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A straightforward route to enantiopure α-substituted derivatives of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid

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Dedicated to Professor Josep Font on the occasion of his 70th birthday

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ABSTRACT

High yielding and remarkably selective alkylations of a suitably protected derivative of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid are described. The fused bicyclic structure of this proline analogue greatly influences the stereochemical outcome of direct alkylation reactions taking place at the α-carbon and provides access to α-substituted analogues with retention of the configuration. The overall procedure allows the preparation of enantiopure α-substituted derivatives of this Oic isomer, suitably protected for their incorporation into peptides, in a straightforward manner.

1. Introduction

Octahydroindole-2-carboxylic acid (Oic, Fig. 1) is a proline analogue that is considered to be a very useful scaffold for the optimization of pharmacologically active peptides.[1] Particularly notable has been the use of Oic in the design of angiotensin-converting enzyme (ACE) inhibitors,[1a,b,f] antagonists for the B2 receptor of bradykinin hormone[1c–e] and prolyl oligopeptidase (POP) inhibitors.[1g,h] Due to its bicyclic structure and lipophilicity, the incorporation of Oic into peptides may be of help to overcome important limitations to the usefulness of small peptides as drugs, such as their great conformational flexibility in solution, their low stability towards proteolytic enzymes and poor bioavailability.[2]

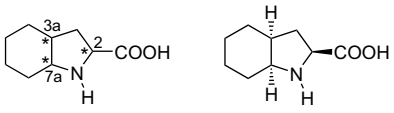

Figure 1. Structure of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid.

Moreover, Oic has been useful to improve the affinity towards certain receptors by providing better hydrophobic recognition interactions at the binding-site.[3] Additionally, some applications of Oic derivatives have been reported in the field of catalysis.[4]

However, the exploitation of this fused bicyclic proline analogue is far from complete because its stereochemical diversity and functionalization remains barely explored. Nearly all of the aforementioned applications refer to (2*S*,3a*S*,7a*S*)-Oic[5] (Fig. 1) and, indeed, most of the reported procedures describe the preparation of this particular Oic stereoisomer.[6]

In the context of functionalized Oic derivatives, synthetic effort has been primarily oriented to the preparation of 6-substituted 2-carboxy octahydroindoles[7b–e] because they constitute the core subunit of a family of marine metabolites (aeruginosins) with activity as protease inhibitors. Besides this substitution pattern, α-substituted Oic derivatives[7a] are very attractive scaffolds as they are the core structure of compounds with anti-arthritic activity. Even more importantly, as α-substituted proline analogues,[8] they are of high intrinsic value in the design of modified peptides. Due to their conformationally well-defined structures,[9] their incorporation into peptides would cause constraints that may lead to enhanced affinity, resistance to proteolysis and bioavailability. Additionally, they could serve as tools to elucidate the bioactive conformations of peptides or the three-dimensional structures of protein receptors.

However, despite their potential value, the preparation of α-tetrasubstituted Oic analogues remains almost unexplored.[7a,10]

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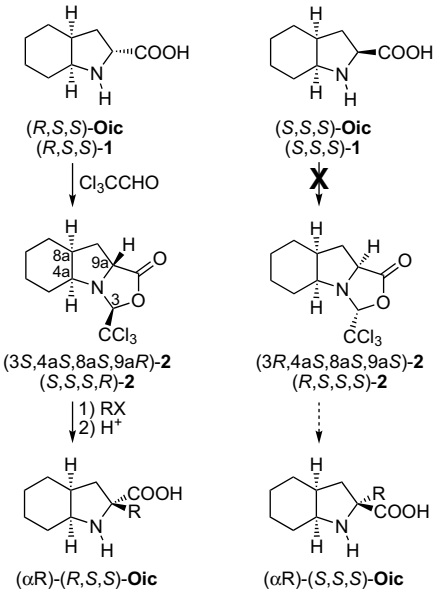
This observation has stimulated our interest in developing efficient routes to produce the different stereoisomers of α-substituted octahydroindole-2-carboxylic acids in enantiomerically pure form—in particular, those with a cis-fused bicyclic structure.

In this context, we have recently described a versatile methodology that provides access to enantiopure α-substituted derivatives of (*R*,*S*,*S*)-Oic that have a cis disposition of the hydrogen atoms at the ring junction and the α-carboxyl group (Scheme 1).[10a] The procedure involves a stereocontrolled carbon–carbon bond-forming reaction on the trichloromethyloxazolidinone (*S*,*S*,*S*,*R*)-**2** derived from (*R*,*S*,*S*)-Oic [(*R*,*S*,*S*)-**1**] as the precursor amino acid.[10a] This methodology is based on Seebach's *self-reproduction of chirality* principle.[11] The proccess involves the generation of an endocyclic lithium enolate, which undergoes alkylation exclusively at the face previously occupied by the α hydrogen. The cyclic nature of the enolate prevents the inversion of the pyramidalized bridgehead nitrogen and ensures absolute stereocontrol towards products with retention of configuration.



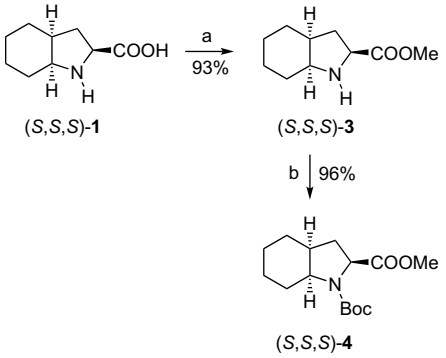
Scheme 1. Reported synthesis for α-alkyl derivatives of (*R*,*S*,*S*)-Oic (Ref. 10a).

Unfortunately, this powerful procedure cannot be applied to the preparation of epimeric α-substituted (*S*,*S*,*S*)-Oic derivatives because the precursor amino acid fails to undergo condensation with trichloroacetaldehyde to produce the corresponding oxazolidinone [(*R*,*S*,*S*,*S*)-**2**, (Scheme 1)].[10a] The steric hindrance introduced by the cyclohexane group in (*S*,*S*,*S*)-**1**, which has a cis orientation relative to the carboxylic function, prevents the formation of the oxazolidinone.

In contrast, the same spatial perturbation should have a beneficial effect on the facial selectivity of direct alkylations taking place on an exocyclic enolate derived from a suitable derivative of (*S*,*S*,*S*)-**1**. In the present work we wish to report the convenience of such an alternative method for the straightforward preparation of enantiopure α-substituted Oic analogues with a cis relative disposition of the hydrogen atoms at the ring junction and the newly introduced substituent. Preliminary results of this work have been communicated in part.[10b]

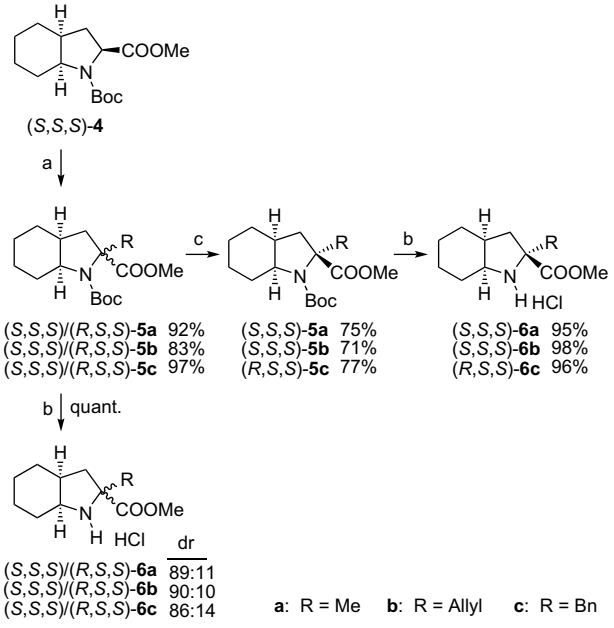
2. Results and discussion

The *N*-Boc amino ester (*S*,*S*,*S*)-**4** (Scheme 2) was selected as the precursor to evaluate the functionalization at the α carbon, since it would easily allow the preparation of α-substituted derivatives suitably protected for their incorporation into peptides. Thus, (*S*,*S*,*S*)-**4** was prepared from enantiomerically pure (*S*,*S*,*S*)-**1**, which in turn was synthesized by hydrogenation of commercially available (*S*)-indoline-2-carboxylic acid as described previously.[6g] Protection of the carboxylic acid and amino functionalities in (*S*,*S*,*S*)-**1** was carried out by treatment with methanol in the presence of thionyl chloride and subsequent reaction with di-*tert*-butyl dicarbonate (Scheme 2).



Scheme 2. Synthesis of enantiopure (*S*,*S*,*S*)-**4**. Reagents and conditions: (a) $SOCl_2$, MeOH, rt; (b) Boc_2O, *i*-Pr_2EtN, 4-dimethylaminopyridine, THF, rt.

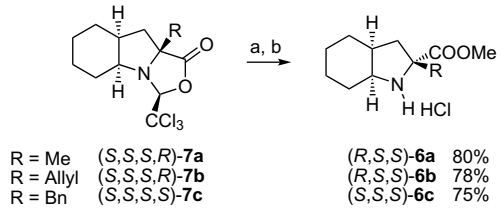
The treatment of (*S*,*S*,*S*)-**4** with LDA in THF at −78 °C generated an intermediate lithium enolate that successfully reacted with methyl iodide to afford (*S*,*S*,*S*)/(*R*,*S*,*S*)-**5a** in high yield (Scheme 3). Despite this initial good result, the effectiveness of other bases was evaluated. In comparison, the use of either LHMDS or KHMDS as a base led to poor conversions (~50%) under similar reaction conditions. Thus, LDA was also the base of choice for the synthesis of α-allyl and α-benzyl derivatives. The diastereomeric mixtures (*S*,*S*,*S*)/(*R*,*S*,*S*)-**5b** and (*S*,*S*,*S*)/(*R*,*S*,*S*)-**5c** were isolated, after 12 h of reaction at −50 °C with allyl bromide and benzyl bromide, in 83 and 97% yields, respectively.



Scheme 3. α-Alkylations of (*S*,*S*,*S*)-**4**. Reagents and conditions: (a) LDA, RX, THF, −78 to −50 °C; (b) 3 N HCl/EtOAc, rt; (c) column chromatography of the diastereomeric mixtures (SiO_2, EtOAc/hexanes 1:10) furnishes pure (*S*,*S*,*S*)-**5a**, (*S*,*S*,*S*)-**5b** and (*R*,*S*,*S*)-**5c**. RX=MeI, AllylBr, BnBr.

The diastereomeric ratios (dr ~ 90:10) were established by analysis of the relative intensities of appropriate signals in the ^{1}H NMR spectra of the mixture of the amino ester hydrochlorides (*S*,*S*,*S*)/(*R*,*S*,*S*)-**6a**–**c**,[12] which were quantitatively obtained by treatment of the crude mixtures of (*S*,*S*,*S*)/(*R*,*S*,*S*)-**5a**–**c** with a saturated solution of hydrogen chloride in ethyl acetate (Scheme 3).

In each case, the absolute configuration of the major isomer was established by comparison of the ^{1}H NMR spectra of the crude mixture of the amino ester hydrochlorides (*S*,*S*,*S*)/(*R*,*S*,*S*)-**6a**–**c** with samples of enantiopure (*R*,*S*,*S*)-**6a**, (*R*,*S*,*S*)-**6b** and (*S*,*S*,*S*)-**6c** (Scheme 4).[13] The latter α-substituted Oic derivatives are characterized by a cis relative disposition of the hydrogen atoms at the ring junction and the α-carboxyl group, and were prepared from the corresponding enantiopure oxazolidinones **7a**–**c**. Thus, oxazolidinones **7a**–**c**, obtained from (*S*,*S*,*S*,*R*)-**2** (Scheme 1) as reported previously,[10a] were treated with sodium methoxide in methanol to afford *N*-formylated amino ester intermediates. These compounds were progressed to the desired amino ester hydrochlorides by heating under reflux in the presence of acetyl chloride (Scheme 4).



Scheme 4. Synthesis of enantiopure (*R*,*S*,*S*)-**6a**, (*R*,*S*,*S*)-**6b** and (*S*,*S*,*S*)-**6c**. Reagents and conditions: (a) MeONa, MeOH, rt; (b) CH_3COCl, MeOH, reflux.

The methyl amino esters (*R*,*S*,*S*)-**6a**, (*R*,*S*,*S*)-**6b** and (*S*,*S*,*S*)-**6c** thus obtained showed spectroscopic data identical to those of the minor stereoisomer in the crude mixtures of (*S*,*S*,*S*)/(*R*,*S*,*S*)-**6a**–**c**. Therefore, the enolate generated from (*S*,*S*,*S*)-**4** undergoes alkylation at the *Re* face to preferentially furnish the isomer with retention of configuration at the α carbon.

In all cases, the major diastereoisomer of the crude mixture, (*S*,*S*,*S*)-**6a**, (*S*,*S*,*S*)-**6b** or (*R*,*S*,*S*)-**6c** could be isolated pure and in good yield (71–77%) after column chromatography (Scheme 3). Subsequent treatment of these compounds in acidic conditions led to the corresponding amino ester hydrochlorides in nearly quantitative yields.

At this stage, the amino ester hydrochloride (*S*,*S*,*S*)-**6a** and the *N*-Boc protected derivative (*R*,*S*,*S*)-**5c** furnished single crystals suitable for X-ray diffraction analysis. The crystal structures (Fig. 2) corroborated the previously assigned stereochemistry, with both compounds exhibiting a cis relative disposition of the hydrogen atoms at the ring junction and the newly introduced substituent.

The boat conformation adopted by the cyclohexane ring in the crystal structure of (*S*,*S*,*S*)-**6a** is noteworthy. In this compound, the pyrrolidine ring assumes a C^{α}-envelope conformation in which the bulkiest substituent at the α carbon is located in a pseudo-equatorial position. In comparison, the six-membered ring in (*R*,*S*,*S*)-**5c** adopts a chair disposition and the pyrrolidine moiety exhibits an envelope conformation, with carbon atom 3a occupying the flap of the envelope. This corresponds to a C^{γ}-*exo* conformation[14] for the proline subunit.

The stereoselectivity attained during the α-alkylation reactions on (*S*,*S*,*S*)-**4** is rather significant given the complex stereochemical problems that can arise in the alkylation of enolates derived from proline esters with additional substituents at the pyrrolidine ring. In fact, the diastereofacial differentiation of the lithium enolate generated from *trans*-4-silyloxy-*N*-Boc-L-proline methyl esters, by treatment with LDA, has been reported to be dependent on the

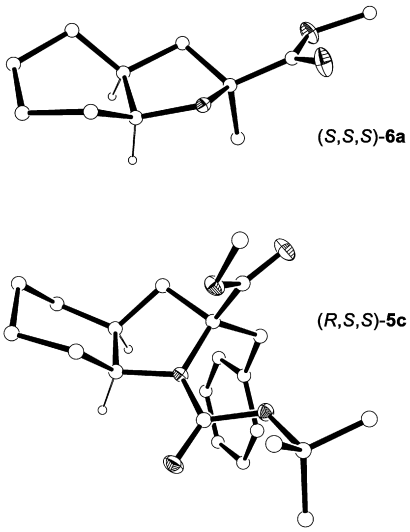
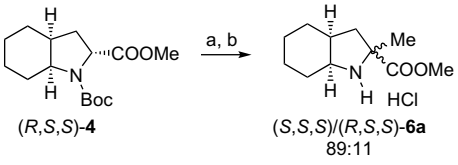


Figure 2. X-ray crystal structures of (*S*,*S*,*S*)-**6a** (the chlorine atom is not shown) and (*R*,*S*,*S*)-**5c**. Heteroatoms are drawn as thermal ellipsoids. Most hydrogens have been omitted for clarity.

nature of the alkylating reagent due to stereoelectronic factors.[15] Thus, contrary to expectations based on 1,3-steric hindrance, aliphatic halides preferentially react from the face cis to the substituent in the ring. In comparison, halides containing π-systems react from the less hindered face. On the other hand, enolates derived from *N*-Boc-L-proline methyl esters substituted either at C3 or C5 have been reported to react with the incoming electrophiles from the face trans to the substituent in the ring.[16] However, meaningful comparisons are not straightforward as it has been shown that the stereocontrol is strongly dependent on the nature of the *N*-protecting group.[15,17]

In our case, the steric hindrance imposed by the cis-fused cyclohexane ring allows an efficient facial stereodifferentiation on the exocyclic enolate that translates into a good diastereoselectivity during the alkylation reaction. Presumably, the concave face of the bicyclic system reflects a more sterically disfavouring situation due to the hydrogens of the cyclohexyl ring, at positions 4 and 6, lying towards the trajectory of the incoming electrophile.

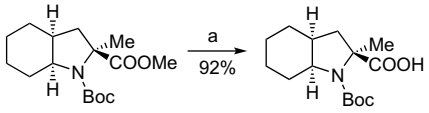
In order to evaluate whether the stereocontrol during the carbon–carbon bond forming reaction is purely driven by this steric effect, the α-methylation reaction was undertaken on epimeric (*R*,*S*,*S*)-**4**. This compound was prepared from enantiopure (*R*,*S*,*S*)-**1**[10a] as previously described for (*S*,*S*,*S*)-**4** (Scheme 2). Thus, treatment of (*R*,*S*,*S*)-**4** with LDA in THF at −78 °C generated a lithium enolate that reacted with methyl iodide to furnish an 89:11 diastereoisomeric mixture identical to that obtained before from (*S*,*S*,*S*)-**4**, with (*S*,*S*,*S*)-**6a** being the major isomer (Scheme 5). According to this observation, both epimers are suitable precursors for the preparation of α-tetrasubstituted derivatives of (*S*,*S*,*S*)-Oic since they give rise to the same intermediate enolate.



Scheme 5. α-Methylation reaction of (*R*,*S*,*S*)-**4**. Reagents and conditions: (a) LDA, MeI, THF, −78 to −50 °C; (b) 3 N HCl/EtOAc, rt.

Additionally, the preparation of α-alkyl derivatives of (*S*,*S*,*S*)-Oic suitably protected for their incorporation into peptides was

exemplified with the synthesis of compound (*S*,*S*,*S*)-**8**, which bears a free carboxylic group and a Boc-protected amino function (Scheme 6). Thus, the α-methyl derivative (*S*,*S*,*S*)-**5a** was heated under reflux in a methanolic solution of potassium hydroxide to afford the desired *N*-Boc amino acid (*S*,*S*,*S*)-**8** in excellent yield.



(*S*,*S*,*S*)-**5a** (*S*,*S*,*S*)-**8a**

Scheme 6. Synthesis of enantiopure (*S*,*S*,*S*)-**8a**. Reagents and conditions: (a) 1 N KOH, MeOH/H_2O, reflux.

3. Conclusion

α-Substituted derivatives of (*S*,*S*,*S*)-Oic with a cis relative disposition of the hydrogen atoms at the ring junction and the newly introduced substituent can be accessed by means of highly diastereoselective α-alkylation reactions on (*S*,*S*,*S*)-**4**. The facial stereodifferentiation imposed by the cyclohexane ring on the exocyclic enolate derived from (*S*,*S*,*S*)-**4** accounts for the selective outcome of the alkylation reactions. Alternatively, identical results can be achieved by using the epimeric compound, (*R*,*S*,*S*)-**4**, as the starting amino ester. Remarkable percentages of retention of configuration at the α carbon can be attained regardless of the open nature of the enolate intermediate or the steric and electronic characteristics of the electrophiles. Such a spatial effect can thus be regarded as a tool for stereocontrol induction during the functionalization at the α carbon for those sterically hindered proline-type substrates where the generation of an endocyclic enolate, through the preparation of a trichloromethyloxazolidinone precursor, is not possible.

4. Experimental

4.1. General

All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on Macherey-Nagel Polygram syl G/UV precoated silica gel polyester plates. The products were visualized by exposure to 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 60 Å silica gel purchased from SDS. Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were registered on a Mattson Genesis or a Nicolet Avatar 360/370 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. Compounds (*S*,*S*,*S*)-**1**,[6g] (*R*,*S*,*S*)-**1**,[10a] (*S*,*S*,*S*,*R*)-**7a**,[10a] (*S*,*S*,*S*,*R*)-**7b**[10a] and (*S*,*S*,*S*,*S*)-**7c**[10a] were prepared according to previously reported methods.

4.2. X-ray diffraction

Colourless single crystals of (*R*,*S*,*S*)-**5c** and (*S*,*S*,*S*)-**6a** were, respectively, obtained by slow evaporation of ethyl acetate or dichloromethane/ethyl acetate solutions. The X-ray diffraction data were collected at room temperature or 150 K, respectively, on an Oxford Diffraction Xcalibur diffractometer provided with a Sapphire CCD detector, using graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS-97[18a] and refinement was performed using SHELXL-97[18b] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were located by calculation (with the exception of the amine protons, which were found on the *E*-map) 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 structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 725593 and 694571. 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 for (*R*,*S*,*S*)-**5c**: trigonal, space group $P3_2$; a, b=9.9849(3) Å, c=18.0716(7) Å; Z=3; d_{calcd}=1.192 g cm^{-3}; 30,858 reflections collected, 4207 unique (R_{int}=0.039); data/parameters: 4207/246; final R indices ($I>2\sigma I$): R_1=0.030, wR_2=0.063; final R indices (all data): R_1=0.051, wR_2=0.067. Highest residual electron density: 0.09 e Å^{-3}.

Crystallographic data for (*S*,*S*,*S*)-**6a**: orthorhombic, space group $P2_12_12_1$; a=7.7814(2) Å, b=8.9278(4) Å, c=17.6054(7) Å; Z=4; d_{calcd}=1.269 g cm^{-3}; 8032 reflections collected, 2640 unique (R_{int}=0.021); data/parameters: 2640/137; final R indices ($I>2\sigma I$): R_1=0.025, wR_2=0.060; final R indices (all data): R_1=0.031, wR_2=0.061. Highest residual electron density: 0.23 e Å^{-3}.

4.3. Synthesis of methyl (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylate, (*S*,*S*,*S*)-3

Thionyl chloride (2.8 mL, 38.12 mmol) was added dropwise to an ice-cooled solution of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid[6g] (3.11 g, 18.39 mmol) in dry methanol (47 mL). The resulting solution was stirred at room temperature for 24 h. The solvent was concentrated in vacuo and the resulting residue was lyophilized and washed with small portions of ethyl acetate to afford pure (*S*,*S*,*S*)-**3** as a white solid (3.76 g, 17.10 mmol, 93% yield). Mp 169–171 °C. $[\alpha]_D$ −19.4 (*c* 0.50, MeOH). IR (Nujol) ν 1743, 1460, 1226, 730 cm^{-1}. ^1H NMR (MeOD, 400 MHz) δ 1.30–1.78 (m, 7H), 1.94 (m, 1H), 2.18 (dt, 1H, J=12.6, 9.3 Hz), 2.41–2.54 (m, 2H), 3.76 (m, 1H), 3.88 (s, 3H), 4.51 (m, 1H). ^{13}C NMR (MeOD, 100 MHz) δ 21.31, 23.65, 25.59, 25.95, 32.07, 38.44, 54.15, 59.34, 60.89, 171.51. HRMS (ESI) $C_{10}H_{18}NO_2$ M^+: calcd 184.1332, found 184.1339.

4.4. Synthesis of methyl (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)octahydroindole-2-carboxylate, (*S*,*S*,*S*)-4

A solution of methyl (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylate (3.76 g, 17.10 mmol) in THF (40 mL) was treated with 4-dimethylaminopyridine (209 mg, 1.71 mmol) and *N*,*N*-diisopropylethylamine (5.9 mL, 34.20 mmol). After stirring at room temperature for 30 min, di-*tert*-butyl dicarbonate (5.59 g, 25.65 mmol) was added. The resulting mixture was stirred at room temperature for an additional 24 h. The reaction mixture was diluted with diethyl ether (150 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate several times and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was concentrated in vacuo and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 10:1) to afford pure (*S*,*S*,*S*)-**4** as a colourless oil (4.65 g, 16.41 mmol, 96% yield). $[\alpha]_D$ −31.8 (*c* 0.48, $CHCl_3$). IR (neat) ν 1753, 1700, 1397, 1169 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.03–1.43 (m, 4H), overlapped with 1.30, 1.37 (two s, 9H), 1.51–1.67 (m, 3H), 1.77–1.98 (m, 2H), 2.06 (m, 1H), 2.28 (m, 1H), 3.60–3.68 (m, 1H), overlapped with 3.62, 3.65 (two s, 3H), 4.14 (m, 1H). ^{13}C NMR (DMSO-d_6,

100 MHz) δ (duplicate signals are observed for most carbons) 19.98, 20.03; 23.13, 23.25; 25.18; 27.09, 27.55; 27.84, 28.04; 30.94, 31.66; 35.62, 36.23; 51.64, 51.72; 56.29, 56.77; 58.27, 58.69; 78.56; 152.19; 172.99, 173.45. HRMS (ESI) $C_{15}H_{25}NNaO_4$ $[M+Na]^+$: calcd 306.1676, found 306.1673.

4.5. Synthesis of methyl (2*R*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)octahydroindole-2-carboxylate, (*R*,*S*,*S*)-4

Thionyl chloride (177 μL, 2.43 mmol) was added dropwise to an ice-cooled solution of (2*R*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid[10a] (241 mg, 1.17 mmol) in dry methanol (3.0 mL). The resulting solution was stirred at room temperature for 24 h. The solvent was concentrated in vacuo and the resulting residue was lyophilized to afford a yellow solid, which was then dissolved in THF (3.0 mL). This solution was treated with 4-dimethylaminopyridine (14 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (407 μL, 2.34 mmol). After stirring at room temperature for 30 min, di-*tert*-butyl dicarbonate (383 mg, 1.76 mmol) was added. The resulting mixture was stirred at room temperature for an additional 24 h. The reaction mixture was diluted with diethyl ether (10 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted several times with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was concentrated in vacuo and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 10:1) to afford pure (*R*,*S*,*S*)-**4** as a colourless oil (266 mg, 0.94 mmol, 80% yield). $[\alpha]_D$ +55.5 (*c* 0.43, $CHCl_3$). IR (neat) ν 1751, 1694, 1394, 1178 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.06–1.42 (m, 4H), overlapped with 1.30, 1.38 (two s, 9H), 1.45–1.70 (m, 4H), 1.84–1.99 (m, 1H), 2.24–2.35 (m, 2H), 3.60–3.75 (m, 1H), overlapped with 3.61, 3.64 (two s, 3H), 4.17 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 20.00, 20.21; 22.79, 23.09; 25.04; 27.11, 27.77; 27.81, 28.01; 30.25, 31.34; 34.14, 34.91; 51.62, 51.68; 56.01, 56.30; 57.38, 57.73; 78.57, 78.60; 152.27, 153.04; 172.77, 173.26. HRMS (ESI) $C_{15}H_{25}NNaO_4$ $[M+Na]^+$: calcd 306.1676, found 306.1679.

4.6. Synthesis of methyl (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)-2-methyloctahydroindole-2-carboxylate, (*S*,*S*,*S*)-5a

A 1.8 M solution of LDA in hexanes (14.2 mL, 25.56 mmol) was added dropwise by syringe to a stirred solution of (*S*,*S*,*S*)-**4** (3.09 g, 10.90 mmol) in anhydrous THF (57 mL) at −78 °C. After stirring at this temperature for 30 min, methyl iodide (2.8 mL, 44.10 mmol) was added dropwise. The resulting solution was then warmed to −50 °C and stirred at this temperature overnight. The reaction mixture was treated with water and extracted with dichloromethane several times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was concentrated in vacuo and the residue was filtered through a short pad of silica gel eluting with hexanes/ethyl acetate 1:1 to afford a 89:11 mixture of (*S*,*S*,*S*)-**5a** and (*R*,*S*,*S*)-**5a** (2.98 g, 10.03 mmol, 92% yield). The purification of the mixture by column chromatography (eluent: hexanes/ethyl acetate 10:1) furnished the major isomer (*S*,*S*,*S*)-**5a** as a colourless oil (2.43 g, 8.17 mmol, 75% yield). $[\alpha]_D$ +9.5 (*c* 0.95, $CHCl_3$). IR (neat) ν 1743, 1693, 1453, 1389, 1259, 1181 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.06 (m, 1H), 1.14–1.50 (m, 3H), overlapped with 1.30, 1.36 (two s, 9H), and with 1.43, 1.45 (two s, 3H), 1.54–1.68 (m, 4H), 1.94–2.10 (m, 1H), 2.11–2.25 (m, 1H), 2.40–2.48 (m, 1H), 3.60–3.72 (m, 1H) overlapped with 3.60, 3.65 (two s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 20.10, 20.21; 21.77, 23.13; 23.00, 23.23; 25.03, 25.11; 25.65, 26.46; 27.85, 28.01; 33.62, 34.54; 38.87, 39.97; 51.86, 52.04; 57.52, 57.68; 64.40; 78.41, 78.52; 151.66, 152.32; 174.37, 174.66. HRMS (ESI) $C_{16}H_{27}NNaO_4$ $[M+Na]^+$: calcd 320.1832, found 320.1832.

4.7. Synthesis of methyl (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)-2-allyloctahydroindole-2-carboxylate, (*S*,*S*,*S*)-5b

Using allyl bromide (247 μL, 2.86 mmol) as the alkylating agent, an identical procedure to that described above was applied to the transformation of (*S*,*S*,*S*)-**4** (200 mg, 0.71 mmol) into a 90:10 mixture of (*S*,*S*,*S*)-**5b** and (*R*,*S*,*S*)-**5b** (190 mg, 0.59 mmol, 83% yield). Purification of the mixture by column chromatography (eluent: hexanes/ethyl acetate 10:1) furnished the major isomer (*S*,*S*,*S*)-**5b** as a colourless oil (162 mg, 0.50 mmol, 71% yield). $[\alpha]_D$ +28.7 (*c* 0.91, $CHCl_3$). IR (neat) ν 1743, 1694, 1389, 1178 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.04 (m, 1H), 1.12–1.26 (m, 1H), 1.28–1.51 (m, 2H), overlapped with 1.32, 1.37 (two s, 9H), 1.49–1.63 (m, 3H), 1.84 (m, 1H), 1.95–2.20 (m, 2H), 2.40 (m, 1H), 2.56–2.87 (m, 2H), 3.61–3.73 (m, 1H), overlapped with 3.62, 3.66 (two s, 3H), 5.04–5.12 (m, 2H), 5.81 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 19.98, 20.11; 22.95, 23.19; 25.07, 25.15; 25.61, 26.55; 27.85, 28.01; 33.37, 34.29; 36.90, 38.09; 38.76, 40.39; 51.96, 52.11; 57.94, 58.05; 66.70, 66.93; 78.51, 78.76; 118.07, 118.20; 134.38; 151.76, 152.57; 174.09, 174.38. HRMS (ESI) $C_{18}H_{29}NNaO_4$ $[M+Na]^+$: calcd 346.1989, found 346.1972.

4.8. Synthesis of methyl (2*R*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)-2-benzyloctahydroindole-2-carboxylate, (*R*,*S*,*S*)-5c

Using benzyl bromide (340 μL, 2.86 mmol) as the alkylating agent, an identical procedure to that described above was applied to the transformation of (*S*,*S*,*S*)-**4** (200 mg, 0.71 mmol) into a 86:14 mixture of (*R*,*S*,*S*)-**5c** and (*S*,*S*,*S*)-**5c** (256 mg, 0.69 mmol, 97% yield). The purification of the mixture by column chromatography (eluent: hexanes/ethyl acetate 10:1) furnished the major isomer (*R*,*S*,*S*)-**5c** as a colourless solid (203 mg, 0.54 mmol, 77% yield). Mp 122–124 °C. $[\alpha]_D$ +91.0 (*c* 0.46, $CHCl_3$). IR (Nujol) ν 1726, 1684, 1459, 1386, 701 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 0.82–0.99 (m, 2H), 1.01–1.18 (m, 2H), 1.19–1.32 (m, 2H), 1.34–1.54 (m, 2H), overlapped with 1.40, 1.44 (two s, 9H), 1.89–2.17 (m, 3H), 2.98, 3.03 (two d, 1H, *J*=13.4 Hz), 3.28 (m, 1H), 3.43, 3.58 (two d, 1H, *J*=13.4 Hz), 3.67, 3.71 (two s, 3H), 7.14 (m, 2H), 7.22–7.32 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (duplicate signals are observed for most carbons) 19.80, 19.95; 22.76, 23.01; 24.87, 24.94; 25.54, 26.47; 27.95, 28.10; 32.47, 33.36; 37.04, 38.13; 38.37, 40.07; 52.11, 52.25; 57.83, 57.85; 67.66, 67.76; 78.60, 79.03; 126.47, 126.55; 128.01, 128.08; 130.00, 130.04; 137.30, 137.35; 151.84, 152.84; 174.25, 174.54. HRMS (ESI) $C_{22}H_{31}NNaO_4$ $[M+Na]^+$: calcd 396.2145, found 396.2151.

4.9. Synthesis of methyl (2*S*,3a*S*,7a*S*)-2-methyloctahydroindole-2-carboxylate hydrochloride, (*S*,*S*,*S*)-6a

A 3 N solution of HCl in anhydrous ethyl acetate (5 mL) was added to (*S*,*S*,*S*)-**5a** (100 mg, 0.34 mmol) and the resulting mixture was stirred at room temperature for 4 h. The solvent was concentrated in vacuo and the resulting white solid was lyophilized to afford pure (*S*,*S*,*S*)-**6a** as the hydrochloride salt (75 mg, 0.32 mmol, 95% yield). Mp 160–162 °C. $[\alpha]_D$ −47.7 (*c* 0.56, $CHCl_3$). IR (Nujol) ν 1746, 1570, 1464, 1379 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28–1.72 (m, 7H), 1.87 (s, 3H), 2.01 (dd, 1H, *J*=13.3, 7.2 Hz), 2.70 (m, 1H), 2.37 (dd, 1H, *J*=13.3, 9.9 Hz), 2.67 (m, 1H), 3.88 (s, 3H), 3.98 (m, 1H), 7.93 (m, 1H), 11.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.33, 22.27, 24.31, 24.36, 24.63, 35.81, 38.98, 53.95, 59.71, 67.20, 172.87. HRMS (ESI) $C_{11}H_{20}NO_2$ M^+: calcd 198.1489, found 198.1497.

4.10. Synthesis of methyl (2*S*,3a*S*,7a*S*)-2-allyloctahydroindole-2-carboxylate hydrochloride, (*S*,*S*,*S*)-6b

An identical procedure to that described above was applied to the transformation of (*S*,*S*,*S*)-**5b** (100 mg, 0.31 mmol) into (*S*,*S*,*S*)-**6b** as the hydrochloride salt (79 mg, 0.30 mmol, 98% yield). Mp 295–297 °C (dec). $[\alpha]_D$ −98.4 (*c* 0.44, $CHCl_3$). IR (Nujol) *ν* 1752, 1552, 1458, 1217 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) *δ* 1.16–1.27 (m, 1H), 1.29–1.39 (m, 3H), 1.45–1.53 (m, 1H), 1.54–1.66 (m, 2H), 1.72–1.80 (m, 1H), 2.07 (dd, 1H, *J*=13.2, 7.3 Hz), 2.36 (dd, 1H, *J*=13.2, 10.8 Hz), 2.43–2.54 (m, 1H), 2.68 (dd, 1H, *J*=14.2, 7.9 Hz), 2.84 (dd, 1H, *J*=14.2, 6.4 Hz), 3.68 (m, 1H), 3.79 (s, 3H), 5.18–5.28 (m, 2H), 5.70 (m, 1H), 8.81 (m, 1H), 10.14 (m, 1H). ^{13}C NMR (MeOD, 100 MHz) *δ* 21.21, 23.47, 25.31, 25.69, 37.53, 38.31, 42.59, 54.56, 61.76, 72.60, 122.25, 130.98, 173.02. HRMS (ESI) $C_{13}H_{22}NO_2$ M^+: calcd 224.1645, found 224.1643.

4.11. Synthesis of methyl (2*R*,3a*S*,7a*S*)-2-benzyloctahydroindole-2-carboxylate hydrochloride, (*R*,*S*,*S*)-6c

An identical procedure to that described above was applied to the transformation of (*R*,*S*,*S*)-**5c** (100 mg, 0.27 mmol) into (*R*,*S*,*S*)-**6c**, which was isolated as the hydrochloride salt (80 mg, 0.26 mmol, 96% yield). Mp 301–303 °C (dec). $[\alpha]_D$ −88.1 (*c* 0.45, $CHCl_3$). IR (Nujol) *ν* 1744, 1459, 1376, 1345, 1271, 1228 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) *δ* 1.23–1.40 (m, 3H), 1.42–1.57 (m, 2H), 1.61–1.74 (m, 2H), 2.03–2.11 (m, 1H), 2.24 (dd, 1H, *J*=13.8, 7.8 Hz), 2.47 (dd, 1H, *J*=13.8, 10.4 Hz), 2.87 (m, 1H), 3.36 (d, 1H, *J*=14.1 Hz), 3.74 (s, 3H), 3.83 (d, 1H, *J*=14.1 Hz), 4.11 (m, 1H), 7.22–7.31 (m, 3H), 7.39–7.41 (m, 2H), 7.99 (m, 1H), 11.62 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 20.10, 22.47, 24.53, 24.58, 35.46, 36.37, 42.93, 53.55, 60.41, 72.18, 127.87, 128.71, 129.75, 133.65, 171.69. HRMS (ESI) $C_{17}H_{24}NO_2$ M^+: calcd 274.1802, found 274.1809.

4.12. Synthesis of methyl (2*R*,3a*S*,7a*S*)-2-methyloctahydroindole-2-carboxylate hydrochloride, (*R*,*S*,*S*)-6a

A solution of trichloromethyloxazolidinone (*S*,*S*,*S*,*R*)-**7a**[10a] (200 mg, 0.64 mmol) in dry methanol (10 mL) was treated with a 1 M solution of sodium methoxide in methanol (1 mL, 1.00 mmol). After stirring the reaction mixture at room temperature for 12 h, acetyl chloride (3 mL, 42.2 mmol) was added. The resulting suspension was stirred under reflux for an additional 24 h. The solvent was concentrated in vacuo and the resulting residue was diluted with dichloromethane. Sodium chloride precipitated upon addition of the solvent and it was filtered off. The solvent was concentrated under reduced pressure and the white solid was lyophilized and washed with small portions of ethyl acetate to afford pure (*R*,*S*,*S*)-**6a** as the hydrochloride salt (120 mg, 0.51 mmol, 80% yield). Mp 114–116 °C. $[\alpha]_D$ +33.8 (*c* 0.40, $CHCl_3$). IR (Nujol) *ν* 1749, 1454, 1381, 1201 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) *δ* 1.31–1.34 (m, 1H), 1.39–1.51 (m, 2H), 1.61–1.76 (m, 2H), 1.82 (m, 1H), 1.92 (m, 1H), 1.95 (s, 3H), 2.06 (dd, 1H, *J*=13.2, 10.4 Hz), 2.24 (m, 1H), 2.38 (m, 1H), 2.47 (dd, 1H, *J*=13.2, 6.4 Hz), 3.86 (s, 3H), 4.04 (m, 1H), 9.33 (m, 1H), 10.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 20.52, 22.18, 24.64, 25.17, 25.51, 36.03, 39.66, 53.89, 59.80, 68.06, 171.84. HRMS (ESI) $C_{11}H_{20}NO_2$ M^+: calcd 198.1489, found 198.1490.

4.13. Synthesis of methyl (2*R*,3a*S*,7a*S*)-2-allyloctahydroindole-2-carboxylate hydrochloride, (*R*,*S*,*S*)-6b

An identical procedure to that described above was applied to the transformation of (*S*,*S*,*S*,*R*)-**7b**[10a] (200 mg, 0.59 mmol) into (*R*,*S*,*S*)-**6b**, which was isolated as the hydrochloride salt (120 mg, 0.46 mmol, 78% yield). Mp 133–135 °C. $[\alpha]_D$ +60.3 (*c* 0.44, $CHCl_3$). IR (Nujol) *ν* 1751, 1446, 1226, 1004 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) *δ* 1.22–1.34 (m, 2H), 1.39–1.63 (m, 3H), 1.70–1.86 (m, 3H), 1.96 (dd, 1H, *J*=13.6, 8.4 Hz), 2.19 (m, 1H), 2.48 (dd, 1H, *J*=13.6, 7.2 Hz), 2.72 (dd, 1H, *J*=14.0, 8.4 Hz), 2.90 (dd, 1H, *J*=14.0, 6.0 Hz), 3.63 (m, 1H), 3.75 (s, 3H), 5.15–5.22 (m, 2H), 5.75 (m, 1H), 9.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 20.62, 21.88, 25.31, 25.47, 35.39, 37.35, 41.67, 53.50, 59.57, 71.78, 120.34, 130.86, 170.12. HRMS (ESI) $C_{13}H_{22}NO_2$ M^+: calcd 224.1645, found 224.1649.

4.14. Synthesis of methyl (2*S*,3a*S*,7a*S*)-2-benzyloctahydroindole-2-carboxylate hydrochloride, (*S*,*S*,*S*)-6c

An identical procedure to that described above was applied to the transformation of (*S*,*S*,*S*,*S*)-**7c**[10a] (200 mg, 0.52 mmol) into (*S*,*S*,*S*)-**6c**, which was isolated as the hydrochloride salt (119 mg, 0.39 mmol, 75% yield). Mp 275–277 °C (dec). $[\alpha]_D$ +33.4 (*c* 0.44, $CHCl_3$). IR (Nujol) *ν* 1749, 1460, 1377 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) *δ* 1.22–1.34 (m, 1H), 1.40–1.56 (m, 2H), 1.63–1.80 (m, 2H), 1.88–2.01 (m, 2H), 2.15 (dd, 1H, *J*=13.0, 11.0 Hz), 2.23–2.40 (m, 2H), 2.53 (dd, 1H, *J*=13.0, 6.6 Hz), 3.43 (d, 1H, *J*=13.8 Hz), 3.74 (s, 3H), 3.87–3.98 (m, 1H), overlapped with 3.94 (d, 1H, *J*=13.8 Hz), 7.24–7.31 (m, 5H), 9.93 (m, 1H), 10.47 (m, 1H). ^{13}C NMR (MeOD, 100 MHz) *δ* 21.69, 22.21, 25.90, 26.84, 36.56, 39.79, 43.61, 54.20, 61.11, 74.68, 129.08, 129.98, 130.58, 135.27, 171.75. HRMS (ESI) $C_{17}H_{24}NO_2$ M^+: calcd 274.1802, found 274.1805.

4.15. Synthesis of (2*S*,3a*S*,7a*S*)-*N*-(*tert*-butoxycarbonyl)-2-methyloctahydroindole-2-carboxylic acid, (*S*,*S*,*S*)-8a

A 1 M solution of KOH in methanol (20 mL) was added to (*S*,*S*,*S*)-**5a** (826 mg, 2.78 mmol) and the resulting mixture was heated under reflux for 24 h. The solvent was evaporated and the residue was acidified with 5% aqueous $KHSO_3$. The mixture was extracted with dichloromethane (2×50 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was concentrated in vacuo to afford pure (*S*,*S*,*S*)-**8a** as a white solid (753 mg, 2.66 mmol, 92% yield). Mp 144–146 °C. $[\alpha]_D$ −21.0 (*c* 0.49, $CHCl_3$). IR (Nujol) *ν* 3500–2500, 1703, 1461, 1380, 1165 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) *δ* 0.98–1.10 (m, 1H), 1.11–1.28 (m, 1H), 1.30–1.52 (m, 2H), overlapped with 1.30, 1.52 (two s, 9H) and 1.39, 1.41 (two s, 3H), 1.54–1.65 (m, 4H), 1.95, 2.05 (two m, 1H), 2.20 (m, 1H), 2.43 (m, 1H), 3.65 (m, 1H), 12.34 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) *δ* (duplicate signals are observed for most carbons) 20.18, 20.30; 21.71, 23.16; 23.07, 23.28; 25.13, 25.20; 25.58, 26.52; 27.92, 28.11; 33.68, 34.51; 39.11, 40.11; 57.61, 57.76; 64.21, 64.31; 78.11, 78.44; 152.00, 152.23; 175.54, 176.02. HRMS (ESI) $C_{15}H_{24}NO_4$ $[M-H]^-$: calcd 282.1711, found 282.1705.

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12. ^{1}H NMR spectra of the crude mixtures of the *N*-Boc protected amino esters (*S*,*S*,*S*)/(*R*,*S*,*S*)-**5a**–**c** were complex and unsuitable for the determination of the diastereomeric ratios due to the presence of conformational rotamers.
13. Although the relative spatial disposition of substituents at the α carbon is identical for all three tetrasubstituted compounds (*R*,*S*,*S*)-**6a**, (*R*,*S*,*S*)-**6b** and (*S*,*S*,*S*)-**6c**, the stereochemical descriptors *R*/*S* giving the absolute configuration of the α carbon centre differ. This is due to the different priority of the substituents in the benzylated derivative in comparison with the methylated and allylated compounds.
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