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An efficient synthesis of new diastereomeric enantiopure 1-aminocyclopentane-1,2,4-tricarboxylic acids

Francesco Caputo, Francesca Clerici, Maria Luisa Gelmi,* Sara Pellegrino and Donato Pocar

Istituto di Chimica Organica 'A. Marchesini', Facoltà di Farmacia, Università di Milano, Via Venezian 21, I-20133 Milano, Italy

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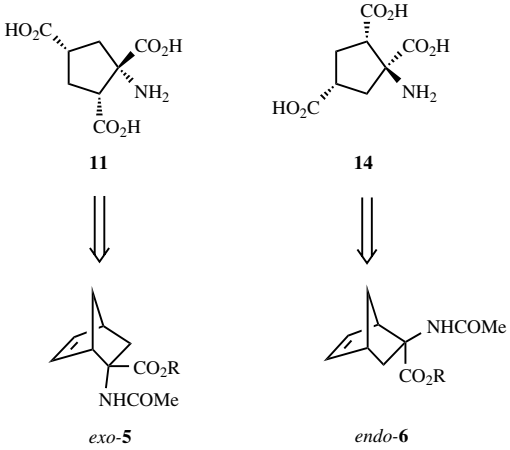
Abstract—Novel 1-aminocyclopentane-1,2,4-tricarboxylic acids **11** and **14** containing the glutamic acid skeleton were prepared as two diastereomers characterized by having the carbonyl groups in positions two and four cis to each other and trans with respect to the 1-carboxylic group and as all cis relationship, respectively. The reaction sequences, that is, Diels–Alder reaction to give norbornene cycloadducts, oxidative cleavage of the double bond of the cycloadducts, ensured the proper stereochemistry of both diastereomers. Each diastereomer was prepared in enantiopure form starting from *exo*- and *endo*-2-amino-norbornene-2-carboxylic acid derivatives **5** and **6** obtained through a very efficient asymmetric synthesis.

1. Introduction

The preparation of constrained carbocyclic amino acids,[1] functionalized with a second carboxylic group in a suitable position, is an important synthetic target, because these compounds contain the skeleton of glutamic acid. This amino acid is one of the most important transmitters in the CNS and is also involved in several brain disorders.[2] The above amino acids are generally characterized by α,α-disubstitution, and for this reason, they have great metabolic stability. Furthermore, the rigidity of the backbone allows us to design different stereoisomers. Depending on the rigidity of the ring, its size and the stereochemistry of the substituents, selectivity toward the different Glu receptors can be gained.[3] These are classified as ionotropic (iGluRs) and metabotropic (mGluRs).[4] As cited above, the different stereoisomers can have different activities toward the different subtypes. For example, the diastereomeric 1-aminocyclopentane-1,3-dicarboxylic acids (ACDP) are characterized by the activity and selectivity on metabotropic mGluRs.[5] The (−)-(1*S*,3*R*)-isomer is a potent agonist on I, II mGluRs, the (+)-(1*S*,3*S*)-isomer is selective on II mGluRs. 2-Aminobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid is a selective agonist for group II mGluRs.[6] The introduction of a third carboxylic group, as a potential group capable of forming ionic or hydrogen bonds, was also considered (i.e., 1-aminocyclopentane-1,3,4-tricarboxylic acids).[1d] In this case, the activity and selectivity of each isomer toward metabotropic receptor subtypes is strictly dependent on the stereochemistry. Accordingly, research in this field is considered to be of great interest.

As part of our research program[7] on α,α-disubstituted carbocyclic amino acid syntheses, we herein report on the preparation of two new diastereomeric 1-aminocyclopentane-1,2,4-tricarboxylic acids **11** and **14** (Scheme 1). The



Scheme 1.

* Corresponding author. Tel.: +39 0250314481; fax: +39 0250314476; e-mail: marialuisa.gelmi@unimi.it

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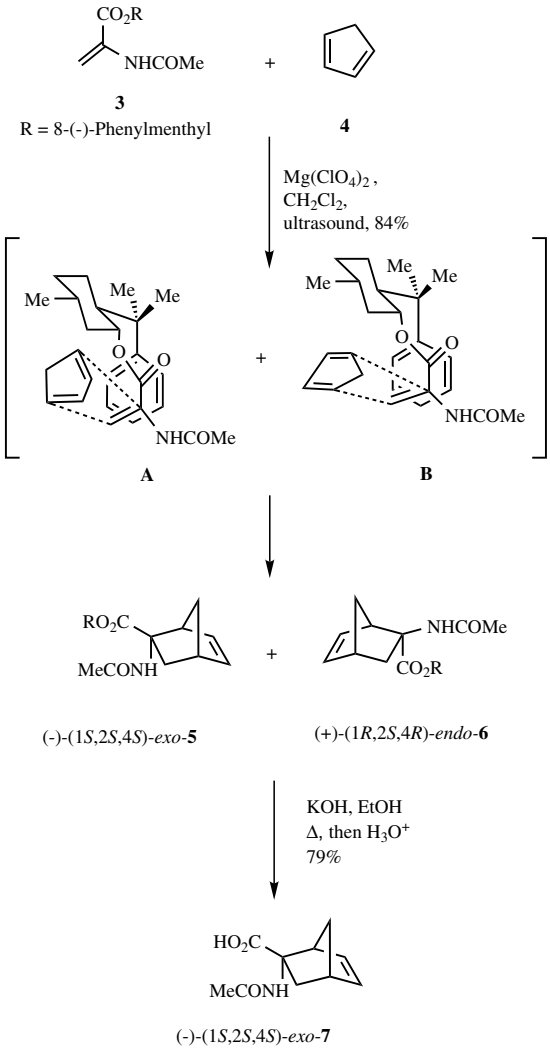
synthetic strategy for their preparation took advantage of using a sequence of simple and efficient reactions, that is, Diels–Alder reaction, which allows us to obtain both *exo*/*endo* norbornene amino acids **5** and **6**; the oxidative cleavage of the C_5–C_6 bond of the cycloadducts giving the cyclopentyl ring functionalized with two new carboxylic groups.

2. Results and discussion

The synthesis of 1-aminocyclopentane-1,2,4-tricarboxylic acids was performed starting from norbornene derivatives *exo*-**5** and *endo*-**6** obtained by reacting aminoacrylates **3** and cyclopentadiene **4** (Scheme 3). (−)-8-Phenylmenthyl acrylate **3** is a known compound, which can be obtained in 47% yield, according to the literature.[8] To improve its yield, a new efficient protocol was adopted, that is, by reacting 2-acetamidoacrylic acid **1** with dicyclohexylcarbodiimide (DCC) in dichloromethane under an inert atmosphere. The corresponding 4-methyleneoxazolone **2** was obtained. It is an unstable compound, very sensitive to moisture. For this reason, after filtration of the dicyclohexylurea under a nitrogen atmosphere and solvent elimination, oxazolone **2** was immediately reacted, in refluxing benzene, with (−)-8-phenylmenthol in the presence of bis-(dibutylchlorotin)oxide as catalyst. Chiral acrylate **3** was obtained in an excellent yield (98%) (Scheme 2).

The asymmetric synthesis of the new cycloadducts *exo*-**5** and *endo*-**6** was carried out by starting from enantiopure acrylate **3** performing the Diels–Alder reaction in dichloromethane as the solvent, $Mg(ClO_4)_2$ (0.3 equiv) as the catalyst and with ultrasound (14 h) (Scheme 3). A mixture of *exo*-**5** and *endo*-**6** (84%) was obtained in 83:17 ratio and with high diastereoselectivity for each *exo* (de 97%) and *endo* (de 96%) couple of diastereomers (HPLC analysis). Pure compounds *exo*-**5** (de 99%) and *endo*-**6** (de 99%) were isolated by chromatographic separation and crystallization.

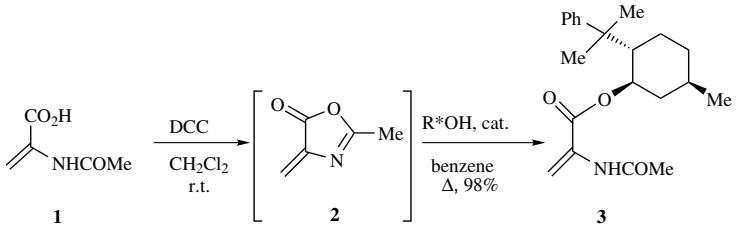
The structure of cycloadducts *exo*-**5** and *endo*-**6** was determined by NMR experiments (^1H, ^{13}C, COSY, NOESY NMRs). ^1H NMR spectra revealed differences between the two diastereomers: typical signals at 5.94–5.89 (m, H-6), 6.37–6.33 (m, H-5), 2.84 (m, H-4, H-1), 2.60 (dd, H-3_{exo}), 1.15 (dd, H-3_{endo}), 1.78 (m, H-7_s), 1.38 (m, H-7_x), 4.88 (NH), and 1.76 (MeCO) are present for the *exo*-adduct. Signals at 5.78–5.74 (m, H-6), 6.36–6.32 (m, H-5), 2.90 (br s, H-4), 1.76 (dd, H-3_{exo}), 2.22 (dd, H-3_{endo}), 2.56 (m, H-1), 1.67 (m, H-7_s), 1.50 (m, H-7_x), 5.42 (NH), and 1.93 (MeCO) characterize the spectrum of the *endo* adduct.



Scheme 3.

As a confirmation of the stereochemistry assigned to the cycloadducts, a significative positive Overhauser effect (Noesy experiments) was observed between the NH and both H-3_{endo} and H-6 in the *exo*-adduct, and between the NH and H-7_s in the *endo*-compound.

The absolute configuration of all the stereocenters in compound *exo*-**5** was assigned indirectly by the hydrolysis of the (−)-8-phenylmenthyl ester function to the corresponding acid (Scheme 3). The known[9] (−)-2-acetylamino-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid *exo*-**7** was obtained,



Scheme 2.

which is characterized by the (1*S*,2*S*,4*S*)-configuration (Scheme 3).

The stereochemical outcome of this reaction showed that the diene attacked the dienophile on the less hindered *Si*-face (intermediates **A** and **B**), which is in agreement with the results observed for the synthesis of the analogous (−)-menthyl[10] or (−)-8-phenylmenthyl derivatives.[11] Accordingly, the stereochemistry assigned to the *endo* adduct (+)-**6** is 1*R*,2*S*,4*R*.

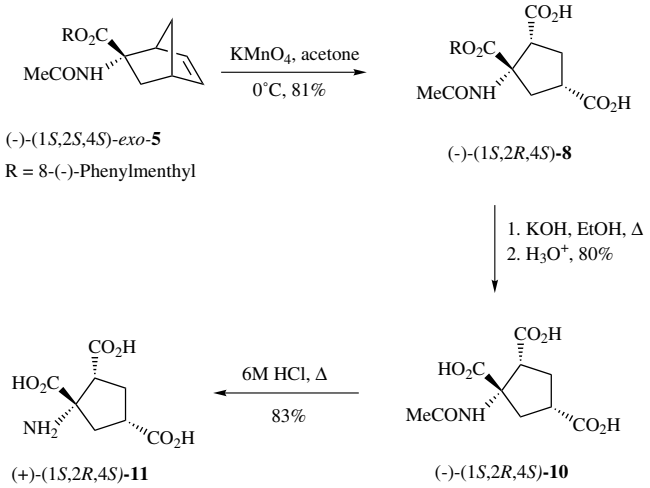
Compounds *exo*-**5** and *endo*-**6** were the key reagents for the preparation of enantiopure diastereomeric 1-aminocyclopentane-1,2,4-tricarboxylic acids **8** and **9**, respectively. This synthetic target was achieved by oxidative cleavage of the double bond of the norbornene ring assuring stereochemical control of the three carboxylic functions.

Compound **5** was treated with an aqueous solution of potassium permanganate (3.3 equiv) at 0 °C in acetone. The exothermic reaction gave the tricarboxylic acid derivative (−)-(1*S*,2*R*,4*S*)-**8**, which was isolated in good yield (81%) (Scheme 4).

The same protocol was adopted starting from norbornene *endo*-**6**. Enantiopure compound (−)-(1*S*,2*S*,4*R*)-**9** (78%) was isolated (Scheme 5).

In both cases, a single diastereomer was obtained containing three stereocenters. Starting from *exo*-**5**, compound **8**, having the 2,4-*cis*-carboxylic groups trans to the 1-carboxylic group, was obtained. Starting from *endo*-**6**, the cis relationship of the three carboxylic groups in **9** was assured.

The hydrolysis of the ester function was achieved under basic conditions. Acid (−)-(1*S*,2*R*,4*S*)-**10** (80%) was obtained by hydrolyzing (−)-8-phenylmenthyl ester **8** using KOH in ethanol at reflux (2 h). Subsequent hydrolysis of the amido function under acidic conditions (6 M HCl, reflux, 14 h) gave diastereomer (+)-(1*S*,2*R*,4*S*)-**11** in 83% yield (Scheme 4).



Scheme 4.

An analogous protocol was followed for the deprotection of **9** (Scheme 5). When **9** was hydrolyzed under basic conditions, amino acid **C** was first formed which was then transformed into anhydride (+)-(3a*S*,5*R*,6a*S*)-**12** (88%) when warming during the work-up. The deprotection of the nitrogen atom under acid conditions gave compound (+)-(3a*S*,5*R*,6a*S*)-**13** (95%). The formation of the anhydride can be ascribed to the cis relationship between the two carboxylic groups at C-1 and C-2 (intermediate C).

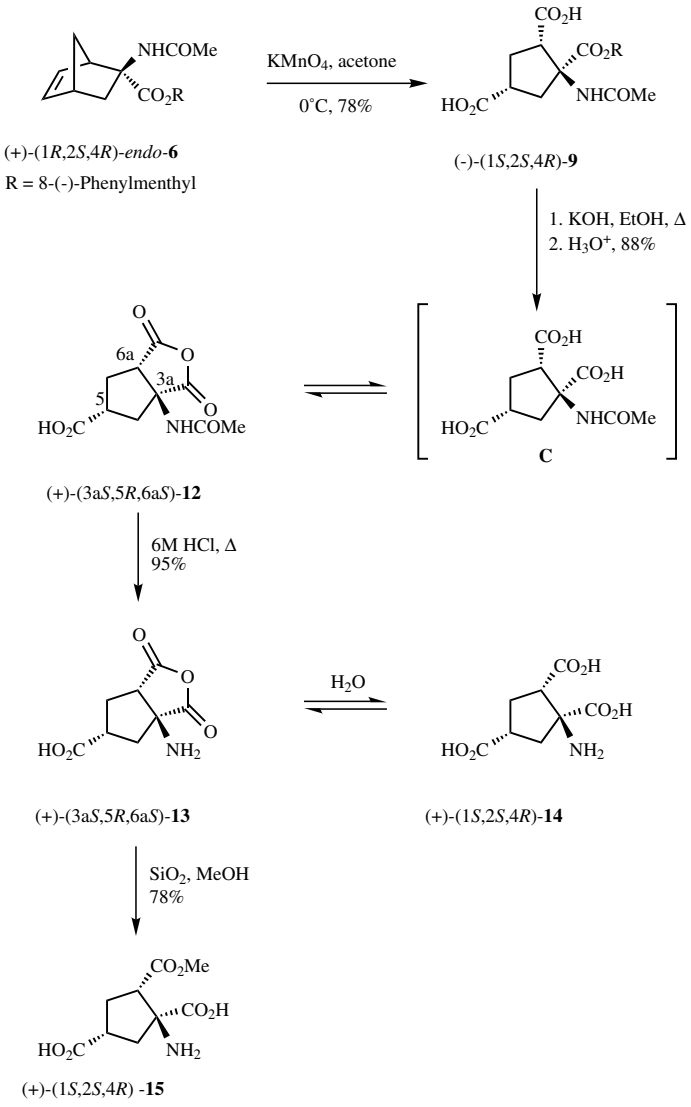
The structure of **12** was confirmed by NMR. The H-6a proton resonates at δ 3.20 (dd, *J* 7.6, 9.8). Signals at 3.07–2.90 (H-5), 2.57 (dd, *J* 9.2, 13.6, H-4), 2.39–2.11 (H-4 and H-6), and 1.88 (Me) δ are present. The ^{13}C NMR spectrum revealed the presence of signals at a lower field with respect to the ester **9** (δ 180.0, 178.1, 176.5, 175.5, 67.6, 55.0, 43.2, 40.5, 33.9, 24.2).

The formation of the anhydride was confirmed by IR spectroscopy of compounds **13**·**HCl** in which an absorption at 1713 cm^{-1} was present, corresponding to the carbonyl of an anhydride function. As expected, compound **13** was very hygroscopic. When a sample of **13** was not stored in a dry atmosphere and the IR spectrum then recovered, a new absorption at 1594 cm^{-1} was present instead of that at 1713 cm^{-1}, the same absorbtion observed in the IR spectrum of diastereomer **11**. We can conclude that the formation of anhydride **13** or of tricarboxylic acid **14** (Scheme 5) is strictly dependent on the presence or absence of moisture.

As further confirmation of the presence of the anhydride function, compound **13** was treated with methanol in the presence of silica gel to give monomethoxy ester **15** (78%) (Scheme 5). The reaction is regioselective with only the carboxylic group at C-2 esterified (see below spectroscopic data).

The structure of all compounds was confirmed by analytical and spectroscopic data (^{1}H, ^{13}C NMR, COSY, C/H Hetcor). Some examples are detailed. The ^{1}H NMR spectrum of amino acid **11**·**HCl** showed signals at 3.22 (dd, *J* 12.8, 8.9, H-2), 3.03–2.95 (m, H-4), 2.65–2.55 (m, H-3), 2.29 (dd, *J* 14.8, 10.4, H-5), 2.08 (dd, *J* 14.8, 3.3, H-5′), and 1.89–1.78 (m, H-3′) δ. The assigned stereochemistry was further confirmed by a NOESY experiment which revealed a positive Overhauser effect between H-3 at low field and H-2 and H-4 and H-3/H-5 (2.29 δ). In particular, the NOE effect between H-2 and H-4 confirms the cis relationship between carboxylic groups at C-2 and C-4.

The ^{1}H NMR of **15** showed signals associated with a methyl group (δ 3.69), H-2 (δ 3.26; dd, *J* 11.3, 8.0), H-4 (δ 3.23–3.13; m), H-5 (δ 2.58; dd, *J* 14.7, 9.1), H-5′ (δ 2.33; dd, *J* 14.4, 9.2), and H-3 (δ 2.50–2.38; m). As shown by a Noesy experiment, a cis relationship was found between protons at 3.26, 3.18, 2.33 δ, thus confirming the assigned stereochemistry. Carbon atoms resonate at 177.8 (CO_2H-4), 174.5 (CO_2H-1), 173.2 (CO_2Me-2), 66.4 (C-1), 52.7 (OMe), 52.2 (C-2), 41.2 (C-4), 39.1 (C-5), 31.6 (C-3). An HMBC experiment assured the regiochemistry of the esterification reaction. In fact, correlations were observed



Scheme 5.

between the carbonyl function of the ester group and the H-2 and H-3 protons but not with H-5 protons.

3. Conclusion

In conclusion, two new diastereomeric 1-aminocyclopentane-1,2,4-tricarboxylic acids of biological interest were prepared through an efficient synthetic procedure, consisting of three steps, that is, the Diels–Alder cycloaddition reaction, the oxidation of a double bond, and the deprotection of the amino acid function. The regiochemical and stereochemical control of three carboxylic groups, that is, two 2,4-*cis* carboxylic groups trans to 1-carboxylic group and all *cis* tricarboxylic groups, was carried out easily and safely, starting from *exo*- and *endo*-norbornene derivatives. Each diastereomeric 1-aminocyclopentane-1,2,4-tricarboxylic acid was prepared in an enantiopure form starting from norbornene derivatives obtained by the way of a very efficient asymmetric synthesis.

4. Experimental

4.1. General

Mps were determined using a Büchi 510 (capillary) apparatus. ^{1}H NMR spectra were recorded with an AVANCE 500 Bruker at 500 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts, relative to TMS as internal standard, are given in δ values. J values are given in Hertz. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60–70 230 ASTM (Merck)] with the eluant indicated. IR spectra were taken with a Perkin–Elmer 1725X FT-IR spectrophotometer. $[\alpha]_D$ were measured with a Perkin–Elmer MODEL343 Plus Polarimeter. DOWEX 50WX 4-50 and Dowex 1×4–400 column ion-exchange resins were used.

4.1.1. 8-(−)-Phenylmenthyl 2-acetylaminoacrylate, (−)-3. Operating under a nitrogen atmosphere, to a stirred suspension of acrylate **1** (2.22 g, 17.2 mmol) in anhydrous

CH_2Cl_2 (80 mL), DCC (3.55 g, 17.2 mmol) was added and the reaction mixture stirred at room temperature. After 2 h, the reaction mixture was cooled at 0 °C and quickly filtered under a nitrogen atmosphere. The resulting solution was evaporated to give oxazolone **2** as a yellow oil. Operating in a screw-cap tube, to a solution of (−)-8-phenylmenthol (2.40 g, 10.3 mmol) and bis(dibutylchlorotin)oxide (1.3 g, 2.35 mmol) in dry benzene (30 mL), compound **2**, dissolved in dry benzene (20 mL), was added in two portions within 24 h. The reaction mixture was stirred and then heated for 36 h at reflux. After solvent evaporation, the crude reaction mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 3:1) to afford pure **3** (3.50 g, 98%) as a yellow oil.

4.1.2. 2-Methyl-4-methylene-5(4*H*)-oxazolone, 2. Crude compound. IR (Nujol) 1820, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.04 (s, 1H), 5.94 (s, 1H), 2.17 (s, 3H). Compound **3**: $[\alpha]_D^{25} = -64.5$ (*c* 0.5, $CHCl_3$); IR (Nujol) 3400, 3360, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.02 (m, 5H), 6.27 (s, 1H), 5.29 (s, 1H), 5.00–4.87 (m, 1H), 2.17–2.10 (m, 1H), 2.05 (s, 3H), 1.95–0.81 (m, 8H), 1.30 (s, 3H), 1.21 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 162.9, 151.3, 130.8, 128.3, 125.4, 125.2, 109.1, 76.6, 50.4, 41.5, 39.6, 34.5, 31.4, 28.1, 26.6, 25.0, 24.7, 21.7.

4.2. Cycloaddition reaction

Operating under a nitrogen atmosphere, to a stirred solution of acrylate **3** (3.65 g, 10.3 mmol) in anhydrous CH_2Cl_2 (100 mL), freshly distilled cyclopentadiene **4** (3.5 mL, 42 mmol) and $MgClO_4$ (0.7 g, 3.14 mmol) were added. The reaction was sonicated for 14 h. After solvent evaporation, the reaction mixture was chromatographed on flash silica gel (cyclohexane/AcOEt, 1:1). Pure *exo*-**5** (2.77 g, 65%), a mixture of *exo*-**5**/*endo*-**6** (0.25 g, 6%) and pure *endo*-**6** (0.56 g, 13%) were isolated and analyzed by HPLC (Phenomenex LUNA C18 column: 250 × 4.6 mm; MeCN/H_2O, 7:3; $T = 30$ °C, flow = 0.8 mL/min, $\lambda = 254$).

4.2.1. (1*S*,2*S*,4*S*)-(−)-8-Phenylmenthyl 2-acetylamino-bicyclo[2.2.1]hept-5-ene-2-carboxylate, (−)-*exo*-5. Mp 188–189 °C (acetone). $[\alpha]_D^{25} = -49.7$ (*c* 0.8, $CHCl_3$); IR (Nujol) cm^{-1} 3390, 1702, 1677; ^1H NMR ($CDCl_3$) δ 7.42–7.15 (m, 5H), 6.37–6.33 (m, 1H), 5.94–5.89 (m, 1H), 4.88 (s, 1H, exch.), 4.76–4.64 (m, 1H), 2.84 (br s, 2H), 2.60 (dd, *J* 12.8, 3.8, 1H), 2.20–2.00 (m, 2H), 1.78–0.81 (m, 11H), 1.76 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 169.9, 152.9, 142.1, 132.0, 128.3, 126.0, 124.9, 77.0, 65.6, 50.4, 50.0, 47.2, 42.9, 41.0, 40.2, 39.9, 35.0, 31.6, 28.6, 27.1, 25.3, 23.2, 22.0. Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.20; H, 8.64; N, 3.39.

4.2.2. (1*R*,2*S*,4*R*)-(−)-8-Phenylmenthyl 2-acetylamino-bicyclo[2.2.1]hept-5-ene-2-carboxylate, (+)-*endo*-6. Mp 230 °C (acetone). $[\alpha]_D^{25} = +79.6$ (*c* 0.6, $CHCl_3$); IR (Nujol) cm^{-1} 3239, 1731, 1636; ^1H NMR ($CDCl_3$) δ 7.39–7.15 (m, 5H), 6.36–6.32 (m, 1H), 5.78–5.74 (m, 1H), 5.40 (s, 1H, exch.), 4.71–4.59 (m, 1H), 2.90 (br s, 1H), 2.56 (br s, 1H), 2.24–1.96 (m, 3H), 1.91 (s, 3H), 1.77–0.70 (m, 11H), 1.37 (s, 3H), 1.19 (s, 3H), 0.84 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.2, 170.2, 152.4, 141.0, 130.3, 128.2, 125.9, 125.2, 77.0, 64.7, 52.2, 50.0, 48.7, 43.0, 41.3, 40.1, 39.3, 35.0, 31.6, 27.4, 27.3, 26.7, 23.4, 22.0. Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.23; H, 8.63; N, 3.40.

4.2.3. (−)-(1*S*,2*S*,4*S*)-2-Acetylamino-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, (−)-7. Operating in a screw-cap tube, to a stirred solution of (−)-*exo*-**5** (1.06 g, 2.6 mmol) in EtOH (5 mL, 95%), KOH (292 mg, 5.2 mmol) was added. The reaction mixture was stirred and heated at 110 °C for 2 h. After solvent evaporation the crude material was dissolved in water and extracted with Et_2O (3 × 10 mL). The aqueous layer was separated and then acidified to pH 5 with 2 N HCl. A solid was separated, filtered, washed with cold water, and dried. Acid (−)-*exo*-**7** (400 mg, 79%) was isolated as colorless crystals. Mp 225 °C (EtOH); $[\alpha]_D^{25} = -118$ (*c* 0.3, $CHCl_3$). Lit.: $[\alpha]_D^{25} = -106$ (*c* 1.2, MeOH).[9] Spetroscopic data are in agreement with the reported data.[10]

4.3. General procedure for the oxidation reaction

A solution of pure cycloadduct (−)-*exo*-**5** or (+)-*endo*-**6** (290 mg, 0.71 mmol) in acetone (10 mL) was added at 0 °C under stirring to a mixture of potassium permanganate (370 mg, 2.34 mmol) in water (2 mL). The temperature was kept below 5 °C during the addition and then allowed to rise at 25 °C. After 3 h, $Na_2S_2O_5$ (444 mg, 2.34 mmol) was added and the mixture stirred for an additional 20 min. The solution was carefully acidified to pH 2 with HCl (37%). The reaction mixture was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude solid, which was purified by crystallization giving (−)-**8** (270 mg, 81%) and (−)-**9** (260 mg, 78%), respectively, as white solids.

4.3.1. (1*S*,2*R*,4*S*)-(−)-8-Phenylmenthyl 1-acetylaminocyclopentane-1,2,4-tricarboxylate, (−)-8. Mp 188–189 °C ($CHCl_3$). $[\alpha]_D^{25} = -41.4$ (*c* 0.9, MeOH); IR (Nujol) 3344, 3192, 1721, 1620 cm^{-1}; ^1H NMR (acetone-d_6) δ 11.50–9.80 (br s, 2H, exch.), 7.42–7.10 (m, 5H), 4.87–4.74 (m, 1H), 3.22 (dd, *J* 8.8, 8.4, 1H), 3.01–2.89 (m, 2H), 2.69 (dd, *J* 13.6, 6.6, 1H), 2.51–2.36 (m, 2H), 2.09–1.94 (m, 4H), 1.84 (s, 3H), 1.55–1.50 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.10–0.75 (m, 2H), 0.84 (d, *J* 6.3, 3H); ^{13}C NMR (acetone-d_6) δ 175.2, 173.7, 170.6, 169.6, 150.9, 128.2, 126.0, 125.4, 76.7, 67.1, 49.6, 49.5, 41.0, 40.3, 39.9, 38.1, 34.5, 31.7, 31.5, 30.4, 27.5, 23.5, 22.3, 21.4. Anal. Calcd for $C_{26}H_{35}NO_7$: C, 65.94; H, 7.45; N, 2.96. Found: C, 65.82; H, 7.40; N, 2.73.

4.3.2. (1*S*,2*S*,4*R*)-(−)-8-Phenylmenthyl 1-acetylaminocyclopentan-1,2,4-tricarboxylate, (−)-9. Mp 185–187 °C (Et_2O); $[\alpha]_D^{25} = -3.7$ (*c* 0.8, CH_3OH); IR (Nujol) 3343, 1722, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.03 (m, 5H), 6.72 (s, 1H, exch.), 5.08–4.95 (m, 1H), 3.76–3.55 (m, 1H), 2.83 (br s, 1H), 2.79 (br s, 1H), 2.35–1.85 (m, 6H), 1.99 (s, 3H), 1.75–0.80 (m, 4H), 1.32 (s, 3H), 1.20 (s, 3H), 0.83 (d, *J* 6.6, 3H); ^{13}C NMR (acetone-d_6) δ 173.9, 172.1, 170.7, 170.4, 150.6, 128.2, 125.9, 125.6, 78.1, 67.0, 54.3,

50.4, 41.5, 41.0, 40.8, 40.4, 34.4, 33.0, 31.5, 31.0, 27.7, 22.8, 22.4, 21.4; Anal. Calcd for $C_{26}H_{35}NO_7$: C, 65.94; H, 7.45; N, 2.96. Found: C, 65.90; H, 7.41; N, 2.76. *m*/*z* 496.4 [M+23].

4.3.3. (1*S*,2*R*,4*S*)-1-Acetylaminocyclopentane-1,2,4-tricarboxylic acid, (−)-10. Operating in a screw-cap tube, KOH (107 mg, 1.9 mmol) was added to a solution of (−)-**8** (150 mg, 0.32 mmol) in EtOH (95%, 3 mL) and the reaction mixture was heated at 120 °C under stirring for 24 h. After removal of the solvent, the residue was dissolved in degassed water (15 mL) and extracted with Et_2O (3 × 10 mL). The aqueous layer was adjusted to pH 9, and the solution deposited on a Dowex 1 × 4–400 column (AcO^-, 200–400 mesh, 1 × 10 cm). The resin was rinsed with boiled water, and the tricarboxylic acid was eluted with 2 M AcOH. Evaporation of AcOH solution gave (−)-**10** (67 mg, 80%) as a white solid. Mp 207–208 °C (THF/AcOEt). $[\alpha]_D^{25} = -63.3$ (*c* 0.5, MeOH); IR (Nujol) 3320, 1743, 1720, 1692, 1600 cm^{-1}; ^1H NMR (D_2O) δ 3.53–3.46 (m, 1H), 3.06–2.88 (m, 1H), 2.48–2.16 (m, 4H), 1.83 (s, 3H); ^{13}C NMR δ (D_2O) 178.8, 176.5, 175.3, 174.3, 67.2, 49.4, 39.7, 38.1, 31.3, 21.7. Anal. Calcd for $C_{10}H_{13}NO_7$: C, 46.34; H, 5.06; N, 5.40. Found: C, 46.25; H, 5.15; N, 5.33.

4.3.4. (1*S*,2*R*,4*S*)-1-Aminocyclopentane-1,2,4-tricarboxylic acid, (+)-11. Operating in a screw-cap tube, a solution of (−)-**10** (94 mg, 0.36 mmol) in 6 M HCl (1 mL) was stirred and heated at 120 °C for 14 h. HCl was removed by evaporation and the crude material dissolved in water (10 mL). The resulting solution was adjusted to pH 4 with 1 M NaOH and deposited on a Dowex 50 × 4 column (H^+, 20–50 mesh, 1 × 10 cm). The resin was rinsed with water and the amino acid eluted with aqueous NH_4OH (0.5 M). Ninhydrin positive fractions were pooled and evaporated to give (+)-**11** (65 mg, 83%) as a solid. TLC CH_2Cl_2/MeOH/NH_4OH (15%) = 5:3:0.9. $[\alpha]_D^{25} = +3.1$ (*c* 0.26, H_2O). IR (Nujol) 3600–2500, 1598 cm^{-1}; ^1H NMR (D_2O) δ 3.22 (dd, *J* 12.8, 8.9, 1H), 3.03–2.95 (m, 1H), 2.65–2.55 (m, 1H), 2.29 (dd, *J* 14.8, 10.4, 1H), 2.08 (dd, *J* 14.8, 3.3, 1H), 1.89–1.78 (m, 1H). ^{13}C NMR δ (D_2O) 185.0, 178.9, 175.7, 68.1, 52.5, 43.8, 39.9, 33.8. Anal. Calcd for $C_8H_{11}NO_6$: C, 44.24; H, 5.11; N, 6.45. Found: C, 43.85; H, 5.54; N, 6.13; *m*/*z* 218.1 [M^+]. Compound **11·HCl**: ^1H NMR (D_2O/DCl) δ 3.62 (dd, *J* 12.4, 8.0, 1H), 3.20–3.00 (m, 1H), 2.62–2.40 (m, 2H), 2.26–1.98 (m, 2H).

4.3.5. (3a*S*,5*R*,6a*S*)-3a-*N*-Acetylamino-1,3-dioxo-hexahydro-cyclopenta[*c*]furan-5-carboxylic acid, (+)-12. Operating in a screw-cap tube, KOH (185 mg, 3.3 mmol) was added to a solution of (−)-**9** (263 mg, 0.55 mmol) in EtOH (4 mL, 95%) and the reaction heated at 120 °C for 48 h under stirring. After removal of the solvent, the residue was dissolved in degassed water (15 mL) and extracted with Et_2O (3 × 10 mL). The aqueous layer was adjusted to pH 9 and the solution deposited on a Dowex 1 × 4–400 column (AcO^-, 200–400 mesh, 1 × 10 cm). The resin was rinsed with degassed water, and the tricarboxylic acid eluted with AcOH (2 M). Evaporation of AcOH solution gave (+)-**12** (127 mg, 88%) as a white solid. $[\alpha]_D^{25} = +14.7$ (*c* 1, CH_3OH); IR (Nujol) 3600–2500, 1713, 1700 cm^{-1}; ^1H NMR (D_2O) δ 3.20 (dd, *J* 7.6, 9.8, 1H), 3.07–2.90 (m, 1H), 2.57 (dd, *J* 9.2, 13.6, 1H), 2.39–2.11 (m, 3H), 1.88 (s, 3H); ^{13}C NMR δ (D_2O) 180.0, 178.1, 176.5, 175.5, 67.6, 55.0, 43.2, 40.5, 33.9, 24.2. Anal. Calcd for $C_{10}H_{11}NO_6$: C, 49.80; H, 4.60; N, 5.81. Found: C, 49.48; H, 4.75; N, 5.67.

4.3.6. (3a*S*,5*R*,6a*S*)-3a-Amino-1,3-dioxo-hexahydro-cyclopenta[*c*]furan-5-carboxylic acid, (+)-13. Operating in a screw-cap tube, a solution of (+)-**12** (120 mg, 0.46 mmol) in 6 M HCl (3 mL) was stirred and heated at 120 °C for 14 h. HCl was removed by evaporation and the crude material dissolved in water (10 mL). The resulting solution was adjusted to pH 4 with 1 M NaOH and deposited on a Dowex 50 × 4 column (H^+, 20–50 mesh, 1 × 10 cm). The resin was rinsed with water and the amino acid was eluted with aqueous NH_4OH (0.5 M). Ninhydrin positive fractions were pooled and evaporated to give (+)-**13** (95 mg, 95%) as a solid. TLC CH_2Cl_2/MeOH/NH_4OH (15%) = 5:3:0.9. $[\alpha]_D^{25} = +6.7$ (*c* 0.25, H_2O). ^1H NMR δ (D_2O) 3.00–2.70 (m, 2H), 2.40–1.90 (m, 4H); ^{13}C NMR δ (D_2O) 181.3, 178.0 (br s), 175.4 (br s), 66.1, 54.6, 43.3, 38.4, 32.8. EI: *m*/*z* 217 (43%), 199 (30%); LCQ: *m*/*z* 216 [M^-] (100%), 198 (15%). Compound **13·HCl**: IR (Nujol) 3600–3150, 1713, 1594 cm^{-1}; ^1H NMR δ (D_2O) 3.30–3.00 (m, 2H), 2.65–2.21 (m, 4H). Compound **14**: IR (KBr) 3418, 3195, 1594 cm^{-1}.

4.3.7. (1*S*,2*S*,4*R*)-1-Aminocyclopentan-1,2,4-tricarboxylic acid 2-methyl ester, (+)-15. Silica gel (50 mg) was added to a stirred solution of (+)-**13** (200 mg, 1 mmol) in MeOH (5 mL) and the mixture was stirred overnight at room temperature. (TLC: CH_2Cl_2/MeOH/NH_4OH(33%)/H_2O, 5:3:0.3:0.6.) After filtration of the silica gel, the solution was evaporated under reduced pressure. Crystallization of the crude material (MeOH/H_2O) afforded pure compound (+)-**15** (180 mg, 78%) as a solid. Mp 265 °C (MeOH/H_2O). $[\alpha]_D^{25} = +14$ (*c* 0.20, H_2O); IR (Nujol) 3343, 1790, 1425 cm^{-1}; ^1H NMR (D_2O) δ 3.69 (s, 3H), 3.26 (dd, *J* 11.3, 8.0, 1H), 3.23–3.13 (m, 1H), 2.58 (dd, *J* 14.7, 9.1, 1H), 2.50–2.38 (m, 2H), 2.33 (dd, *J* 14.4, 9.2, 1H); ^{13}C NMR (D_2O) δ 177.8, 174.5, 173.2, 66.4, 52.7, 52.2, 41.2, 39.1, 31.6. Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.51; H, 5.71; N, 5.88. *m*/*z* [M^+] = 232.1.

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References

1. (a) Curry, K.; Peet, M. J.; Magnuson, D. S. K.; McLennan, H. *J. Med. Chem.* **1988**, *31*, 864–867; (b) Ezquerra, J.; Yruretagoyena, B.; Avendano, C.; de la Cuesta, E.; Gonzales, R.; Prieto, L.; Pedregal, C.; Espada, M.; Prowse, W. *Tetrahedron* **1995**, *51*, 3271–3278; (c) Tellier, F. J.; Acher, F. C.; Brabet, I. N.; Pin, J.-P.; Bockaert, J.; Azerad, R. *Biorg. Med. Chem. Lett.* **1995**, *5*, 2627–2632; (d) Acher, F. C.; Tellier, F. J.; Azerad, R.; Brabet, I. N.; Fagni, L.; Pin, J.-P. R. *J. Med. Chem.* **1997**, *40*, 3119–3129; (e) Ma, D.; Ma, J.;

Dai, L. *Tetrahedron: Asymmetry* **1997**, *8*, 825–827; (f) Kozikowski, A. P.; Steensma, D.; Araldi, G. L.; Tuckmantel, W.; Wang, S.; Pshenichkin, S.; Surina, E.; Wroblewski, J. T. *J. Med. Chem.* **1998**, *41*, 1641–1650; (g) Pellicciari, R.; Marinozzi, M.; Costantino, G.; Natalini, B.; Moroni, F.; Pellegrini, D. *J. Med. Chem.* **1999**, *42*, 2716–2720; (h) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613–7617; (i) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613; (j) Baudy, R. B.; Sze, J. Y.; Butera, J. A. *Synth. Commun.* **2004**, *34*, 3949–3954; (k) Ung, A. T.; Pyne, S. G.; Batenburg-Nguyen, U.; Davis, A. S.; Sherif, A.; Bischoff, F.; Lesage, A. S. J. *Tetrahedron* **2005**, *61*, 1803–1812.

2. (a) Choi, D. W. *J. Neurosci.* **1988**, *1*, 623–634; (b) Choi, D. W. *J. Neurosci.* **1990**, *10*, 2493–2501; (c) *Excitatory Amino Acids and Synaptic Transmissions*; Wheal, H. V., Thomson, A. M., Eds.; Academic Press: London, 1995; (d) Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Prog. Neurobiol.* **1998**, *54*, 581–618; (e) Braüner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645; (f) Lee, H.; Zhu, X.; O'Neill, M.; Webber, K.; Casadesus, G.; Marlatt, M.; Raina, A. K.; Perry, G.; Smith, M. A. *Acta Neurobiol. Exp.* **2004**, *64*, 89–98.
3. (a) Ornstein, P. L.; Schoepp, D. D.; Monn, J. A. *Curr. Pharm. Des.* **1995**, *1*, 355; (b) Jullian, N.; Brabet, I.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **1999**, *42*, 1546–1555; (c) Bertrand, H.-O.; Bessis, A.-S.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2002**, *45*, 3171–3183.
4. (a) Nakasihi, S. *Sciences* **1992**, *258*, 597–603; (b) Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31–108; (c) Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417–1426; (d) Conn, P. J.; Pin, J. P. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205–237.
5. (a) Palmer, E.; Monaghan, D. T.; Cotman, C. W. *Eur. J. Pharmacol.* **1989**, *166*, 585–587; (b) Joly, C.; Gomeza, J.; Brabet, I.; Curry, K.; Bockaert, J.; Pin, J.-P. *J. Neurosci.* **1995**, *15*, 3970–3981.
6. Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. *J. Med. Chem.* **1997**, *40*, 528–537.
7. (a) Clerici, F.; Gelmi, M. L.; Pocar, D. *J. Org. Chem.* **1999**, *64*, 726–730; (b) Clerici, F.; Gambini, A.; Gelmi, M. L. *J. Org. Chem.* **1999**, *64*, 5764–6767; (c) Clerici, F.; Gambini, A.; Gelmi, M. L. *J. Org. Chem.* **2000**, *65*, 6138–6141; (d) Clerici, F.; Gambini, A.; Gelmi, M. L. *J. Org. Chem.* **2001**, *65*, 4941–4944; (e) Abbiati, G.; Clerici, F.; Gambini, A.; Gelmi, M. L.; Pilati, T. *J. Org. Chem.* **2001**, *65*, 6299–6304; (f) Clerici, F.; Gambini, A.; Gelmi, M. L.; Nava, D. *Tetrahedron* **2001**, *57*, 6429–6438; (g) Clerici, F.; Gambini, A.; Gelmi, M. L.; Pilati, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2663–2669; (h) Caputo, F.; Clerici, F.; Gelmi, M. L.; Nava, D.; Pellegrino, S. *Tetrahedron* **2006**, *62*, 1288–1294.
8. Cativiela, C.; Diaz de Villegas, M. D.; Galvez, J. A. *Synthesis* **1990**, *25*, 198–199.
9. Cativiela, C.; Loper, P.; Mayoral, J. A. *Tetrahedron: Asymmetry* **1991**, *6*, 449–456.
10. Cativiela, C.; Loper, P.; Mayoral, J. A. *Tetrahedron: Asymmetry* **1990**, *1*, 379–388.
11. Caputo, F.; Clerici, F.; Gelmi, M. L.; Pellegrino, S.; Pilati, T. *Tetrahedron: Asymmetry* **2006**, *17*, 61–67.