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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2358–2364

Efficient access to *N*-protected derivatives of (*R*,*R*,*R*)- and (*S*,*S*,*S*)-octahydroindole-2-carboxylic acid by HPLC resolution

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Received 20 August 2007; accepted 7 September 2007

Dedicated to Professor Vicente Gotor on the occasion of his 60th birthday

Abstract—The preparation of the proline analogue (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid (Oic) and its enantiomer, (2*R*,3a*R*,7a*R*)-Oic, is described. A racemic precursor has been synthesized in good yield and subjected to HPLC resolution on a chiral column. The high efficiency of both the synthetic and chromatographic procedures has allowed the isolation of multigram quantities of each amino acid in enantiomerically pure form and suitably protected for use in peptide synthesis.

1. Introduction

Biologically active peptides are involved in a large number of physiological events and are therefore targets for medicinal applications.[1] However, most natural peptides exhibit low metabolic stability and lack selectivity towards a specific receptor, which greatly limits their use as therapeutic agents. In the search for molecules with a more convenient pharmacological profile, the modification of peptides through the incorporation of non-proteinogenic amino acids is an area of active investigation.[2]

Most deservedly, proline analogues[3] have attracted particular interest in this field. Due to its cyclic nature, proline is endowed with unique conformational properties amongst proteinogenic amino acids, for which reason it plays an outstanding role in defining the structural and biological behaviour of peptides.[4] Proline analogues combine the particular conformational properties of the parent amino acid with new functionalities that might be of help in stabilizing the molecule towards proteolytic enzymes, enhancing lipophilicity or providing favourable interactions with the receptor binding-site.

One of the most remarkable proline analogues in this context is octahydroindole-2-carboxylic acid (Oic). This bicyclic amino acid is present in the dipeptide Perindopril (Fig. 1), one of the best antihypertensive drugs on the market,[5] and has found application in the prevention of cardiovascular disorders like heart failure.[5a,d,6]

The Oic derivative S 17092 (Fig. 1) is amongst the most potent inhibitors of prolyl oligopeptidase (POP), an enzyme involved in the degradation of neuropeptides and related with the symptomatology of neurodegenerative diseases, in particular, with the loss of memory.[7] Compound S 17092 has been found to be a highly potent, long-lasting, specific POP inhibitor with antiamnesic and cognitive-enhancing effects, that has entered clinical evaluation.[7a–c,8]

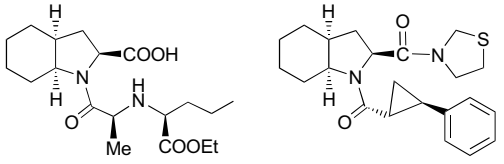

Figure 1. Structure of some Oic derivatives with pharmacologically relevant properties.

Also remarkable is the incorporation of Oic in larger peptide systems, such as the analogues of the nonapeptide hormone bradykinin. The development of competitive antagonists for the B2 receptor of this hormone has been

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doi:10.1016/j.tetasy.2007.09.006

actively pursued through the incorporation of a wide variety of non-proteinogenic amino acids.[9] Amongst them, the Oic-containing analogue HOE-140 (Icatibant or JE-049) displays potent anti-inflammatory, antiallergic and analgesic effects, and has recently completed phase III clinical trials as a treatment for hereditary angioedema.[9,10]

These examples provide clear evidence for the promise of Oic in the development of drugs. However, the exploitation of this proline analogue in the design of systems of pharmacological interest is far from complete, not to mention the possible applications—to the best of our knowledge, not yet explored—in fields such as organocatalysis.[11] Moreover, in the case of Oic, three stereogenic centres are present in the molecule and, as a consequence, eight different stereoisomers are possible. This stereochemical diversity greatly increases the potential of this proline surrogate since, for a given configuration at the α carbon, four different dispositions of the fused cyclohexane ring are possible, each of them conferring particular conformational properties to the molecule, which will lead to different behaviours as a part of a biologically relevant molecule or when mediating an organocatalytic process.

As a matter of fact, only the (2*S*,3a*S*,7a*S*)-isomer (Fig. 2), that is, the analogue of L-proline [(*S*) configuration at the α-carbon] with all three hydrogen atoms at stereocentres exhibiting a *cis* relative orientation, has been studied. Indeed, all the biologically significant compounds mentioned above incorporate this Oic stereoisomer, usually referred to as L-Oic,[12] whereas the behaviour of the other seven stereoisomers when included into peptides or other systems remains almost completely unexplored.

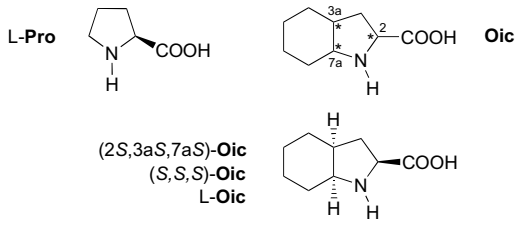


Figure 2. Comparison of the structures of proline (Pro) and octahydroindole-2-carboxylic acid (Oic). The position of the chiral carbons is indicated for the latter. The most frequently studied stereoisomer of Oic, usually referred to as L-Oic, is shown.

The accessibility of enantiomerically pure material is actually the main limitation to the use of this proline analogue in different applications. L-Oic has been the subject of several synthetic studies[13–15] and, very recently, has become commercially available, albeit at a very high price. In contrast, only a few methodologies have been reported for the preparation of the other stereoisomers and the development of efficient procedures for their synthesis still constitutes a challenge for organic chemists.

This situation prompted us to embark on a project aimed at the preparation of significant quantities of all eight stereoisomers of octahydroindole-2-carboxylic acid in enantiomerically pure form. In the first part of the series, we herein report an efficient method to obtain L-Oic and its enantiomer in enantiomerically pure form by the combination of a racemic synthesis and a chromatographic resolution.

2. Results and discussion

Several methodologies have been reported[13–15] for the synthesis of enantiopure L-Oic and involve either stereoselective processes[13] or resolution procedures.[14,15] Due to the presence of three stereogenic centres in the molecule, the former require highly elaborated starting products and usually occur with low stereocontrol. This is probably the reason why resolution procedures have been profusely investigated. Crystallization of diastereomeric salts of different (*S**,*S**,*S**)-Oic derivatives or precursors has been reported,[14] with most of them providing only moderate yields of enantiomerically pure material after extensive crystallization and when working on a large scale. In recent years, enzymatic resolutions have emerged as an alternative.[15]

In particular, Vincent et al.[14a] carried out the synthesis of L-Oic by hydrogenation of enantiomerically pure (*S*)-indoline-2-carboxylic acid using palladium/carbon as a catalyst. Similarly, (*R*)-indoline-2-carboxylic acid provided the L-Oic enantiomer, (*R*,*R*,*R*)-Oic. The main drawback of this methodology is the isolation of the starting enantiopure indolines, which were obtained by chemical resolution using (*R*)- or (*S*)-1-phenylethylamine as crystallizing agents.

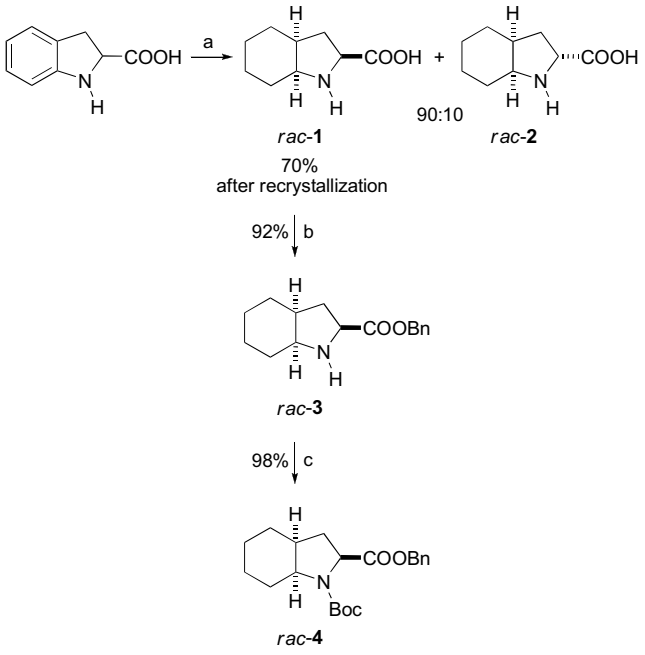
The catalytic reduction of the aromatic ring in (*S*)-indoline-2-carboxylic acid is indeed a very convenient way to access L-Oic since it ensures the *cis* relative disposition of the two bridgehead hydrogen atoms. Moreover, hydrogenation takes place preferably on the less hindered face of the molecule, which leads to a *cis* orientation of these two hydrogens with respect to that at the α-position, that is, the stereochemistry of L-Oic (Fig. 2).

On this basis, we considered the possibility of applying the methodology reported by Vincent[14a] to a racemic starting material, bearing in mind the idea of carrying out a subsequent resolution procedure using chiral HPLC. Thus, inexpensive, commercially available indoline-2-carboxylic acid was hydrogenated to afford *rac*-**1** and *rac*-**2** in a 9:1 ratio (Scheme 1), in a similar way to that described[14a] for the reduction of the enantiopure compounds. A study of the hydrogenation conditions allowed us to complete this process at an atmospheric pressure using platinum oxide as the catalyst instead of palladium/carbon, for which a high pressure of hydrogen is necessary.[14a] In our case, the different solubility of *rac*-**1** and *rac*-**2** in comparison with that reported for the enantiopure compounds[14a] required the optimization of the recrystallization conditions, which finally allowed the isolation of pure *rac*-**1** in 70% yield.

Next, we addressed the protection of the amino and carboxylic acid functionalities in *rac*-**1**, in order to obtain a suitable derivative for the subsequent chromatographic resolution procedure. Different combinations of protecting groups were considered and the benzyl ester and

tert-butoxycarbonyl (Boc) moieties were finally selected as the most convenient ones. These can be eliminated in a selective manner and under very mild conditions. The latter point is of particular relevance since, once the enantiomers are separated, it is essential that any transformation can be performed without risking epimerization at the α-carbon. In this case, a simple hydrogenation reaction would afford the *N*-protected derivatives necessary for standard peptide synthesis. The benzyl ester group has the added advantage of absorbing in the UV range, thus favouring monitoring of the chromatographic process.

The introduction of the mentioned protective groups was carried out by the reaction of *rac*-**1** with benzyl alcohol in the presence of *p*-toluenesulfonic acid and subsequent treatment of the ester *rac*-**3** thus obtained with di-*tert*-butyl dicarbonate (Scheme 1). In this way, several grams of the fully protected, racemic derivative *rac*-**4** were prepared in 63% overall yield from indoline-2-carboxylic acid.



Scheme 1. Synthesis of protected (*S**,*S**,*S**)-Oic in racemic form. Reagents and conditions: (a) H_2, PtO_2, AcOH, 60 °C; (b) $PhCH_2OH$, *p*-toluenesulfonic acid, toluene, reflux; (c) Boc_2O, $Me_4N(OH)$, DMAP, THF, rt.

Once this precursor of Oic was obtained in racemic form, we envisaged the isolation of the two enantiomers by carrying out a HPLC resolution process. Amongst the chiral stationary phases that can be used for this purpose, those derived from polysaccharides are particularly suitable due to their excellent chiral recognition ability and high loading capacity.[16] Moreover, very recently, amylose- and cellulose-based columns in which the chiral support is covalently bonded to the silica gel matrix have been launched to the market.[17] This feature makes these stationary phases compatible with all organic solvents and, therefore, particularly appropriate for resolutions on a preparative scale.[18,19] Phases of this type, either commercial or made at the laboratory, have been used in our group for the preparative enantioseparation of several protected amino acids with excellent results.[20]

The resolution of *rac*-**4** was firstly tested at the analytical level using 250 × 4.6 mm ID Chiralpak® IA and Chiralpak® IB columns that, respectively, contain 3,5-dimethylphenylcarbamate of amylose or cellulose as the chiral selector.[17] Very poor resolution was observed on the latter column, whereas Chiralpak® IA showed excellent enantiodiscrimination ability with a variety of mobile phases. After screening different elution conditions, the optimal separation of enantiomers was achieved when a mixture of *n*-hexane/2-propanol/*tert*-butyl methyl ether 91/3/6 was used as the eluent at a flow rate of 0.8 mL/min (Fig. 3).

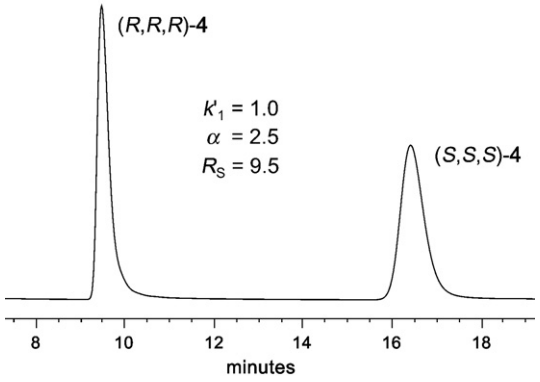


Figure 3. HPLC resolution of *rac*-**4** at the analytical level. Column: Chiralpak® IA (250 × 4.6 mm ID). Eluent: *n*-hexane/2-propanol/*tert*-butyl methyl ether 91/3/6. Flow rate: 0.8 mL/min. UV detection: 210 nm. See Section 4.2 for definition of the chromatographic parameters.

The extension of the analytical conditions to the preparative scale proved extremely efficient. Thus, injection of 4.65 g of *rac*-**4** on a 250 × 20 mm ID Chiralpak® IA column afforded as much as 4.60 g of enantiomerically pure material (about 2.30 g of each enantiomer) in a single passage of the racemate through the column. The enantiomeric purity of the resolved enantiomers was assessed at the analytical level (Fig. 4).

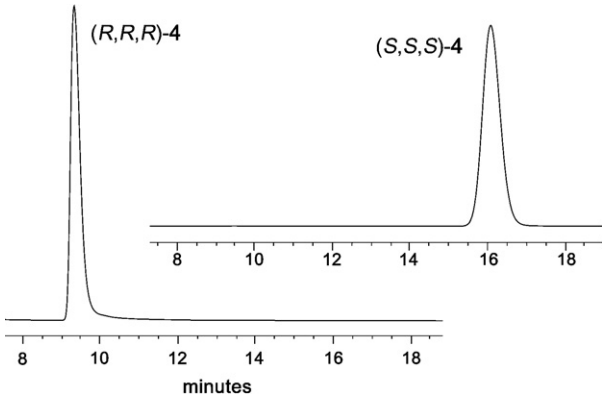


Figure 4. HPLC analytical profile of the resolved enantiomers of **4**. Column: Chiralpak® IA (250 × 4.6 mm ID). Eluent: *n*-hexane/2-propanol/*tert*-butyl methyl ether 91/3/6. Flow rate: 0.8 mL/min. UV detection: 210 nm.

At this stage, single crystals of the second eluted enantiomer of **4** were obtained and subjected to X-ray diffraction analysis. The crystalline structure (Fig. 5) confirmed the *cis* ring junction as well as the *cis* relative disposition of the cyclohexane and benzyl ester groups.

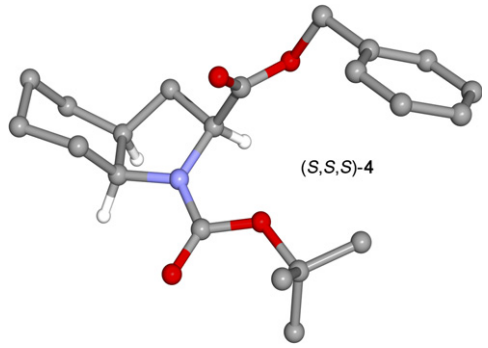
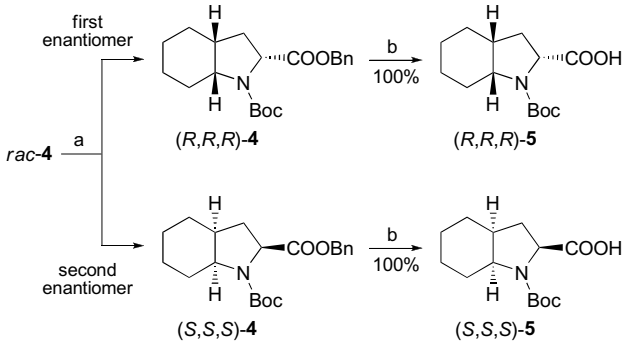


Figure 5. X-ray crystal structure of the second eluted enantiomer of **4** [the (*S*,*S*,*S*) absolute stereochemistry was assigned after elimination of the benzyl ester, see text]. All hydrogens, except those attached to chiral carbons, have been omitted for clarity.

Finally, the isolated enantiomers were subjected to catalytic hydrogenation to provide the desired enantiopure *N*-Boc amino acids in quantitative yield (Scheme 2). These Oic derivatives are suitably protected for use in standard peptide synthesis.



Scheme 2. Synthesis of enantiomerically pure Oic derivatives. Reagents and conditions: (a) chiral HPLC; (b) H_2, Pd/C, EtOAc, rt.

The absolute stereochemistry of all the enantiomerically pure compounds was established after isolation of the final *N*-Boc amino acids. Thus, comparison of the specific rotation observed for these compounds with that measured for a commercial sample of (*S*,*S*,*S*)-**5** (Boc-L-Oic)[21] allowed us to assign an (*R*,*R*,*R*) configuration to the first eluted enantiomer of **4** and an (*S*,*S*,*S*) stereochemistry to the more strongly retained enantiomer of **4** (Fig. 3, Scheme 2).

3. Conclusion

We have developed an efficient and practical method for the synthesis of the proline analogues (2*S*,3a*S*,7a*S*)- and (2*R*,3a*R*,7a*R*)-octahydroindole-2-carboxylic acids in enantiomerically pure form and suitably protected for incorporation into peptides. A racemic intermediate has been prepared in high overall yield through only three steps from inexpensive commercial indoline-2-carboxylic acid and subjected to HPLC resolution on an amylose-derived chiral column. The procedure has been applied to the isolation of multigram quantities of enantiomerically pure compounds and can be easily scaled up to the production of larger amounts.

4. Experimental

4.1. General

All reagents were used as received from commercial suppliers without further purification. The progress of the reactions was monitored by thin layer chromatography (TLC) on Macherey-Nagel Polygram syl G/UV precoated silica gel polyester plates. The products were visualized under UV light (254 nm), iodine vapour or submersion in cerium molybdate stain [aqueous solution of phosphomolybdic acid (2%), $CeSO_4{\cdot}4H_2O$ (1%) and H_2SO_4 (6%)]. Column chromatography was performed using SDS 60 Å silica gel (35–70 μm). Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument at room temperature using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. Optical rotations were measured at room temperature using a JASCO P-1020 polarimeter. High-resolution mass spectra were obtained on a Bruker Microtof-Q spectrometer.

4.2. High performance liquid chromatography

HPLC was carried out using a Waters 600 HPLC system equipped with a 2996 photodiode array detector and a 2487 dual wavelength absorbance detector (respectively, used for monitoring analytical and preparative separations). The solvents used as mobile phases were of chromoscan grade. Analytical assays were performed on Chiralpak® IA and Chiralpak® IB columns (Daicel Chemical Industries Ltd., Japan) of 250 × 4.6 mm ID using mixtures of *n*-hexane/2-propanol, *n*-hexane/acetone, *n*-hexane/2-propanol/chloroform and *n*-hexane/2-propanol/*tert*-butyl methyl ether as eluents (flow rate 0.7–0.9 mL/min). The preparative resolution was carried out on a 250 × 20 mm ID Chiralpak® IA column eluting with *n*-hexane/2-propanol/*tert*-butyl methyl ether 91/3/6 (see Section 4.7 for further details). The capacity (k'), selectivity (α) and resolution (R_S) factors are defined as follows: $k' = (t_r - t_0)/t_0$, $\alpha = k'_2/k'_1$, $R_S = 1.18(t_2 - t_1)/(w_2 + w_1)$, where subscripts 1 and 2 refer to the first and second eluted enantiomers, t_r ($r = 1, 2$) are their retention times, and w_1 and w_2 denote their half-height peak widths; t_0 is the dead time.

4.3. X-ray diffraction

Colourless single crystals of (*S*,*S*,*S*)-**4** were formed upon concentration of an *n*-hexane/2-propanol/*tert*-butyl methyl ether solution. The X-ray diffraction data were collected at room temperature on an Oxford Diffraction Xcalibur diffractometer provided with a Sapphire CCD detector, using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using SHELXS-97[22a] and refinement was performed using SHELXL-97[22b] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were located by calculation and affected by an isotropic thermal factor fixed to 1.2 times the U_{eq} of the carrier atom (1.5 for the methyl protons). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 656555. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Crystallographic data: monoclinic, space group $P2_1$; $a = 6.2467(4)$ Å, $b = 16.6392(10)$ Å, $c = 9.9856(8)$ Å, β 100.967(7)°; $Z = 2$; $d_{calcd} = 1.172$ g cm^{-3}; 6795 reflections collected, 3455 unique ($R_{int} = 0.0325$); data/parameters: 3455/236; final R indices ($I > 2\sigma I$): $R_1 = 0.0296$, $wR_2 = 0.0535$; final R indices (all data): $R_1 = 0.0607$, $wR_2 = 0.0581$. Highest residual electron density: 0.09 e Å^{-3}.

4.4. Synthesis of (2*S**,3a*S**,7a*S**)-octahydroindole-2-carboxylic acid, *rac*-1

A solution of indoline-2-carboxylic acid (4.0 g, 24.54 mmol) in acetic acid (80 mL) was hydrogenated at 60 °C in the presence of PtO_2 (400 mg). After 24 h, the catalyst was filtered off and washed with acetic acid. The solvent was evaporated to dryness and the resulting residue was first crystallized from ethanol and then from a mixture of dioxane–water to afford pure *rac*-**1** as a white solid (2.90 g, 17.18 mmol, 70% yield). Mp 233–234 °C (dec). IR (KBr) ν 3600–2200, 1623 cm^{-1}. ^{1}H NMR (D_2O, 400 MHz) δ 4.06 (m, 1H), 3.65 (m, 1H), 2.36–2.25 (m, 2H), 2.01–1.91 (m, 1H), 1.82–1.73 (m, 1H), 1.64–1.23 (m, 7H). ^{13}C NMR (D_2O, 100 MHz) δ 175.42, 59.70, 59.34, 36.91, 32.36, 25.06, 24.38, 21.36, 20.88. HRMS (ESI) $C_9H_{16}NO_2$ $[M+H]^+$: calcd 170.1176, found 170.1177.

4.5. Synthesis of benzyl (2*S**,3a*S**,7a*S**)-octahydroindole-2-carboxylate *p*-toluenesulfonate, *rac*-3

To a solution of *rac*-**1** (2.90 g, 17.18 mmol) in toluene (60 mL), *p*-toluenesulfonic acid monohydrate (4.73 g, 24.91 mmol) and benzyl alcohol (6.66 mL, 64.42 mmol) were added. The resulting system was heated at reflux for 4 h using a Dean–Stark trap. After evaporation to dryness, the residue was triturated with diisopropyl ether and the white solid formed was collected by filtration (6.81 g, 15.81 mmol, 92% yield). Mp 135–137 °C. IR (Nujol) ν 1743, 1577 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.46 (m, 1H), 7.77 (d, 2H, $J = 8.1$ Hz), 7.55 (m, 1H), 7.38–7.31 (m, 5H), 7.16 (d, 2H, $J = 8.1$ Hz), 5.23 (d, 1H, $J = 12.0$ Hz), 5.17 (d, 1H, $J = 12.0$ Hz), 4.71 (m, 1H), 3.88 (m, 1H), 2.54 (m, 1H), 2.38 (m, 1H), 2.34 (s, 3H), 2.01–1.90 (m, 2H), 1.62–1.20 (m, 7H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.11, 141.85, 140.15, 134.34, 128.80, 128.66, 128.57, 125.95, 68.57, 59.63, 57.85, 36.51, 31.66, 24.85, 24.71, 22.32, 21.32, 20.49. HRMS (ESI) $C_{16}H_{22}NO_2$ M^+: calcd 260.1645, found 260.1642.

4.6. Synthesis of benzyl (2*S**,3a*S**,7a*S**)-*N*-(*tert*-butoxycarbonyl)octahydroindole-2-carboxylate, *rac*-4

Compound *rac*-**3** (6.0 g, 13.92 mmol) dissolved in THF (100 mL) was treated with tetramethylammonium hydroxide pentahydrate (2.52 g, 13.92 mmol) and 4-(dimethylamino)pyridine (170 mg, 1.39 mmol). The resulting solution was kept at room temperature for 30 min and then di-*tert*-butyl dicarbonate (4.55 g, 20.88 mmol) was added. After stirring for an additional 2 h, the reaction mixture was diluted with diethyl ether (100 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue obtained was purified by column chromatography (eluent: hexanes/ethyl acetate 10/1) to provide *rac*-**4** as a colourless oil (4.90 g, 13.64 mmol, 98% yield). IR (neat) ν 1738, 1696 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.40–7.30 (m, 5H), 5.21–5.05 (m, 2H), 4.20 (dd, 1H, $J = 7.7$, 9.8 Hz), 3.67 (m, 1H), 2.27 (m, 1H), 2.10 (m, 1H), 1.96–1.79 (m, 2H), 1.66–1.51 (m, 3H), 1.43–1.02 (m, 4H), overlapped with 1.37 and 1.24 (each s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 172.76, 172.28; 153.03, 152.24; 136.02, 135.82; 128.36, 128.27; 128.05, 127.96; 127.83, 127.45; 78.58; 65.88, 65.57; 58.71, 58.52; 56.78, 56.36; 36.22, 35.61; 31.77, 30.92; 28.03, 27.76; 27.52, 27.08, 25.17; 23.23, 23.13; 20.06, 20.00. HRMS (ESI) $C_{21}H_{29}NO_4Na$ $[M+Na]^+$: calcd 382.1989, found 382.1991.

4.7. Resolution of *rac*-4: isolation of benzyl (2*R*,3a*R*,7a*R*)- and (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)octahydroindole-2-carboxylate, (*R*,*R*,*R*)-4 and (*S*,*S*,*S*)-4

HPLC resolution of compound *rac*-**4** (4.650 g) dissolved in chloroform (9.30 mL) was carried out by successive injections of 0.80 mL on a 250 × 20 mm ID Chiralpak® IA column. A mixture of *n*-hexane/2-propanol/*tert*-butyl methyl ether 91/3/6 was used as the eluent working at a flow rate of 16 mL/min and with UV monitoring at 220 nm. Three separate fractions were collected. Enantiomerically pure (*R*,*R*,*R*)-**4** (2.300 g) and (*S*,*S*,*S*)-**4** (2.298 g) were, respectively, obtained by evaporation of the first and third fractions. The second fraction contained 29 mg of a 26/74 mixture of (*R*,*R*,*R*)-**4**/(*S*,*S*,*S*)-**4**.

(*R*,*R*,*R*)-**4**: White solid. Mp 67–69 °C. $[\alpha]_D = +38.1$ (*c* 0.96, $CHCl_3$). HRMS (ESI) $C_{21}H_{29}NO_4Na$ $[M+Na]^+$: calcd 382.1989, found 382.1985.

(*S*,*S*,*S*)-**4**: White solid. Mp 67–69 °C. $[\alpha]_D = -39.7$ (*c* 0.94, $CHCl_3$). HRMS (ESI) $C_{21}H_{29}NO_4Na$ $[M+Na]^+$: calcd 382.1989, found 382.1988.

Spectroscopic data for (*R*,*R*,*R*)- and (*S*,*S*,*S*)-**4** are identical to those given above for the racemic compound.

4.8. Synthesis of (2*R*,3a*R*,7a*R*)-*N*-(*tert*-butoxycarbonyl)-octahydroindole-2-carboxylic acid, (*R*,*R*,*R*)-5

A solution of (*R*,*R*,*R*)-**4** (2.28 g, 6.35 mmol) in ethyl acetate (50 mL) was hydrogenated at room temperature in the presence of 10% palladium–carbon (230 mg). After 18 h, filtration of the catalyst and evaporation of the solvent afforded pure (*R*,*R*,*R*)-**5** as a white solid (1.70 g, 6.32 mmol, 100% yield). Mp 134–136 °C. $[\alpha]_D = +22.6$ (*c* 0.50, MeOH). IR (Nujol) *v* 3600–2500, 1695 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.49 (br s, 1H), 4.03 (m, 1H), 3.63 (m, 1H), 2.24 (m, 1H), 2.06 (m, 1H), 1.95–1.76 (m, 2H), 1.67–1.52 (m, 3H), 1.43–1.01 (m, 4H), overlapped with 1.37 and 1.32 (each s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 174.55, 174.00; 153.02, 152.44; 78.35, 78.30; 58.77, 58.48; 56.84, 56.35; 36.22, 35.65; 31.67, 31.01; 28.09, 27.90; 27.54, 27.01; 25.26; 23.29, 23.17; 20.07, 20.04. HRMS (ESI neg.) $C_{14}H_{22}NO_4$ $[M-H]^-$: calcd 268.1554, found 268.1555.

4.9. Synthesis of (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)-octahydroindole-2-carboxylic acid, (*S*,*S*,*S*)-5

An identical procedure to that described above was applied to transform (*S*,*S*,*S*)-**4** (2.28 g, 6.35 mmol) into (*S*,*S*,*S*)-**5** (1.71 g, 6.34 mmol, 100% yield). Mp 134–136 °C. $[\alpha]_D = -23.2$ (*c* 0.50, MeOH).[21] HRMS (ESI neg.) $C_{14}H_{22}NO_4$ $[M-H]^-$: calcd 268.1554, found 268.1549. Spectroscopic data are the same as those described for (*R*,*R*,*R*)-**5**.

Acknowledgements

Financial support from the Ministerio de Educación y Ciencia–FEDER (Project CTQ2004-5358) and Gobierno de Aragón (Project PIP206/2005 and research group E40) is gratefully acknowledged. The authors thank Ana Lidia Bernad for technical assistance with HPLC. This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under contract number NO1-CO-12400. The content of this publication does not necessarily reflect the view of the policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organization imply endorsement by the US Government. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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