DOI: 10.1002/ejoc.201100229

Stereodivergent Synthesis of Two Novel α-Aminophosphonic Acids Characterised by a *cis*-Fused Octahydroindole System

Alicia Arizpe,[a] Francisco J. Sayago,[a] Ana I. Jiménez,[a] Mario Ordóñez,*[b] and Carlos Cativiela*[a]

Keywords: Phosphoproline analogues / Fused-ring systems / Diastereoselectivity / Amino acids / Aminophosphonic acids

The synthesis of two new α-aminophosphonic acids, namely (2*S**,3a*S**,7a*S**)- and (2*R**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acids, is described. They are analogues of phosphoproline with a cyclohexane ring fused to the pyrrolidine moiety. The ring junction has *cis* stereochemistry in both cases, but the two compounds differ in the relative orientation of the cyclohexane and phosphonate moieties. The two amino acids were prepared from a common starting material following stereodivergent routes that provide the desired stereoisomer with complete stereocontrol. The relative configurations of the compounds synthesised were confirmed by X-ray diffraction analysis.

Introduction

α-Aminophosphonic acids are surrogates of α-amino acids in which the planar carboxylic acid (CO_2H) has been replaced by a sterically more demanding tetrahedral phosphonic acid [$P(O)(OH)_2$]. This replacement brings about important differences not only in molecular shape but also in acidity and other properties. α-Aminophosphonic acids are currently attracting a great deal of interest in medicinal chemistry, as well as in agrochemistry, due to their outstanding biological and pharmacological properties.[1,2] Thus, some of these compounds and their derivatives, including short peptides that contain them, find application as anti-bacterial, anti-viral and anti-fungal agents or as insecticides and herbicides. Others show promising anti-cancer activity or have proven to be effective in the treatment of osteoporosis.

The important properties exhibited by α-aminophosphonic acids have stimulated the development of methods for the synthesis of these compounds.[1,2a,3] Much effort has been devoted in the last decades to the preparation of phosphonic analogues of the 20 proteinogenic amino acids[4] and, as a result, procedures for the synthesis of most of them are now available. Having achieved this goal, the current challenge is the search for new structures other than those analogous to the coded α-amino acids. In this context, the wide variety of non-coded α-amino acids synthesised in recent years by the introduction of different types of modifications on to the coded residues provides an invaluable source of inspiration. In particular, those non-proteinogenic α-amino acids that have already shown exceptional properties are ideal candidates to serve as models for the construction of new α-aminophosphonic acids.

Among such non-coded α-amino acids is octahydroindole-2-carboxylic acid (known in the abbreviated form as Oic, Figure 1). Oic is a proline analogue with a cyclohexane ring fused to the pyrrolidine cycle. Because of synthetic limitations, only the (2*S*,3a*S*,7a*S*) stereoisomer, characterised by a *cis* ring fusion and usually referred to as L-Oic (Figure 1), has been widely investigated. This amino acid has allowed the development of highly potent, long-lasting peptides or peptide-related molecules that have found application as anti-inflammatory, anti-allergic and analgesic agents, in the treatment of neurodegenerative diseases and in the prevention of cardiovascular disorders, among others.[5,6] Some of these L-Oic-containing compounds are already commercially available (like the dipeptide Perindopril, one of the leading anti-hypertensive drugs on the market[6g,6i]) and others have entered clinical evaluation. Synthetic methods for the preparation of the remaining Oic stereoisomers are now available, some of them having been developed in our laboratories.[5]

The high value of L-Oic, together with our experience in the synthesis of different Oic stereoisomers and our interest in aminophosphonic acids, prompted us to undertake the preparation of two phosphonic surrogates of Oic, namely those exhibiting a *cis* ring junction and either a *cis* or a *trans* stereochemistry between the six-membered cycle and the phosphonic group, that is, (2*R**,3a*S**,7a*S**)- and (2*S**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acids, respectively (Figure 1).

[a] Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza – CSIC, 50009 Zaragoza, Spain
Fax: +34-976-761210
E-mail: cativiela@unizar.es
[b] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, 62209 Cuernavaca, Mexico
Fax: +52-7773297997
E-mail: palacios@ciq.uaem.mx

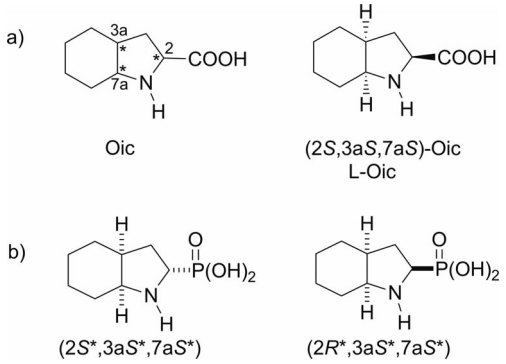
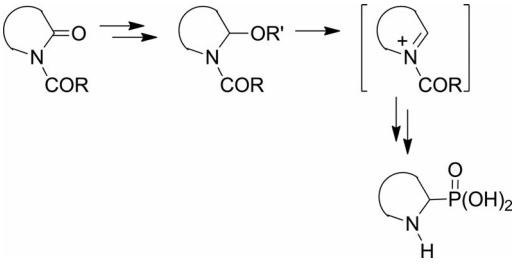


Figure 1. a) Structure of the proline analogue octahydroindole-2-carboxylic acid (Oic) (the positions of the chiral carbons are indicated). The most widely studied stereoisomer of Oic (L-Oic) is shown. b) Structures of the phosphonic surrogates of Oic, the synthesis of which is described in this work.

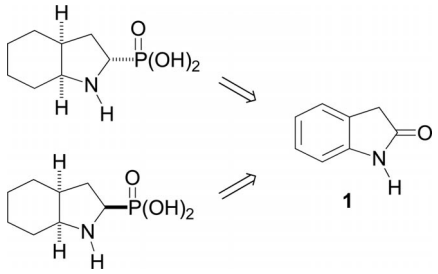
Results and Discussion

The target compounds share a *cis* stereochemistry at the ring junction and differ in the stereochemistry at the α carbon. Our experience[5] in the synthesis of Oic derivatives made us consider hydrogenation of an unsaturated precursor of the octahydroindole system as the most convenient procedure to ensure a *cis* ring fusion. On the other hand, we reasoned that a lactam system could provide the appropriate scaffold for creating the desired α-aminophosphonate functionality (Scheme 1). This consideration was based on two synthetic precedents described in the literature: 1) the well-known reduction of the carbonyl group at the C-5 position of *N*-acylpyroglutamic acid (5-oxoproline) derivatives to give the corresponding hemiaminal and subsequent transformation into an aminal and then into an *N*-acyliminium ion, which undergoes nucleophilic addition to yield 5-substituted prolines;[7] 2) the reaction of trialkyl phosphites with *N*-acyliminium ions derived from α-methoxy carbamates, first reported by Shono et al.[8]



Scheme 1. Use of a lactam as a precursor of an α-aminophosphonic acid.

These considerations made us select commercially available 2-indolinone (**1**; Scheme 2) as the starting material for the synthesis of the target compounds. This substrate bears a γ-lactam appropriate for the generation of the α-aminophosphonate functionality. At the same time, it contains the desired bicyclic system with a double bond at the ring junction, which ensures a *cis* fusion upon hydrogenation. Most importantly, the sequence in which these key transformations are performed is crucial to define the stereochemistry of the final product, as explained in the following.

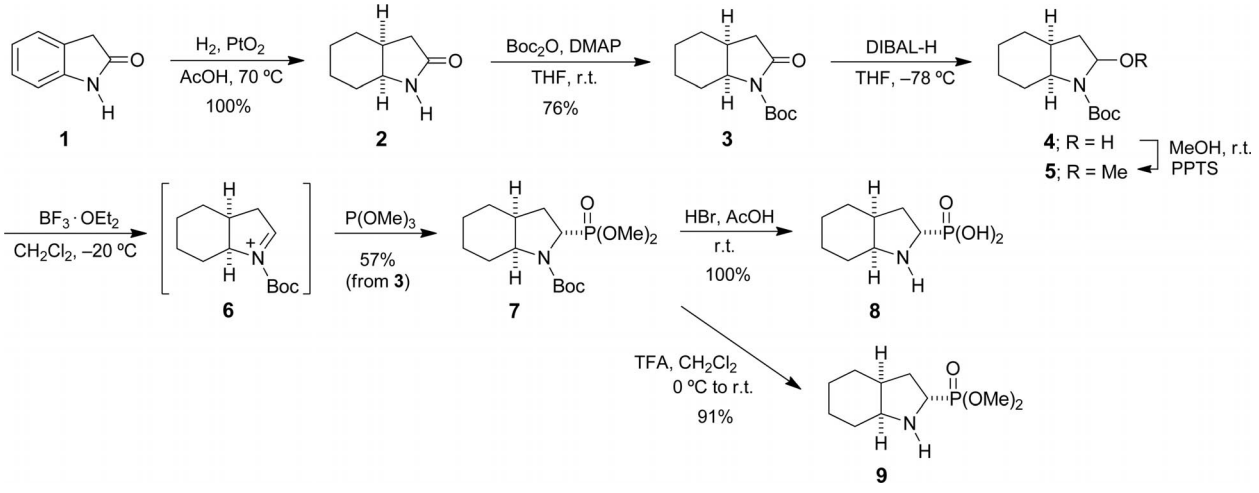


Scheme 2. Structure of 2-indolinone (also named 2-oxindole, **1**), selected as a common precursor of the target aminophosphonic acids.

First, we focused on the preparation of the derivative with a *trans* relative disposition between the phosphonic group and the six-membered cycle, that is, (2*S**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acid. The first step in the synthesis involved hydrogenation of the aromatic ring in **1** (Scheme 3). The process proceeded smoothly under an atmospheric pressure of hydrogen gas using platinum(IV) oxide as the catalyst and provided *cis*-octahydroindol-2-one (**2**) in quantitative yield. Such reaction conditions were selected on the basis of our previous experience in the preparation of Oic derivatives. We have observed[9] that PtO_2 allows the hydrogenation of indoline derivatives to proceed under mild reaction conditions whereas other catalytic systems based on palladium or rhodium have been reported[5,10] to require high pressures of hydrogen gas.

Compound **2** exhibits the desired *cis* stereochemistry at the ring junction and bears a γ-lactam functionality. Introduction of an acyl group on to the nitrogen atom is a prerequisite for the subsequent transformation into an α-aminophosphonate, as outlined in Scheme 1. An acyl substituent of the carbamate type, namely the *tert*-butoxycarbonyl (Boc) group, was selected for this purpose because subsequent deprotection to generate the amino function can be accomplished under mild conditions. Treatment of **2** with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) afforded the desired *N*-Boc-protected derivative **3** in good yield (Scheme 3).

This compound was allowed to react with diisobutylaluminium hydride (DIBAL-H) to yield the unstable hemiaminal **4**, which was not isolated but treated immediately with methanol and catalytic pyridinium *p*-toluenesulfonate (PPTS) to provide the methoxyaminal **5**. Subsequent reaction with trimethyl phosphite in the presence of boron trifluoride–diethyl ether[8] led to the formation of **7** via the intermediate *N*-acyliminium **6**. Notably, the desired dimethyl *N*-Boc-octahydroindole-2-phosphonate (**7**) was obtained as a single stereoisomer with no trace of the epimer



Scheme 3. Synthesis of (2*S**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acid.

at the α carbon being detected by either ^{1}H or ^{31}P NMR analysis of the crude product. The isolated compound presumably exhibits a (2*S**,3a*S**,7a*S**) relative configuration because the nucleophilic attack of trimethyl phosphite on **6** most probably occurs from the less hindered face of the molecule, that is, opposite the six-membered cycle. X-ray diffraction analysis of single crystals of **7** (Figure 2) confirmed the expected (2*S**,3a*S**,7a*S**) stereochemistry, characterised by a *trans* arrangement of the cyclohexane and phosphonate moieties.

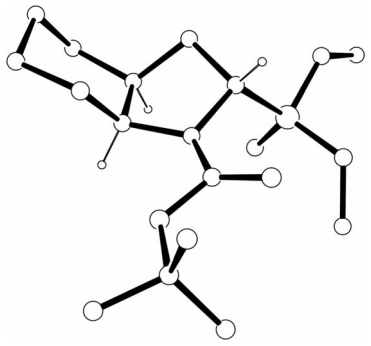
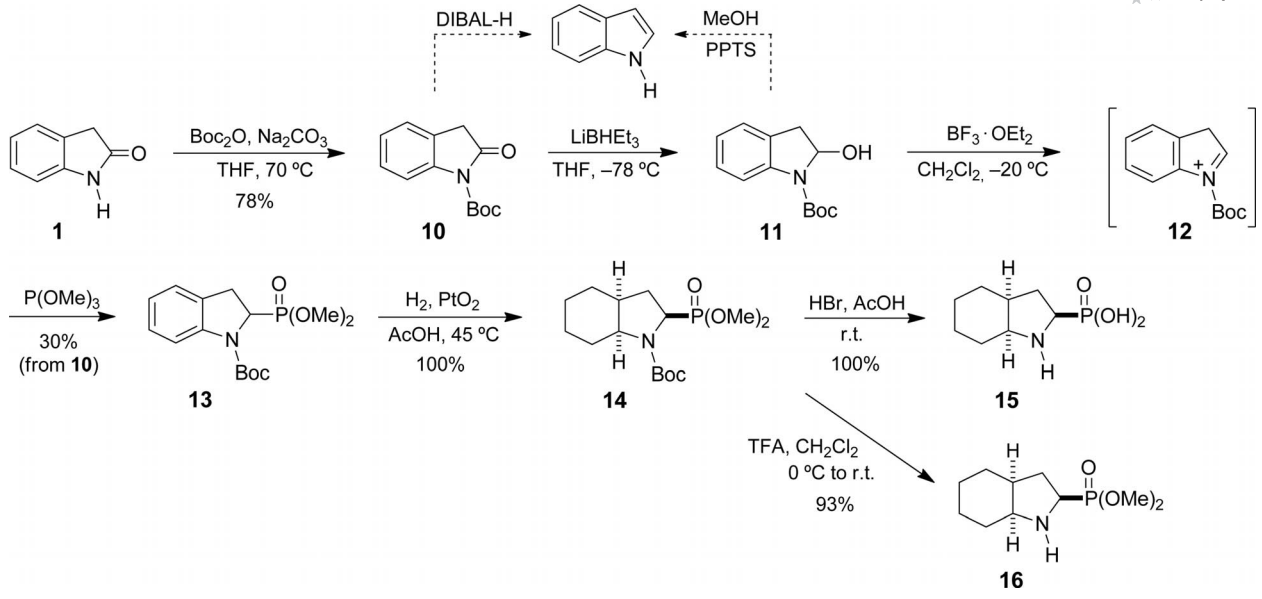


Figure 2. X-ray crystal structure of **7** characterized by a (2*S**,3a*S**,7a*S**) relative stereochemistry (only one enantiomer is shown). All hydrogen atoms, except those attached to chiral carbons, have been omitted for clarity.

Removal of the protecting groups to obtain the free aminophosphonic acid **8** was accomplished by treatment with a 33% solution of hydrogen bromide in acetic acid (Scheme 3). In addition, selective deprotection of the amino function was attempted to generate the aminophosphonate **9**, which may be of use for further derivatisation. Unfortunately, the phosphonate ester proved not to be completely stable under the reaction conditions typically used to remove the Boc group. Thus, treatment of **7** with either 3 N hydrogen chloride in ethyl acetate or a 4:6 mixture of trifluoroacetic acid (TFA) and dichloromethane resulted in partial deprotection of the dimethyl phosphonate and, as a consequence, a mixture of products (including the ester, the hemiester and the free acid) was isolated. Selective cleavage of the *N*-Boc protecting group in **7** was finally achieved with a highly diluted solution of TFA in dichloromethane (0.5 N), as previously reported by Ricci and co-workers.[11] This procedure afforded the α-aminophosphonate **9** in excellent yield (Scheme 3).

The synthesis of the epimeric derivative, (2*R**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acid, was next addressed. In this case, the introduction of the phosphonate group was envisaged prior to the reduction of the benzene ring to favour the desired *cis* relative disposition between the cyclohexane and phosphonate moieties. Accordingly, the first step in the route involved the introduction of a Boc protecting group into 2-indolinone (**1**). This process was not straightforward because the nitrogen atom is flanked by an aromatic ring and a carbonyl group. As seen in Scheme 3, the presence of a carbonyl moiety contiguous to the nitrogen atom in **2** does not hamper reaction with di-*tert*-butyl dicarbonate provided that catalytic DMAP is present. We have also observed[12] that the same conditions are effective for the *N*-Boc protection of the amino group in indoline-derived systems in which it is adjacent to a benzene ring. However, both situations coexist in 2-indolinone (**1**), which presents, in addition, a highly reactive position towards electrophiles. It was, therefore, not unexpected that the conditions used for the *N*-Boc protection of **2** failed when applied to **1**. No reaction was observed when tetrahydrofuran (THF) was used as the solvent, whereas acetonitrile afforded a complex mixture of compounds, including **10** and several products arising from a single or multiple acylation of the 1- (*N*-), 2- (*O*-acylation) or 3-positions of the five-membered cycle. Similar products have been reported[13] to be formed when triethylamine is added to the THF/DMAP system. Fortunately, the conditions developed for the carbamoylation of 2-indolinones based on the use of sodium carbonate in THF[14] proved successful and allowed the isolation of **10** in good yield (Scheme 4).



Scheme 4. Synthesis of (2*R**,3a*S**,7a*S**)-octahydroindole-2-phosphonic acid.

The introduction of a phosphonate group into **10** was next attempted by the formation of the intermediate hemiaminal, aminal and iminium derivatives, as reported above for the *trans* compound (Scheme 3). However, in this case the reduction of **10** with DIBAL-H did not afford the expected hemiaminal **11** (Scheme 4). Instead, *N*-Boc-indole was formed, presumably due to a straightforward aromatisation of the reduced compound. In contrast, when lithium triethylborohydride (Super-Hydride®) was used as the reducing agent, the desired hemiaminal **11** was obtained (Scheme 4). Difficulties were also encountered when this compound was treated with methanol to form the methoxyaminal. Again, *N*-Boc-indole was isolated instead of the expected *O*-methylated product.

These difficulties prompted us to consider the direct transformation of the hemiaminal **11** into the iminium functionality without the formation of the intermediate aminal derivative, as reported by some authors.[15] On this basis, compound **11** was directly treated with boron trifluoride–diethyl ether and trimethyl phosphite to afford the *N*-Boc-indoline-2-phosphonate **13** (Scheme 4). Although a significant amount of *N*-Boc-indole was also formed in this process, the desired compound was isolated in 30% overall yield from **10**.

The aromatic ring in **13** was hydrogenated by using PtO_2 as catalyst under the conditions described above and afforded the octahydroindole derivative quantitatively. Notably, this hydrogenation process provided exclusively dimethyl (2*R**,3a*S**,7a*S**)-octahydroindole-2-phosphonate (**14**) with no trace of the (2*S**,3a*S**,7a*S**) epimer **7** being observed in the ^1H and ^{31}P NMR spectra. Hydrogenation of the benzene ring in **13** takes place from the less hindered face, that is, that opposite the phosphonate group. As a consequence, the cyclohexane moiety in the reduced system is *cis* to the phosphonate substituent, as confirmed by X-ray diffraction analysis of **14** (Figure 3). The complete stereoselectivity of the process is highly remarkable and superior to that observed when the homologous carboxylic acid derivative was hydrogenated under similar conditions.[5,9] In the latter case, a 90:10 mixture of epimers was obtained, with the *cis* derivative predominating. The higher selectivity observed in this work may be attributed to the larger steric hindrance of the dimethyl phosphonate group relative to the carboxylate moiety.

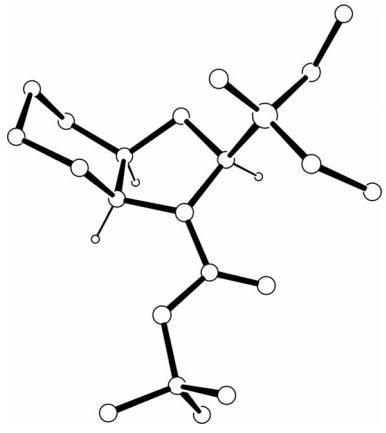


Figure 3. X-ray crystal structure of **14** characterized by a (2*R**,3a*S**,7a*S**) relative stereochemistry (only one enantiomer is shown). All hydrogen atoms, except those attached to chiral carbons, have been omitted for clarity.

Finally, acidic treatment of **14** under similar conditions to those described for the *trans* derivative allowed the isolation of the free amino acid **15** and the dimethyl aminophosphonate **16** in excellent yields (Scheme 4).

Conclusions

Two stereoisomers of octahydroindole-2-phosphonic acid characterized by a *cis* ring fusion and different stereochemistries at the α carbon have been synthesised for the first time. The procedure relies on the use of a common, inexpensive, commercially available precursor, which is transformed into the desired compounds following stereodivergent routes. Full stereochemical control is achieved in both cases by efficiently combining the appropriate chemical transformations in the right order. Thus, when the hydrogenation step is performed before the introduction of the phosphonate group, only the compound with a *trans* relative disposition between the phosphonate and cyclohexane moieties is obtained. Conversely, when the phosphonate functionality is introduced prior to the hydrogenation of the aromatic ring, the *cis* stereoisomer is exclusively obtained. Thus, a simple change in the order in which the two key reaction steps are carried out has allowed the simple and effective transformation of a common starting substrate into either of the target aminophosphonic acids with full stereochemical control. The compounds isolated are analogues of phosphoproline and may be of use in the development of biologically important materials.

Experimental Section

General: All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on Macherey–Nagel Polygram® SIL G/UV_{254} precoated silica gel polyester plates. The products were visualised by exposure to UV light (254 nm), iodine vapour or charring with cerium molybdate stain [aqueous solution of phosphomolybdic acid (2%), $CeSO_4{\cdot}4H_2O$ (1%) and H_2SO_4 (6%)]. Column chromatography was performed by using 60 M (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined with a Gallenkamp apparatus. IR spectra were recorded with a Nicolet Avatar 360 FTIR spectrophotometer; $\tilde{\nu}_{max}$ is given for the main absorption bands. ^1H, ^{13}C and ^{31}P NMR spectra were measured with a Bruker AV-400 spectrometer 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 Hz. High-resolution mass spectra were recorded with a Bruker Microtof-Q spectrometer.

X-ray Structures: Single crystals of **7** and **14** were obtained by slow evaporation from dichloromethane/hexanes solutions. The X-ray diffraction data were collected at 150 K with an Oxford Diffraction Xcalibur diffractometer equipped with a Sapphire CCD detector using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-97[16a] and refinement was performed using SHELXL-97[16b] 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} value of the carrier atom (1.5 for the methyl protons).

CCDC-812002 (for **7**) and -812003 (for **14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Summary of the Crystallographic Data for 7: $C_{15}H_{28}NO_5P$, monoclinic, space group $P2_1/c$, a = 16.0908(6), b = 9.8211(4), c = 11.1937(4) Å, β = 91.996(3)°, Z = 4, $d_{calcd.}$ = 1.252 g cm^{-3}, 16834 reflections collected, 3129 unique (R_{int} = 0.0838), data/parameters: 3129/201, final R indices ($I > 2\sigma I$): R_1 = 0.058, wR_2 = 0.140, final R indices (all data): R_1 = 0.111, wR_2 = 0.154, goodness of fit: 0.918, highest residual electron density: 0.74 e Å^{-3}.

Summary of Crystallographic Data for 14: $C_{15}H_{28}NO_5P$, monoclinic, space group $P2_1/c$, a = 15.9271(7), b = 9.7690(5), c = 11.4281(5) Å, β = 101.002(4)°, Z = 4, $d_{calcd.}$ = 1.269 g cm^{-3}, 17919 reflections collected, 3416 unique (R_{int} = 0.037), data/parameters: 3416/201, final R indices ($I > 2\sigma I$): R_1 = 0.033, wR_2 = 0.076, final R indices (all data): R_1 = 0.052, wR_2 = 0.080, goodness of fit: 0.968, highest residual electron density: 0.40 e Å^{-3}.

***cis*-Octahydroindol-2-one (2):** A mixture of 2-indolinone (1.00 g, 7.51 mmol) and PtO_2 (100 mg) in acetic acid (50 mL) was heated at 70 °C under an atmospheric pressure of hydrogen for 48 h. Filtration of the catalyst and evaporation of the solvent provided **2** as a colourless oil (1.04 g, 7.50 mmol, 100% yield). IR (neat): $\tilde{\nu}$ = 1692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.69 (br. s, 1 H, NH), 3.65 (q, J = 5.1 Hz, 1 H, 7a-H), 2.36–2.25 (m, 2 H, 3-H, 3a-H), 2.05–1.95 (m, 1 H, 3-H′), 1.68–1.54 (m, 3 H, cyclohexane CH_2), 1.53–1.20 (m, 5 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.09 (CO), 53.44 (C-7a), 38.15 (C-3), 34.44 (C-3a), 28.76 (cyclohexane CH_2), 27.35 (cyclohexane CH_2), 22.80 (cyclohexane CH_2), 20.66 (cyclohexane CH_2) ppm. HRMS (ESI): calcd. for $C_8H_{13}NNaO$ $[M + Na]^+$ 162.0889; found 162.0886.

***cis*-*N*-(*tert*-Butoxycarbonyl)octahydroindol-2-one (3):** A mixture of **2** (262 mg, 1.88 mmol), 4-(dimethylamino)pyridine (23 mg, 0.19 mmol) and di-*tert*-butyl dicarbonate (1.03 g, 4.71 mmol) in THF (15 mL) was stirred at room temperature for 12 h. Evaporation of the solvent followed by column chromatography (eluent: hexanes/ethyl acetate, 4:1) afforded **3** as a white solid (344 mg, 1.44 mmol, 76% yield); m.p. 61–63 °C. IR (KBr): $\tilde{\nu}$ = 1785, 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.01–3.94 (m, 1 H, 7a-H), 2.54–2.41 (m, 2 H, 3-H, 3a-H), 2.31–2.25 (m, 1 H, 3-H′), 2.22–2.14 (m, 1 H, cyclohexane CH_2), 1.76–1.44 (m, 4 H, cyclohexane CH_2) overlapped with 1.50 (s, 9 H, *t*Bu), 1.35–1.11 (m, 3 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.31 (CO), 150.06 (COO), 82.59 (*t*Bu C), 57.82 (C-7a), 35.77 (C-3), 31.64 (C-3a), 28.17 (*t*Bu CH_3), 28.15 (cyclohexane CH_2), 25.94 (cyclohexane CH_2), 22.88 (cyclohexane CH_2), 20.37 (cyclohexane CH_2) ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NNaO_3$ $[M + Na]^+$ 262.1414; found 262.1418.

Dimethyl (2*S,3a*S**,7a*S**)-*N*-(*tert*-Butoxycarbonyl)octahydroindole-2-phosphonate (7):** A 1 M solution of diisobutylaluminium hydride in hexanes (1.60 mL, 1.60 mmol) was slowly added to a solution of **3** (252 mg, 1.05 mmol) in anhydrous THF (5 mL) kept at –78 °C under argon. After stirring at this temperature for 2 h, the reaction was treated with a saturated aqueous solution of sodium acetate (3 mL) and warmed to room temperature. A 3:1 mixture of diethyl ether and a saturated aqueous solution of ammonium chloride (16 mL) was then added and the resulting mixture was stirred at room temperature until a suspension was formed. The solid was filtered off under reduced pressure and washed with diethyl ether (2 × 10 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried, filtered and evaporated to provide the hemiaminal **4** as an oil. This was dissolved in methanol (5 mL) and treated with pyridinium *p*-toluenesulfonate (26 mg, 0.11 mmol). After stirring at

room temperature for 2 h, triethylamine (48 mg, 0.07 mL, 0.47 mmol) was added. The solvent was evaporated and the crude methoxyaminal **5** thus obtained was dissolved in anhydrous dichloromethane (4 mL) and kept under argon. Trimethyl phosphite (131 mg, 0.12 mL, 1.05 mmol) was added and the resulting solution was cooled to –20 °C. Boron trifluoride–diethyl ether (149 mg, 0.13 mL, 1.05 mmol) was added dropwise and the reaction mixture was slowly warmed to room temperature and stirred for 12 h. After quenching with water (2 mL), the two layers were separated and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried, filtered and concentrated. Purification by column chromatography (eluent: ethyl acetate/hexanes, 4:1) afforded **7** as a white solid (199 mg, 0.60 mmol, 57% yield); m.p. 63–65 °C. IR (KBr): $\tilde{\nu}$ = 1702, 1244, 1072, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; an asterisk * indicates a duplicate signal corresponding to the minor rotamer): δ = 4.21–4.14 (m, 1 H, 2-H), 4.13*–4.07* (m, 1 H, 2-H), 3.73 (d, J = 10.5 Hz, 3 H, OMe), 3.72 (d, J = 10.5 Hz, 3 H, OMe), 3.70–3.62 (m, 1 H, 7a-H), 2.77–2.66 (m, 1 H, 3a-H), 2.61*–2.49* (m, 1 H, 3a-H), 2.41*–2.31* (m, 1 H, 3-H), 2.30–2.10 (m, 2 H, 3-H), 2.05–1.95 (m, 1 H, cyclohexane CH_2), 1.74–1.53 (m, 3 H, cyclohexane CH_2), 1.49–1.39 (m, 1 H, cyclohexane CH_2) overlapped with 1.44 (s, 9 H, *t*Bu), 1.28–0.92 (m, 3 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; an asterisk * indicates a duplicate signal corresponding to the minor rotamer): δ = 154.61 (COO), 80.07* (*t*Bu C), 79.75 (*t*Bu C), 57.50 (C-7a), 57.11* (C-7a), 53.86* (d, J = 158.9 Hz, C-2), 53.43* (d, J = 7.0 Hz, OMe), 52.79 (d, J = 160.5 Hz, C-2), 52.61 (d, J = 7.1 Hz, OMe), 36.23 (C-3a), 35.60* (C-3a), 29.73* (C-3), 28.50 (*t*Bu CH_3), 28.35* (*t*Bu CH_3), 27.81 (C-3), 26.82* (cyclohexane CH_2), 26.01 (cyclohexane CH_2), 23.97 (cyclohexane CH_2), 23.58* (cyclohexane CH_2), 21.02* (cyclohexane CH_2), 20.73 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, $CDCl_3$; an asterisk indicates a duplicate signal corresponding to the minor rotamer): δ = 28.52*, 28.31 ppm. HRMS (ESI): calcd. for $C_{15}H_{28}NNaO_5P$ $[M + Na]^+$ 356.1597; found 356.1619.

(2*S,3a*S**,7a*S**)-Octahydroindole-2-phosphonic Acid Hydrobromide (8):** A 33% solution of hydrogen bromide in acetic acid (2 mL) was added to **7** (50 mg, 0.15 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was taken up in water and lyophilised to afford **8** as a white solid (43 mg, 0.15 mmol, 100% yield); m.p. 262–264 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3411, 1153, 1079 cm^{-1}. ^1H NMR (400 MHz, [D_6]-DMSO): δ = 9.33–9.01 (m, 2 H, NH_2), 4.66 (br. s, 2 H, OH), 3.77–3.65 (m, 1 H, 2-H), 3.54–3.45 (m, 1 H, 7a-H), 2.31–2.21 (m, 1 H, 3a-H), 2.12–1.96 (m, 2 H, 3-H), 1.74–1.42 (m, 5 H, cyclohexane CH_2), 1.39–1.18 (m, 3 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 59.16 (d, J = 3.5 Hz, C-7a), 51.50 (d, J = 150.0 Hz, C-2), 36.43 (d, J = 4.9 Hz, C-3a), 29.87 (C-3), 24.82 (cyclohexane CH_2), 23.58 (cyclohexane CH_2), 21.36 (cyclohexane CH_2), 20.42 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, [D_6]-DMSO): δ = 16.11 ppm. HRMS (ESI): calcd. for $C_8H_{17}NO_3P$ $[M – Br]^+$ 206.0941; found 206.0944.

Dimethyl (2*S,3a*S**,7a*S**)-Octahydroindole-2-phosphonate (9):** An ice-cooled solution of **7** (43 mg, 0.13 mmol) in dichloromethane (2.6 mL) was treated with trifluoroacetic acid (148 mg, 0.10 mL, 1.30 mmol) and stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (10 mL) and a saturated aqueous solution of sodium hydrogencarbonate (5 mL) was added. The layers were separated and the aqueous phase was further extracted with dichloromethane (10 mL). The combined organic layers were washed with brine (10 mL), dried and filtered. Evaporation of the solvent afforded **9** as a white solid (28 mg, 0.12 mmol, 91% yield); m.p. 173–175 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3428, 1236, 1045 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (d, J = 10.3 Hz, 3 H, OMe), 3.71 (d, J = 10.2 Hz, 3 H, OMe), 3.54 (ddd, J = 9.3, 7.8, 5.2, 1 H, 2-H), 3.15–3.10 (m, 1 H, 7a-H), 2.11 (br. s, 1 H, NH), 2.03–1.91 (m, 2 H, 3-H, 3a-H), 1.80–1.70 (m, 1 H, 3-H′), 1.61–1.39 (m, 4 H, cyclohexane CH_2), 1.33–1.25 (m, 2 H, cyclohexane CH_2), 1.20–1.07 (m, 2 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.55 (d, J = 6.3 Hz, C-7a), 53.11 (d, J = 7.1 Hz, OMe), 52.98 (d, J = 7.3 Hz, OMe), 51.31 (d, J = 168.4 Hz, C-2), 38.07 (d, J = 4.6 Hz, C-3a), 32.22 (C-3), 27.28 (cyclohexane CH_2), 26.65 (cyclohexane CH_2), 23.59 (cyclohexane CH_2), 20.95 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.47 ppm. HRMS (ESI): calcd. for $C_{10}H_{21}NO_3P$ $[M + H]^+$ 234.1254; found 234.1247.

***N*-(*tert*-Butoxycarbonyl)-2-indolinone (10):** A mixture of 2-indolinone (2.00 g, 15.04 mmol), di-*tert*-butyl dicarbonate (8.20 g, 37.59 mmol) and sodium carbonate (14.34 g, 135.32 mmol) in THF (60 mL) was heated at 70 °C for 12 h. The solid was filtered off and the solvent was evaporated. Purification by column chromatography (eluent: hexanes/ethyl acetate, 9:1) afforded **10** as a white solid (2.72 g, 11.66 mmol, 78% yield); m.p. 63–66 °C. IR (KBr): $\tilde{\nu}$ = 1788, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.8, 1 H, Ar), 7.32–7.27 (m, 1 H, Ar), 7.26–7.22 (m, 1 H, Ar), 7.13 (td, J = 7.8, 1.0 Hz, 1 H, Ar), 3.65 (s, 2 H, 3-H), 1.64 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.24 (CO), 149.31 (COO), 141.11 (Ar), 128.19 (Ar), 124.33 (Ar), 124.32 (Ar), 123.34 (Ar), 115.18 (Ar), 84.48 (*t*Bu C), 36.68 (C-3), 28.23 (*t*Bu CH_3) ppm. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$ $[M + Na]^+$ 256.0944; found 256.0948.

Dimethyl *N*-(*tert*-Butoxycarbonyl)indoline-2-phosphonate (13): A solution of **10** (2.61 g, 11.20 mmol) in anhydrous THF (60 mL) was cooled to –78 °C under argon. A 1 M solution of lithium triethylborohydride in THF (16.80 mL, 16.80 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. It was treated with water (10 mL) and then warmed to room temperature. A saturated aqueous solution of sodium hydrogencarbonate (25 mL) was then added followed by 30% aqueous hydrogen peroxide (10 mL). The resulting mixture was stirred vigorously for 1 h and then extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), dried and filtered. Evaporation of the solvent afforded the hemiaminal **11** as a yellow oil. The crude product was dissolved in anhydrous dichloromethane (40 mL) and trimethyl phosphite (1.39 g, 1.32 mL, 11.20 mmol) was added at room temperature under argon. The solution was cooled to –20 °C and boron trifluoride–diethyl ether (1.59 g, 1.41 mL, 11.20 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. After quenching with water (10 mL), the two layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried, filtered and concentrated. Purification by column chromatography (eluent: ethyl acetate/hexanes, 4:1) gave **13** as an oil (1.09 g, 3.32 mmol, 30% yield). IR (neat): $\tilde{\nu}$ = 1702, 1250, 1060, 1031 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.54 (br. s, 1 H, Ar), 7.22 (d, J = 7.4 Hz, 1 H, Ar), 7.16 (t, J = 7.7 Hz, 1 H, Ar), 6.96 (dt, J = 7.4, 1.0 Hz, 1 H, Ar), 4.84 (ddd, J = 11.2, 4.3, 2.3 Hz, 1 H, 2-H), 3.61 (d, J = 10.5 Hz, 3 H, OMe), 3.57–3.45 (m, 1 H, 3-H) overlapped with 3.54 (d, J = 10.5 Hz, 3 H, OMe), 3.22–3.08 (m, 1 H, 3-H′), 1.52 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 151.38 (COO), 141.72 (Ar), 130.45 (Ar), 127.20 (Ar), 124.58 (Ar), 122.90 (Ar), 115.24 (Ar), 81.08 (*t*Bu C), 54.30 (d, J = 156.4 Hz, C-2), 52.89 (d, J = 6.9 Hz, OMe), 52.74 (d, J = 6.5 Hz,

OMe), 29.68 (C-3), 27.81 (*t*Bu CH_3) ppm. ^{31}P NMR (162 MHz, [D_6]DMSO): δ = 25.82 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}NNaO_5P$ $[M + Na]^+$ 350.1128; found 350.1123.

Dimethyl (2*R,3a*S**,7a*S**)-*N*-(*tert*-Butoxycarbonyl)octahydroindole-2-phosphonate (14):** A mixture of **13** (206 mg, 0.63 mmol) and PtO_2 (21 mg) in acetic acid (10 mL) was heated at 45 °C under an atmospheric pressure of hydrogen for 12 h. Filtration of the catalyst and evaporation of the solvent afforded **14** as a white solid (209 mg, 0.63 mmol, 100% yield); m.p. 72–74 °C. IR (KBr): $\tilde{\nu}$ = 1693, 1230, 1034 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 4.08–4.01 (m, 1 H, 2-H), 3.81–3.74 (m, 1 H, 7a-H), 3.65 (d, *J* = 10.5 Hz, 3 H, OMe), 3.64 (d, *J* = 10.5 Hz, 3 H, OMe), 2.20–1.98 (m, 3 H, 3-H, 3a-H), 1.72–1.53 (m, 4 H, cyclohexane CH_2), 1.49–1.34 (m, 2 H, cyclohexane CH_2) overlapped with 1.40 (s, 9 H, *t*Bu), 1.28–1.02 (m, 2 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 153.81 (COO), 78.94 (*t*Bu C), 58.35 (C-7a), 52.92 (d, *J* = 6.6 Hz, OMe), 52.18 (d, *J* = 5.7 Hz, OMe), 52.00 (d, *J* = 163.9 Hz, C-2), 35.87 (d, *J* = 5.9 Hz, C-3a), 29.00 (C-3), 27.96 (*t*Bu CH_3), 27.32 (cyclohexane CH_2), 25.19 (cyclohexane CH_2), 23.55 (cyclohexane CH_2), 19.85 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.04 ppm. HRMS (ESI): calcd. for $C_{15}H_{28}NNaO_5P$ $[M + Na]^+$ 356.1597; found 356.1599.

(2*R,3a*S**,7a*S**)-Octahydroindole-2-phosphonic Acid Hydrobromide (15):** A 33% solution of hydrogen bromide in acetic acid (2 mL) was added to **14** (50 mg, 0.15 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was taken up in water and lyophilised to afford **15** as a white solid (43 mg, 0.15 mmol, 100% yield); m.p. 138–140 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3413, 1179, 1024 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 9.62 (br. s, 1 H, NH), 8.68 (br. s, 1 H, NH), 4.68 (br. s, 2 H, OH), 3.61–3.48 (m, 2 H, 2-H, 7a-H), 2.32–2.22 (m, 1 H, 3a-H), 2.14–2.03 (m, 1 H, 3-H), 2.02–1.91 (m, 1 H, 3-H′), 1.84–1.74 (m, 1 H, cyclohexane CH_2), 1.72–1.46 (m, 4 H, cyclohexane CH_2), 1.41–1.16 (m, 3 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 58.62 (C-7a), 53.07 (d, *J* = 147.8 Hz, C-2), 36.56 (d, *J* = 8.2 Hz, C-3a), 28.73 (C-3), 24.70 (cyclohexane CH_2), 24.25 (cyclohexane CH_2), 22.05 (cyclohexane CH_2), 20.22 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, [D_6]-DMSO): δ = 14.66 ppm. HRMS (ESI): calcd. for $C_8H_{17}NO_3P$ $[M - Br]^+$ 206.0941; found 206.0936.

Dimethyl (2*R,3a*S**,7a*S**)-Octahydroindole-2-phosphonate (16):** An ice-cooled solution of **14** (64 mg, 0.19 mmol) in dichloromethane (3.8 mL) was treated with trifluoroacetic acid (219 mg, 0.15 mL, 1.92 mmol) and stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (15 mL) and a saturated aqueous solution of $NaHCO_3$ (8 mL) was added. The layers were separated and the aqueous phase was further extracted with dichloromethane (15 mL). The combined organic layers were washed with brine (10 mL), dried and filtered. Evaporation of the solvent provided **16** as a white solid (42 mg, 0.18 mmol, 93% yield); m.p. 123–125 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3391, 1230, 1198, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (d, *J* = 10.3 Hz, 3 H, OMe), 3.77 (d, *J* = 10.4 Hz, 3 H, OMe), 3.41 (ddd, *J* = 9.2, 8.4, 5.7 Hz, 1 H, 2-H), 3.08–3.03 (m, 1 H, 7a-H), 2.24 (br. s, 1 H, NH), 2.07–197 (m, 2 H, 3-H, 3a-H), 1.83–1.71 (m, 1 H, 3-H′), 1.68–1.55 (m, 2 H, cyclohexane CH_2), 1.53–1.42 (m, 4 H, cyclohexane CH_2), 1.34–1.17 (m, 2 H, cyclohexane CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.60 (d, *J* = 13.1 Hz, C-7a), 52.67 (d, *J* = 164.5 Hz, C-2), 53.41 (d, *J* = 6.8 Hz, OMe), 52.98 (d, *J* = 7.2 Hz, OMe), 38.26 (d, *J* = 7.7 Hz, C-3a), 32.05 (d, *J* = 1.9 Hz, 3-C), 28.70 (cyclohexane CH_2), 27.77 (cyclohexane CH_2), 23.68 (cyclohexane CH_2), 21.91 (cyclohexane CH_2) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.05 ppm. HRMS (ESI): calcd. for $C_{10}H_{21}NO_3P$ $[M + H]^+$ 234.1254; found 234.1253.

Acknowledgments

The authors thank the Ministerio de Ciencia e Innovación (project CTQ2010-17436), the Consejo Superior de Investigaciones Científicas (project 2008MX0044; JAE predoctoral fellowship to A. A.), the Gobierno de Aragón (group E40) and the Consejo Nacional de Ciencia y Tecnología (CONACYT-MEXICO; projects 62271 and J000.400/2009) for financial support.

[1] V. P. Kukhar, H. R. Hudson (Eds.), *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, Wiley, Chichester, **2000**.
[2] For recent reviews, see: a) F. Orsini, G. Sello, M. Sisti, *Curr. Med. Chem.* **2010**, *17*, 264–289; b) E. D. Naydenova, P. T. Todorov, K. D. Troev, *Amino Acids* **2010**, *38*, 23–30; c) B. Lejczak, P. Kafarski, *Top. Heterocycl. Chem.* **2009**, *20*, 31–63.
[3] For recent reviews, see: a) M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **2009**, *65*, 17–49; b) K. Moonen, I. Laureyn, C. V. Stevens, *Chem. Rev.* **2004**, *104*, 6177–6215.
[4] For a review, see: M. Ordóñez, J. L. Viveros-Ceballos, C. Cativiela, A. Arizpe, *Curr. Org. Synth.*, in press.
[5] F. J. Sayago, P. Laborda, M. I. Calaza, A. I. Jiménez, C. Cativiela, *Eur. J. Org. Chem.* **2011**, 2011–2028, and references cited therein.
[6] For some medicinally useful compounds containing L-Oic, see: a) J. Lawandi, S. Gerber-Lemaire, L. Juillerat-Jeanneret, N. Moitessier, *J. Med. Chem.* **2010**, *53*, 3423–3438; b) K. Ersmark, J. R. Del Valle, S. Hanessian, *Angew. Chem. Int. Ed.* **2008**, *47*, 1202–1223; c) R. P. Hicks, J. B. Bhonsle, D. Venugopal, B. W. Koser, A. J. Magill, *J. Med. Chem.* **2007**, *50*, 3026–3036; d) J. M. Stewart, L. Gera, D. C. Chan, E. J. York, V. Simkeviciene, P. A. Bunn Jr., L. Taraseviciene-Stewart, *Peptides* **2005**, *26*, 1288–1291; e) J. M. Stewart, *Peptides* **2004**, *25*, 527–532; f) S. Reissmann, D. Imhof, *Curr. Med. Chem.* **2004**, *11*, 2823–2844; g) M. Hurst, B. Jarvis, *Drugs* **2001**, *61*, 867–896; h) B. Portevin, M. Lonchampt, E. Canet, G. De Nanteuil, *J. Med. Chem.* **1997**, *40*, 1906–1918; i) P. A. Todd, A. Fitton, *Drugs* **1991**, *42*, 90–114.
[7] For reviews, see: a) S. K. Panday, J. Prasad, D. K. Dikshit, *Tetrahedron: Asymmetry* **2009**, *20*, 1581–1632; b) C. Nájera, M. Yus, *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
[8] T. Shono, Y. Matsumura, K. Tsubata, *Tetrahedron Lett.* **1981**, *22*, 3249–3252.
[9] F. J. Sayago, A. I. Jiménez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 2358–2364.
[10] a) R. N. Kankan, D. R. Rao, PCT Int. Appl. WO 2005100317, **2005**; *Chem. Abstr.* **2005**, *143*, 367597; b) M. Vincent, B. Marchand, G. Rémond, S. Jaguelin-Guinamant, G. Damien, B. Portevin, J.-Y. Baumal, J.-P. Volland, J.-P. Bouchet, P.-H. Lambert, B. Serkiz, W. Luitjen, M. Laubie, P. Schiavi, *Drug Des. Discovery* **1992**, *9*, 11–28; c) C. Pascard, J. Guilhem, M. Vincent, G. Rémond, B. Portevin, M. Laubie, *J. Med. Chem.* **1991**, *34*, 663–669; d) M. Vincent, J. Baliarda, B. Marchand, G. Remond, U.S. Patent 4914214, **1990**; *Chem. Abstr.* **1989**, *111*, 115749.
[11] F. Fini, G. Micheletti, L. Bernardi, D. Pettersen, M. Fochi, A. Ricci, *Chem. Commun.* **2008**, 4345–4347.
[12] F. J. Sayago, M. J. Pueyo, M. I. Calaza, A. I. Jiménez, C. Cativiela, *Chirality* **2011**, DOI: 10.1002/chir.20952.
[13] M. Porcs-Makkay, G. Argay, A. Kálmán, G. Simig, *Tetrahedron* **2000**, *56*, 5893–5903.

[14] W. G. Rajeswaran, L. A. Cohen, *Tetrahedron* **1998**, *54*, 11375–11380.
[15] See, for example: a) R. A. Batey, D. B. MacKay, V. Santhakumar, *J. Am. Chem. Soc.* **1999**, *121*, 5075–5076; b) M. Kaname, H. Mashige, S. Yoshifuji, *Chem. Pharm. Bull.* **2001**, *49*, 531–536.
[16] a) G. M. Sheldrick, *SHELXS-97*, *Program for the Solution of Crystal Structures*, University of Göttingen, Göttingen, **1997**; b) G. M. Sheldrick, *SHELXL-97*, *Program for the Refinement of Crystal Structures*, University of Göttingen, Göttingen, **1997**.

Received: February 20, 2011
Published Online: April 21, 2011

