered cake was washed with acetone. The combined acetone solutions were evaporated *in vacuo*. The white solid was dissolved in CH_2Cl_2 and any undissolved material was removed by filtration. Evaporation of the filtrate to dryness gave a white solid that was purified by rapid passage though a short silica gel column using ethyl acetate as eluent, to give 81 mg (0.30 mol, 79%) of **(+)-9**. Similarly **(-)-7.** gave **(-)-9** in 76% yield. Mp 133 °C. ^{1}H-NMR ($CDCl_3$) δ 1,58-2.20 (m, 9H, methylene protons); 2.25-2.35 (m, 1H, H-2); 2.90-3.00 (m, 1H, H-5); 3.02 (s, 3H, N_3'-CH_3); 3.74 (s, 3H, OCH_3); 6.52 (s, 1H, H-1') ppm. ^{13}C NMR ($CDCl_3$) δ:179.4, 175.3, 156.3, 70.3, 60.3, 52.9, 49.4, 47.4, 45.0, 36.7, 32.7, 25.1 and 24.9. Analysis calc. for $C_{13}H_{18}N_2O_4$: 58.63; H, 6.81; N, 10.52. Found: C, 58.12; H, 6.66; N, 10.27.

Chiral-HPLC analysis was performed on a Waters LC apparatus equipped with a MAXIMA 820 software, using a chiral-AGP columm (10 cm, 1 ml/min) and 2-propanol (0.5%) in 0.01 M sodium phosphate buffer pH 5.5, as mobile phase. A Waters 490 Uv detector (236 nm) was used. The retention time for **(+)-9** was 7 min being 9 min for **(-)-9**. The enantiomeric excess (e.e.) was ≥ 99 %.

(±)-(1*S, 3*R**, 5*R**)-3-Aminobicyclo[3.3.0]octane-1,3-dicarboxylic acid (2).**

A solution of racemic **7** (0.365 g, 1.53 mmol) in NaOH 1N (8 ml), was refluxed for one day. After cooling in ice and acidification with diluted HCl to pH = 4, the formed precipitate was filtered. After purification by ion exchange resin (Dowex 50X8-100) pure **2** was obtained (99 mg, 30% yield). Mp > 200 °C. ^{1}H-NMR (Py-d_5) δ: 0.76-0.81 (m, 1H); 0.96-1.27 (m, 5H); 1.56-1.98 (m, 4H) and 2.25-2.35, (m, 1H) ppm. ^{13}C-NMR (Py-d_5) δ: 184.9, 174.6, 68.5, 60.3, 48.0, 46.3, 41.7, 35.7, 30.8, 23.0 ppm. IR (KBr): 3350-2000, 1695, 1590 and 1405 cm^{-1}. Analysis calc. for $C_{10}H_{15}NO_4$.1/2 H_2O: C, 54.03; H, 7.27; N, 6.30. Found: C, 54.20; H, 6.81; N, 5.84.

(+)-2 and (-) -2.

They were similarly prepared from **(+)-** and **(-)-7**. Found rotatory powers: (+)-2, yield= 27%, $[\alpha]_D$ = +53.8 (c=1, 1*N* NaOH) ; (-)-2, yield= 30%, $[\alpha]_D$ = -53.1 (c=1, 1*N* NaOH).

(±)-(1*S, 3*R**, 5*R**)-3-Aminobicyclo[3.3.0]octane-1,3-dicarboxylic acid (3).**

Hydantoin **8** was hydrolyzed following the same procedure as for compound **2**. Yield= 21%, Mp > 200 °C. ^{1}H-NMR (D_2O/MeOH-d_4) δ: 1.54-1.86 (m, 8H); 2.43-2.54 (m, 1H); 2.96-3.03 (m, 1H) and 3.14-3.31 (m, 1H). ^{13}C-NMR (D_2O/MeOH-d_4) δ: 183.1, 177.7, 66.2, 61.0, 48.6, 45.5, 43.2, 41.2, 33.6, 25.6 ppm. IR (KBr): 3500-2000, 1690, 1585,1395 and 1275 cm^{-1}. Analysis calc. for $C_{10}H_{15}NO_4$ .1/3H_2O: C, 54.77; H, 7.22; N, 6.39. Found: C, 55.17, H, 6.95, N, 6.40.

REFERENCES AND NOTES

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2 Though for the IUPAC or *Chem. Abstr.* nomenclature for compound **1** should be (1*S*,* 3*R**)-1-aminocyclopentane-1,3-dicarboxylic acid, we use the more familiar acronysm *trans*-ACPD as it is more used in the pharmacological literature. For an editorial of "*trans* -ACPD: problems of nomenclature" see: Schoepp, D.; Bockaert, J.; Sladeczek, F. *TiPS*, **1990**, *11*, 508-515.

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