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Towards the stereoselective synthesis of α -methylated (2*S*,3*aS*,7*aS*)-octahydroindole-2-carboxylic acid

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Abstract

A high yielding and remarkably stereoselective α -methylation reaction of the (2*S*,3*aS*,7*aS*) stereoisomer of octahydroindole-2-carboxylic acid, (*S,S,S*)-Oic, suitably protected is described. The severe steric hindrance imposed by the fused cyclohexane ring, which prevents the application of Seebach's *self-reproduction of chirality* methodology, accounts for the formation of (*S,S,S*)-(α Me) Oic with high selectivity and retention of configuration.

Keywords

quaternary amino acid; bicyclic proline analogue; perhydroindole-2-carboxylic acid; α -alkylation

The incorporation of conformationally constrained α -amino acids into bioactive peptides is an effective strategy to circumvent the toughest issues in the development of peptide drugs: proteolytic degradation and poor bioavailability.¹ Quaternary α -amino acids have proved particularly useful to produce modified peptides with drug-like properties.² The introduction of an alkyl chain at the α -carbon of an amino acid elicits, when incorporated into a peptide, conformational constraints that cannot only enhance the biological activity, but also improve the resistance to proteolysis and ultimately increase the bioavailability. Additionally, quaternary α -amino acids are invaluable tools to elucidate the receptor-bound conformation of bioactive peptides and to gain insight on the three dimensional structure of protein receptors that play critical roles in physiological processes.

Quaternary proline analogues³ have received considerable attention as these residues limit the conformational freedom of peptides. The modulation of the *cis-trans* proline amide geometry can allow stable arrangements of turns, which are fundamental recognition elements for peptide function.

Octahydroindole-2-carboxylic acid (Oic, Fig. 1) is a proline surrogate with a fused bicyclic structure shown to be a very useful scaffold. Among the eight different stereoisomers, (2*S*,3*aS*,7*aS*)-Oic (Fig. 1) has application in the elaboration of medicinally relevant drugs already in the market.⁴ This particular isomer has also been used as a surrogate of proline in large peptide systems such as bradykinin, thereby making feasible the preparation of orally available antagonists to the B₂ receptor of this hormone, with attractive anti-cancer properties and enhanced resistance to degrading enzymes.⁵ It has also served as a β -turn inducer in the design of alternative non-peptidic bradykinin B₂ antagonists.⁶ Additionally, some applications of (*S,S,S*)-Oic⁷ derivatives have been reported in the field of organocatalysis.⁸ Given the interest

of this Oic stereoisomer, considerable efforts have been directed towards its preparation. The strategies reported in the literature include stereoselective processes,⁹ chemical resolutions of diastereomeric salts,¹⁰ and chromatographic¹¹ and enzymatic¹² resolutions.

As quaternary proline surrogates, (α Me)Oic derivatives are highly valuable systems for peptide engineering purposes due to their conformationally well-defined structures. Moreover, a number of quaternary Oic derivatives have been reported to be the core structure of investigational compounds with potential applications for treating osteoarthritis.¹³ However, the preparation of C $^{\alpha}$ -tetrasubstituted Oic analogues remains almost unexplored.^{13,14} The lack of effective methodologies for ready accessibility to their enantiomerically pure forms constitutes the main hurdle for their exploitation.

Recently, we have described a very convenient and concise route leading to enantiopure (*R,S,S*)-(α Me)Oic¹⁴ (Scheme 1) through a completely diastereoselective α -methylation reaction of the trichloromethyloxazolidinone¹⁵ derived from enantiopure (*R,S,S*)-Oic [(*R,S,S*)-**1**; Scheme 1]. The preparation of the (*S,S,S*)-(α Me)Oic stereoisomer has only been disclosed in a patent,¹³ where no experimental data to sustain the configurational assignment made for the α carbon are given.

On approaching the preparation of enantiopure (*S,S,S*)-(α Me)Oic, Seebach's *self reproduction of chirality* methodology¹⁵ could not be applied because the precursor amino acid (*S,S,S*)-**1** fails to undergo condensation with trichloroacetaldehyde¹⁴ to produce the desired oxazolidinone (Scheme 1). The steric hindrance of the cyclohexane group in (*S,S,S*)-**1**, on a *cis* relative orientation with respect to the carboxylic function precludes the formation of oxazolidinone (*R,S,S*)-**2**. Such a tricyclic system would suffer from severe steric clash¹⁴ between nearby hydrogens at the inner concave face. In fact, we proved¹⁴ that the aforementioned condensation reaction constitutes a very effective tool for the separation of epimeric mixtures of (*R,S,S*)-**1** and (*S,S,S*)-**1**.

Although the steric shielding imposed by the cyclohexane ring in (*S,S,S*)-**1** was truly advantageous for the selective preparation of (*R,S,S*)-(α Me)Oic,¹⁴ it prevents the application of the *self-reproduction of chirality* strategy¹⁵ when the synthesis of the epimeric (*S,S,S*)-(α Me)Oic is pursued. In that sense, it is rather unfortunate because this powerful methodology would formally allow α -methylation with complete retention of configuration.

We then found that the steric shielding introduced by the cyclohexane moiety could inflict unambiguous facial stereodifferentiation on the enolate derived from (*S,S,S*)-**1**. On this basis, it seems reasonable to consider that this spatial effect could effectively govern the stereochemical outcome of direct alkylations performed on a suitably protected derivative of (*S,S,S*)-**1** such as (*S,S,S*)-**3** (Fig. 2).

Compound (*S,S,S*)-**3** was prepared from enantiomerically pure (*S,S,S*)-**1**, which, in turn, was obtained in a single step and high yield from commercially available (*S*)-indoline-2-carboxylic acid as already described.¹¹ 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).

Next, we addressed the study of the α -methylation reaction of (*S,S,S*)-**3** through the generation of an intermediate enolate. It appears that the treatment of (*S,S,S*)-**3** with LDA in THF at -78°C generated a lithium enolate that successfully reacted with methyl iodide in high yield. Thus, a mixture of the two possible diastereoisomers, (*S,S,S*)-**4** and (*R,S,S*)-**4**, was isolated in 92% yield, after 12 h of reaction at -60°C (Scheme 3). In comparison, the use of either LHMDS or KHMDS as a base, led to poor conversions ($\sim 50\%$) under similar reaction conditions.

A 89:11 diastereomeric ratio was established by analysis of the relative intensities of appropriate signals in the ^1H NMR spectra of the amino ester hydrochlorides (*S,S,S*)-**5** and (*R,S,S*)-**5**,¹⁶ that were quantitatively obtained after treatment of the crude mixture of (*S,S,S*)-**4**/*(R,S,S)*-**4** with a saturated solution of hydrogen chloride in ethyl acetate.

The stereoselectivity attained is rather significant given that the direct α -methylation reaction of equally protected L-proline furnishes racemic (αMe)Pro.¹⁷ In the case of *N*-Boc prolines with additional substituents at the ring, the reported diastereoselectivities are low to moderate, with few exceptions.¹⁸ In our case, the high steric hindrance imposed by the *cis*-fused cyclohexane ring allows an efficient facial stereodifferentiation that translates into a good diastereoselectivity.

The major diastereoisomer of the (*S,S,S*)-**4**/*(R,S,S)*-**4** mixture was isolated pure¹⁹ in 75% yield after column chromatography (Scheme 4). Subsequent acidic treatment led to the corresponding amino ester hydrochloride, which furnished colourless single crystals suitable for X-ray diffraction analysis.²⁰ The crystalline structure (Fig. 3) showed an (*S,S,S*) stereochemistry, with a *cis* relative disposition of the hydrogen atoms at the ring junction and the α -methyl group, thus confirming that the alkylation reaction proceeded with retention of configuration at the quaternary stereocenter.

Additionally, the basic hydrolysis of (*S,S,S*)-**4** furnished the *N*-Boc amino acid (*S,S,S*)-**6** in excellent yield (Scheme 4). This Oic derivative is suitably protected for incorporation into peptides.

In conclusion, this initial study shows that enantiopure (*S,S,S*)-(αMe)Oic can be accessed by means of a diastereoselective α -methylation reaction on (*S,S,S*)-**3**, which is easily derived from (*S,S,S*)-Oic. The facial stereodifferentiation imposed by the cyclohexane ring on the nucleophilic enolate carbon derived from (*S,S,S*)-**3** accounts for the selective outcome of the α -methylation reaction. Such a spatial effect can thus be regarded as an effective tool for stereocontrol induction during the functionalization at the α carbon for those sterically hindered proline-type substrates where the formation of a trichloromethyloxazolidinone is not possible.

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16. ^1H NMR of the crude mixture of the *N*-Boc protected esters (*S,S,S*)-**4** and (*R,S,S*)-**4** was complex and unsuitable for the determination of the diastereomeric ratio due to the presence of conformational rotamers.
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19. Analytical and spectroscopic data for (*S,S,S*)-**4**: Oil. $[\alpha]_{\text{D}}^{25} +9.5$ (c 0.95, CHCl_3). IR (neat) ν 1743, 1693 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{DMSO}-d_6$, 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) $\text{C}_{16}\text{H}_{27}\text{NO}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: calcd. 320.1832, found 320.1832.
20. Crystallographic data for (*S,S,S*)-**5** · HCl: orthorhombic, space group $\text{P}2_12_12_1$; $a = 7.7814(2)$ Å, $b = 8.9278(4)$ Å, $c = 17.6054(7)$ Å; $Z = 4$; $d_{\text{calcd}} = 1.269$ g·cm $^{-3}$; 8032 reflections collected, 2640 unique ($R_{\text{int}} = 0.021$); 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 $^{-3}$. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 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].

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

Figure 2.
Proposed precursor for the synthesis of (S,S,S)-(αMe)Oic.

Figure 3.
X-ray crystal structure of (S,S,S)-5·HCl. Most hydrogens have been omitted for clarity.

Scheme 1. Reported synthesis for $(R,S,S)\text{-(}\alpha\text{Me)Oic}$ (ref. 14).

Scheme 2.

Synthesis of enantiomerically pure (S,S,S)-3. Reagents and conditions: (a) See ref. 11; (b) SOCl_2 , MeOH, r.t.; (c) Boc_2O , $i\text{Pr}_2\text{EtN}$, 4-dimethylaminopyridine, THF, r.t.

Scheme 3.

α -Methylation reaction of (S,S,S)-3. Reagents and conditions: (a) LDA, MeI, THF, -78 to -60 $^{\circ}\text{C}$; (b) 3N HCl / EtOAc, r.t.

Scheme 4.

Synthesis of enantiopure (S,S,S) -(α Me)Oic derivatives. Reagents and conditions: (a) LDA, MeI, THF, -78 to -60 °C; column chromatography of the mixture (SiO₂, EtOAc/Hexanes 1:10) furnishes pure (S,S,S) -4; (b) 3N HCl / EtOAc, r.t.; (c) 1N KOH, MeOH / H₂O, reflux.