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A new strategy for the regio- and stereoselective hydroxylation of *trans*-2-aminocyclohexenecarboxylic acid

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Dedicated to Professsor Pal Sohar on his 70th birthday

Abstract—A simple and novel method for the introduction of an extra hydroxy group into an aminocyclohexanecarboxylic acid via stereoselective epoxidation and regioselective opening of the oxirane ring is presented. This method permits the preparation of the enantiomerically pure hydroxylated amino acid.
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1. Introduction

In recent years, significant interest has been demonstrated in conformationally constrained alicyclic β-amino acids as a consequence of their pharmacological potential. These compounds are found in a large number of natural products, β-lactams and antibiotics. They are also considered as important building blocks for the synthesis of peptide oligomers.[1] The presence of a polar side chain in a peptide oligomer not only exerts strong influence on the formation of its secondary structure, but can also have an enormous effect on its biological activity in an amphiphilic structure.[2] Apart from this, the hydroxy-functionalized derivatives (taxol, bestatin and related molecules) are of considerable interest, in view of their promising biological properties as potential therapeutic agents.[3] Among the alicyclic hydroxy-β-amino acids, the natural oryzoxymycin exhibits moderate activity against *Xanthomonas oryzae*.[4] Whilst a number of methods have been developed for the diastereo- and enantioselective preparation of cyclic β-amino acids, only a few examples are available for the synthesis of hydroxy-substituted 2-aminocyclohexanecarboxylic acids.[3e,5] One short method is the base-induced fragmentation of β-amino esters with an oxanorbornene or oxanorbornane skeleton.[6] The introduction of a hydroxy group onto the cyclohexane ring can also be accom-

plished stereoselectively from *cis*- and *trans*-2-amino-cyclohexenecarboxylic acids by iodolactonization or via the corresponding oxazine derivatives.[7]

Epoxidation of a mono N-protected alkene (carbamate or amide) with peracids is known to proceed with a high degree of cis selectivity (presumably via a hydrogen-bonding interaction in the transition state).[8] Consequently, transformation of a 2-aminocyclohexenecarboxylic acid through epoxidation may be expected to lead, stereoselectively, to the hydroxylated derivative of the alicyclic amino acid. For this reason, the Z- and Boc-protected *trans*-β-amino esters **1a** and **1b** were submitted to epoxidation (Scheme 1).

The reactions were carried out in the presence of *m*-chloroperbenzoic acid (MCPBA) as the oxidant in CH_2Cl_2. In both cases, the reaction furnished in a diastereoselective manner, only the *cis*-epoxides **2a** and **2b** as single diastereomers (Scheme 1). The stereochemistry of the rigid ring system of **2a** was established using NMR spectroscopy and molecular modelling. Both the 4S,5R (a cis epoxide ring relative to NHZ) and the
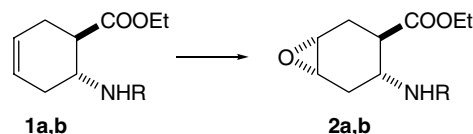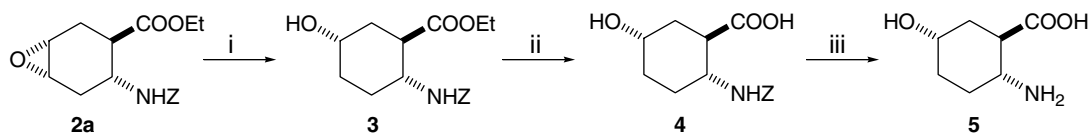
**Scheme 1.** Epoxidation of ethyl *trans*-2-amino-4-cyclohexenecarboxylate (**a**: R = Z, **b**: R = Boc). MCPBA, CH_2Cl_2, rt, 6 h, **2a**: 59%; **2b**: 65%.

Table 1. Calculated geometry and measured characteristic NMR spectral parameters for **2a** and **2b**

Atom pair	Dihedral angle for 4R,5S (deg)	Dihedral angle for 4S,5R (deg)	Measured ^3J (Hz)	Distances for 4R,5S (Å)	Distances for 4S,5R (Å)	NOESY cross-peak rel. int.
H4–H3eq	66	18	2.1	2.58	2.36	2.30
H4–H3ax	52	99	1.5	2.48	2.82	2.25
H5–H6eq	18	65	5.5	2.36	2.57	3.11
H5–H6ax	100	52	<0.5	2.82	2.48	1.00

Scheme 2. Synthesis of *rac*-(*r*-1,*t*-2,*t*-5)-2-amino-5-hydroxycyclohexanecarboxylic acid. Reagents and conditions: (i) NaBH$_4$, EtOH, rt, 2 h, 66%; (ii) NaOH, MeOH/H$_2$O, rt, 3 h, 89%; (iii) H$_2$, Pd/C, MeOH, rt, 6 h, 91%.
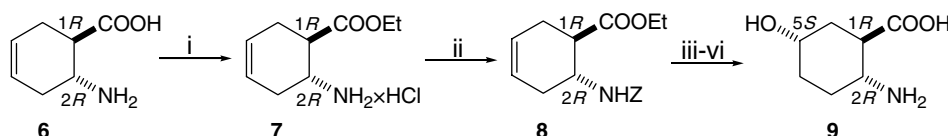
Scheme 3. Synthesis of (1R,2R,5S)-2-amino-5-hydroxycyclohexanecarboxylic acid. Reagents and conditions: (i) SOCl$_2$, EtOH, 70 °C, 4 h, 89%; (ii) Z-Cl, Et$_3$N, THF, rt, 16 h, 91%; (iii) MCPBA, CH$_2$Cl$_2$, rt, 6 h, 56%; (iv) NaBH$_4$, EtOH, rt, 2 h, 66%; (v) NaOH, MeOH/H$_2$O, rt, 3 h, 87%; (vi) H$_2$, Pd/C, MeOH, rt, 6 h, 86%.

4R,5S (a trans epoxide ring relative to NHZ) forms were modelled at the HF/3-21G* level. The calculated geometrical features around H4 and H5 and the characteristic NMR spectral parameters are listed in Table 1. Comparison of the pattern of the experimental parameters with the calculated geometrical features of the corresponding diastereomers strongly supports the 4S,5R relative configuration (a cis oxirane ring relative to the NHZ group).

The attack on the double bond occurred from the side of the alkoxycarbonylamine moiety, the oxirane ring being formed on the amide side of the cyclohexane skeleton. The selectivity of the epoxidation reaction was determined by ^{1}H NMR and GC analyses of the crude products.

This nitrogen-mediated directing effect in the epoxidation reactions suggested a stereocontrolled route to the hydroxy-substituted aminocyclohexanecarboxylic acid. Furthermore, the reductive opening of the oxirane ring of **2a**, with NaBH$_4$ in EtOH at room temperature, proceeded regioselectively, affording only compound **3**, in which the hydroxy group is in position 5 on the cyclohexane ring of the alicyclic amino ester (Scheme 2). The other regioisomer (4-OH derivative) was not detected in the reaction mixture.

The relative configuration and the position of the hydroxy group on the cyclohexane skeleton were determined by means of NMR analyses. For compound **3**, the COSY connectivity pattern unequivocally supported the constitution depicted in Scheme 2. The vicinal couplings and the clear 1,3-diaxial NOE interactions proved the chair conformation with *trans*-diequatorial COOEt and NHZ substituents. The exclusively small coupling

constants observed for H4 and the NOE interactions HO-H6eq and HO-H3eq revealed the axial arrangement (*S* relative configuration) of the OH substituent. Alkaline hydrolysis of the ester group of compounds **3** and subsequent deprotection of the amino group by catalytic hydrogenation in MeOH afforded 2-amino-5-hydroxycyclohexanecarboxylic acid **5**.

The reactions were also performed for enantiomeric substances (Scheme 3). The (1R,2R) enantiomer **6** was prepared from the corresponding racemic ester by enzyme-catalyzed kinetic resolution, using 2,2,2-trifluoroethyl chloroacetate as the acyl donor with lipase PS in diethyl ether.[9]

In conclusion, a new and effective approach to the hydroxy-functionalized β-amino acids has been developed based on a diastereoselective epoxidation and hydroxylation involving regioselective opening of the oxirane ring. We are currently studying the application of these transformations for the synthesis of other hydroxylated β-amino acids in both racemic and optically pure forms.

2. Experimental

The experimental details are given only for enantiomeric substances. For the synthesis of racemates, the same conditions were used.

2.1. Ethyl (1R,2R)-2-amino-4-cyclohexenecarboxylate hydrochloride (7)

To a solution of (1R,2R)-2-amino-4-cyclohexenecarboxylic acid **6** (1 g, 7.1 mmol) (for the synthesis of the

racemic and enantiomeric compounds, see Refs. 10 and 9, respectively) in EtOH (15 mL), SOCl$_2$ (0.9 mL, 12.5 mmol) was added dropwise at −10 °C over a period of 30 min, and the mixture was stirred for 3 h at room temperature and then for 1 h under reflux. The mixture was concentrated giving the crude product, which was used further without purification. White solid, mp 97–98 °C, yield 89%, $[\alpha]_D^{25}$ −120 (c 0.75, EtOH). ^{1}H NMR (400 MHz, D$_2$O): δ 1.30 (t, 3H, J = 7.1 Hz, CH$_3$), 2.15–2.50 (m, 4H, CH$_2$), 2.92–2.98 (m, 1H, H-1), 3.77–3.81 (m, 1H, H-2), 4.22–4.27 (m, 2H, OCH$_2$), 5.68 (m, 1H, CH), 5.77 (m, 1H, CH); Anal. Calcd for C$_9$H$_{16}$ClNO$_2$: C, 52.68; H, 7.80; N, 6.83; Cl, 17.29. Found: C, 52.60; H, 7.54; N, 6.76; Cl, 16.98.

2.2. Ethyl (1R,2R)-2-(benzyloxycarbonylamino)-4-cyclohexenecarboxylate (8)

To a solution of amino ester 7 (1.2 g, 5.85 mmol) and Et$_3$N (1.8 mL, 17.8 mmol) in THF (40 mL), benzyl chloroformate (1.5 g, 8.8 mmol) was added at 0 °C. After stirring for 16 h, the mixture was taken up in EtOAc (60 mL), and the solution was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. White solid (n-hexane), mp 70–73 °C, yield 91%, $[\alpha]_D^{25}$ −18 (c 0.3, EtOH). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.23 (t, 3H, J = 7.1 Hz, CH$_3$), 2.00–2.04 (m, 1H, CH$_2$), 2.30–2.35 (m, 1H, CH$_2$), 2.51–2.56 (m, 2H, CH$_2$), 2.71–2.73 (m, 1H, H-1), 4.11–4.17 (m, 3H, OCH$_2$, H-2), 4.93 (d, 1H, J = 5.5 Hz, N-H), 5.11 (s, 2H, OCH$_2$), 5.61–5.65 (m, 1H, H-5), 5.68–5.70 (m, 1H, H-4), 7.33–7.39 (m, 5H, Ar-H); Anal. Calcd for C$_{17}$H$_{21}$O$_4$N: C, 67.32; H, 6.98; N, 4.62. Found: C, 67.24; H, 6.90; N, 4.51.

2.3. Ethyl (1R,2R,4S,5R)-2-(benzyloxycarbonylamino)-4,5-epoxycyclohexanecarboxylate [(−)-2a]

To a solution of amino ester 7 (5.85 mmol) in CH$_2$Cl$_2$ (40 mL), MCPBA (7 mmol) was added at 0 °C. After stirring for 5 h, CH$_2$Cl$_2$ (90 mL) was added and the mixture was washed with saturated NaHCO$_3$ solution in H$_2$O. The organic layer was then dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was chromatographed over silica gel (n-hexane/EtOAc 3:1). White solid (n-hexane), mp 82–85 °C, yield 59%, $[\alpha]_D^{25}$ −24.7 (c 0.35, EtOH). ^{1}H NMR (CDCl$_3$): δ = 1.13 (t, 3H, J = 7.1 Hz, CH$_3$), 1.82–1.88 (m, 1H, CH$_2$), 2.11–2.22 (m, 3H, CH$_2$), 2.56–2.58 (m, 1H, H-1), 3.08 (m, 1H, H-5), 3.17 (m, 1H, H-4), 3.99–4.06 (m, 3H, OCH$_2$ and H-2), 5.01 (s, 2H, OCH$_2$), 5.28–5.30 (d, 1H, J = 5.5 Hz, N–H), 7.18–7.24 (m, 5H, Ar-H); Anal. Calcd for C$_{17}$H$_{21}$NO$_5$: C, 63.95; H, 6.58; N, 4.39. Found: C, 63.77; H, 6.65; N, 4.32.

2.4. Ethyl (1R,2R,5S)-2-(benzyloxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(−)-3]

To a solution of epoxide (−)-2a (800 mg, 2.52 mmol) in EtOH (25 mL), NaBH$_4$ (240 mg, 6.3 mmol) was added in portions. The mixture was stirred at room temperature for 18 h, and the solvent was then evaporated off. The residue was taken up in EtOAc (70 mL) and the

solution was washed with H$_2$O, dried (Na$_2$SO$_4$) and concentrated. The crude oily product was chromatographed over silica gel (n-hexane/EtOAc 1:2). White solid, mp 68–70 °C, yield 66%, $[\alpha]_D^{25}$ −4.5 (c 0.35, EtOH). ^{1}H NMR (CDCl$_3$): δ = 1.19 (t, 3H, J = 7.1 Hz, CH$_3$), 1.68–1.95 (m, 6H, CH$_2$), 2.75–2.77 (m, 1H, H-1), 3.81–3.83 (m, 1H, H-2), 4.07–4.15 (m, 3H, OCH$_2$ and H-5), 4.96–4.98 (d, 1H, J = 5.5 Hz, N-H), 5.08 (s, 2H, OCH$_2$), 7.30–7.35 (m, 5H, Ar-H); Anal. Calcd for C$_{17}$H$_{23}$NO$_5$: C, 63.55; H, 7.16; N, 4.36. Found: C, 63.43; H, 7.11; N, 4.30.

2.5. (1R,2R,5S)-2-(Benzyloxycarbonylamino)-5-hydroxy-cyclohexanecarboxylic acid [(−)-4]

To a solution of amino ester (−)-3 (300 mg, 0.93 mmol) in THF (25 mL), NaOH (130 mg, 3.25 mmol) in H$_2$O (15 mL) was added. After stirring for 24 h, 10% HCl was added at 0 °C until pH 5, and the mixture was then extracted with CHCl$_3$ (3 × 40 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. White solid, mp 65–68 °C, yield 86%, $[\alpha]_D^{25}$ −3.5 (c 0.37, EtOH). ^{1}H NMR (DMSO): δ = 1.23–1.63 (m, 6H, CH$_2$), 2.63–2.66 (m, 1H, H-1), 3.50–3.54 (m, 1H, H-2), 3.82 (m, 1H, H-5), 4.54 (d, 1H, J = 5.5 Hz, N-H), 4.99 (s, 2H, OCH$_2$), 7.26–7.37 (m, 5H, Ar-H), 12.06 (1H, COOH); Anal. Calcd for C$_{15}$H$_{19}$NO$_5$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.39; H, 6.49; N, 4.59.

2.6. (1R,2R,5S)-2-Amino-5-hydroxycyclohexanecarboxylic acid (9)

A solution of amino acid (−)-4 (295 mg, 1.5 mmol) and 10% Pd/C (80 mg) in MeOH (30 mL) was stirred under H$_2$ for 2 h. The Pd was then filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from MeOH/Et$_2$O. White crystals, mp 272–275 °C, yield 87%, $[\alpha]_D^{25}$ −18.5 (c 0.33, H$_2$O). ^{1}H NMR (D$_2$O): δ = 1.60–1.92 (m, 5H, CH$_2$), 2.15–2.19 (m, 1H, CH$_2$), 2.57–2.62 (m, 1H, H-1), 3.30–3.32 (m, 1H, H-2), 4.15–4.17 (m, 1H, H-5); Anal. Calcd for C$_7$H$_{13}$NO$_3$: C, 52.83; H, 8.18; N, 8.80. Found: C, 52.60; H, 8.06; N, 8.69.

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