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c-4-Amino-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylic acid and *cis*-4-amino-3-oxo-1-cyclohexanecarboxylic acid — mimetics of dipeptides with a twisted *cis*-amide bond

Krzysztof Krajewski, Zbigniew Ciunik and Ignacy Z. Siemion *

Faculty of Chemistry, Wrocław University, Joliot-Curie 14, 50-383 Wrocław, Poland

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Abstract

The stereoselective synthesis of the title compounds has been performed. The relative configuration of methyl *c*-4-(*tert*-butoxycarbonylamino)-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate was confirmed by X-ray diffraction methods and its conformation in solution analyzed by NMR. The peptides containing this compound were synthesized and resolved into pure diastereoisomeric forms. Their absolute configuration was determined by independent stereospecific synthesis.

1. Introduction

The *cis*/*trans* isomerization of a Xaa-Pro amide bond is often the slowest step in protein folding. In vivo it is catalyzed by peptidyl-prolyl *cis*/*trans* isomerases (PPIases, rotamases, immunophilins).[1] In crystal structures of complexes of rotamases with peptide substrates the ligands Xaa-Pro peptide bond adopts a nonplanar *cis*-conformation ($\omega \sim 0°$–$45°$).[2] The *cis*/*trans* amide bond isomerization takes place when a complex of PPIase (cyclophilin A) with cyclosporin A (CsA), an immunosuppressive drug and a rotamase inhibitor, is formed.[3,4] In the free CsA molecule there exists one *cis*-amide bond which undergoes isomerization during complex formation. The *cis*-amide bond (between two Pro residues) appears also in the molecule of cyclolinopeptide A [CLA, c-(Leu-Ile-Ile-Leu-Val-**Pro**-**Pro**-Phe-Phe)],[5] the nonapeptide isolated from linseed.[6] CLA and its analogues (extensively investigated in our laboratory) exhibit a distinct immunosuppressive activity, comparable to that of CsA,[7] moreover, the mechanism of action is the same as in the case of CsA.[8,9]

The modifications directed to improve the affinity of CLA to rotamases (cyclophilins), by introduction of amino acid residues that mimic the transition state of *cis*/*trans* isomerization, could be a very promising

* Corresponding author. E-mail: siemion@wchuwr.chem.uni.wroc.pl

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way to construct more effective immunosupressors. We proposed to modify CLA through replacement of the -Pro-Pro- fragment (with a *cis*-peptide bond between proline residues involved in complex formation) by the transition state mimetic.

On the basis of structures of the peptide substrates in complexes with cyclophilins we designed a new mimetic *cis*-4-amino-3-oxo-1-cyclohexanecarboxylic acid which is a conformationally restricted analogue of the twisted *cis*-peptide bond (torsion angle Ω about 50°, Fig. 1). Many syntheses of analogues of peptides with a constrained *cis*-amide bond have been described, but to our knowledge this is the first mimetic of the transition state of the *cis*/*trans* isomerization of an amide bond.

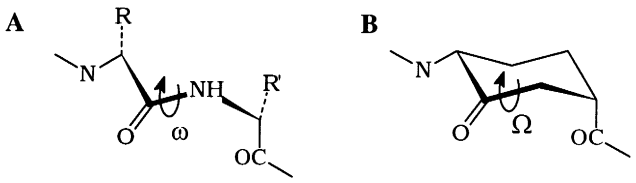


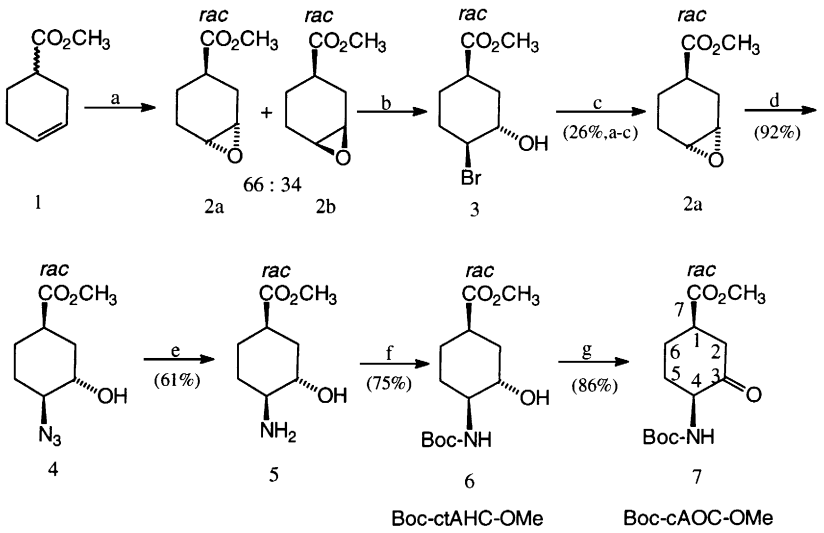
Fig. 1. The schematic representation of the twisted *cis*-peptide bond (**A**) and its mimetic (**B**)

2. Results and discussion

We synthesized methyl *c*-4-amino-*t*-3-hydroxy-1-*r*-cyclohexanecarboxylate (**5**, ctAHC-OMe), a useful substrate for the synthesis of CLA analogues with the 4-amino-3-oxo-1-cyclohexanecarboxylic acid residue. This compound was prepared (Scheme 1) from methyl 3-cyclohexene-1-carboxylate **1** via epoxidation with *m*-CPBA (step a), elimination of the unwanted *cis*-epoxide (**2b**, steps b and c), opening the *trans*-epoxide **2a** with NaN_3 (step d) and catalytic reduction of methyl *c*-4-azido-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate (**4**, step e). Because only the opening of *trans*-epoxide **2a** gives **4** we invented a method of elimination of **2b**. The epoxides **2a** and **2b** were converted to bromohydrins that were heated with *p*-TSA in toluene. Under these conditions methyl *t*-3-bromo-*c*-4-hydroxy-*r*-1-cyclohexanecarboxylate (from **2b**) underwent decomposition via transesterification to a bromolactone whereas *c*-4-bromo-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate (**3**, from **2a**) was more stable, and **2a** was recreated by reaction of **3** with aqueous NaOH. To our knowledge this is the first method for obtaining **2a** from a mixture of epoxides other than preparative GC.[10,11] The *trans*-epoxide **2a** underwent regio- and stereoselective reaction with NaN_3 giving **4**.[12] A catalytic reduction of **4** (10% Pd–C) gives **5**, the substrate for peptide synthesis. Methyl *c*-4-(*tert*-butoxycarbonylamino)-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate (Boc-ctAHC-OMe, **6**) was prepared from **5** by reaction with Boc_2O (step f). The product was crystallized from EtOAc:hexane. The X-ray structure of **6** confirms its relative configuration (Fig. 3). This structure indicates that **6** possesses a chair conformation with an axial $-CO_2CH_3$ group. The same ring conformation, as a result from NMR spectra, predominates in $CDCl_3$ solution (see Experimental).

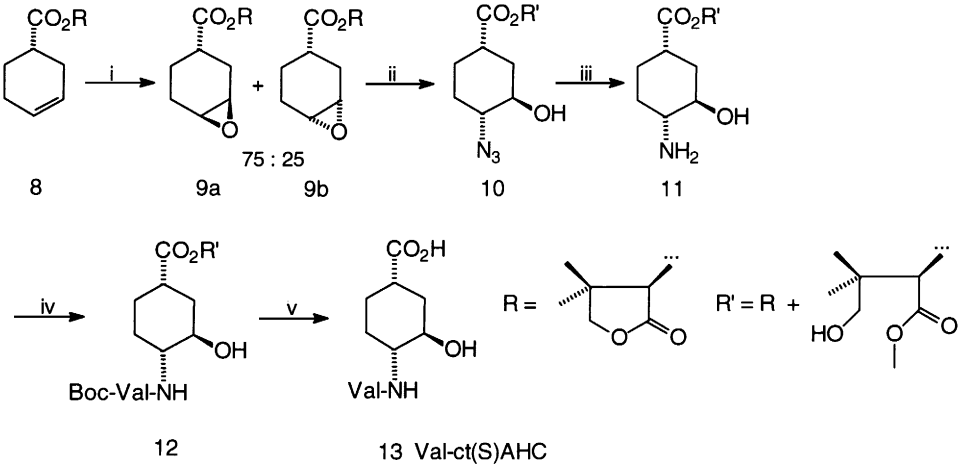
The racemic methyl *c*-4-amino-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate, was converted to diastereoisomeric dipeptides (Xaa-ctAHC) by acylation with Boc-Xaa (Xaa=Val, Ala, Phe) and deprotection.

These dipeptides are easily separable into diastereoisomers by preparative HPLC and can be used in solid-phase peptide synthesis (with BOP as a coupling reagent). The experimental details of Xaa-ctAHC synthesis, separation into diastereoisomers (Xaa-ct(*R*)AHC and Xaa-ct(*S*)AHC) and synthesis of CLA analogues with both enantiomers of ctAHC will be published elsewhere. To determine the absolute configuration of the ctAHC residue in both diastereoisomers of Val-ctAHC we performed a small scale synthesis of **13** (Scheme 2) from (*R*)-pantolactone (*S*)-3-cyclohexene-1-carboxylate **8**.[13] This synthesis



Scheme 1. (a) *m*-CPBA, $CHCl_3$; (b) HBr aq., $CHCl_3$, then *p*-TSA, toluene, Δ; (c) NaOH aq., *i*PrOH; (d) NaN_3, NH_4Cl, MeOH, Δ; (e) H_2, 10% Pd–C; (f) Boc_2O, DMAP, acetone; (g) PDC, DMF

was performed without isolation of intermediate products. After comparison of retention times (Fig. 2) we found that the diastereoisomer with the longer retention time (**13**) contains (1*S*,3*R*,4*R*)-4-amino-3-hydroxy-1-cyclohexanecarboxylic acid residue (ct(*S*)AHC) and the one with the shorter retention time contains (1*R*,3*S*,4*S*)-4-amino-3-hydroxy-1-cyclohexanecarboxylic acid residue (ct(*R*)AHC) (the same results were obtained for Ala-ctAHC).



Scheme 2. (i) *m*-CPBA, $CHCl_3$, 0°C; (ii) NaN_3, NH_4Cl, MeOH, Δ; (iii) H_2, 10% Pd–C; (iv) Boc-Val, DCC, DCM; (v) LiOH, THF, H_2O, then TFA, DCM

We also tested the oxidation of **6** to methyl *cis*-4-(*tert*-butoxycarbonylamino)-3-oxo-1-cyclohexanecarboxylate (**7**, step g) with pyridinium dichromate (PDC).[14] The positive result of the oxidation allows us to expect that the ctAHC residue could be oxidized under mild conditions after incorporation into CLA.

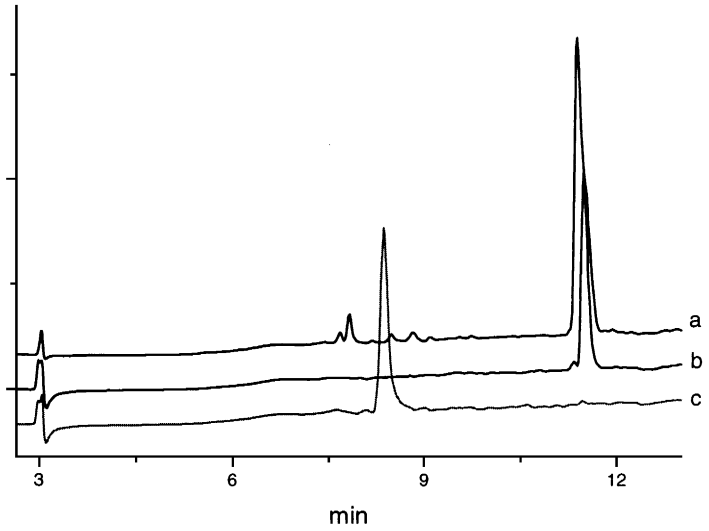


Fig. 2. The HPLC chromatograms of **13** (a) and two diastereoisomers of Val-ctAHC after preparative HPLC (b, c)

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-300 spectrometer in the indicated solvents; chemical shifts are given in ppm. The NMR signal assignment was based on COSY and HETCOR experiments. ESIMS spectra were recorded on a Finnigan MAT TSQ700 instrument. Analytical HPLC analyses were performed on reverse phase ODS column (Vydac 218TP) eluting with an increasing linear gradient of CH_3CN (1.6%/min) in the presence of 0.1% TFA. Melting and boiling points are uncorrected.

3.2. Preparation of methyl t-3,4-epoxy-r-1-cyclohexanecarboxylate **2a**

To a solution of methyl 3-cyclohexene-1-carboxylate **1**[15] (14.0 g, 100 mmol) in $CHCl_3$ (50 mL) cooled to 0°C, in an ice-water bath, a solution of *m*-CPBA (0.35 M, 315 mL, 110 mmol) in $CHCl_3$ was added. The solution was stirred at room temperature for 2.5 h (after 15 min a white precipitate was formed). The mixture was cooled to 0°C and filtered. To the filtrate Na_2SO_3 (5.5 g) was added. The mixture was stirred for 5 min and filtered again. The resulting solution was washed with satd $NaHCO_3$ aq. (2×100 mL) and dried over anhydrous $MgSO_4$. Concentration of the filtrate, followed by low-pressure distillation (56–58°C/0.8 mmHg) afforded 12.6 g (81 mmol) of colorless liquid. Its analysis (^{1}H NMR, ^{13}C NMR and GC–MS) revealed that this is a 33:67 mixture of methyl *c*-**2b** and *t*-3,4-epoxy-*r*-1-cyclohexanecarboxylate (**2a**, desired product, 67%). The proportion of diastereoisomers is similar to that obtained from reactions with peroxybenzoic acid and 4-nitroperoxybenzoic acid (34:66).[10]

A solution of this mixture (3.90 g, 25.0 mmol) in $CHCl_3$ (50 mL) was vigorously stirred for 25 min with 40% HBr aq. (30 mL). The organic layer was immediately separated, washed with satd $NaHCO_3$ aq. and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue and *p*-TSA·H_2O (30 mg, 0.15 mmol) were dissolved in toluene (30 mL). Half of the solvent was very slowly distilled (~15 mL, 3.5 h) using a short Vigreux column. The rest of the solvent was evaporated under reduced pressure. The brown residue was dissolved in *i*-PrOH (15 mL) and titrated with 1 M NaOH aq. (14.6 mL) in the presence of phenolphthalein. This solution, after addition of water (20 mL), was extracted

with Et_2O (2×30 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated. Distillation of the residue (53–56°C/0.7 mmHg) gave a colorless liquid (1.25 g, 8.0 mmol). According to GC–MS and ^{1}H NMR analysis this product contains 94% of **2b** and 6% of **2a**. Prolonging the toluene distillation time to 5 h increases the purity of the product to 97% but decreases the yield. Overall yield (from **1**) was 26%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 3-CH_3), 3.18 (m, 1-H3), 3.09 (m, 1-H4), 2.46 (m, 1-H1), 2.21 (ddd, 1-H2′), 1.94 (m, 3-H2, H5, H5′), 1.72 (m, 1-H6′), 1.36 (m, 1-H6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.68 (C7), 52.00 (C3), 51.55 (C4), 51.18 (*C*H_3), 35.58 (C1), 27.02 (C2), 22.73 (C6), 22.63 (C5). $[n]_D^{25}$ 1.4625 (lit. 1.4610,[10] 1.4631[11]).

3.3. *Preparation of methyl* c-*4-azido*-t-*3-hydroxy*-r-*1-cyclohexanecarboxylate* ***4***

To the solution of **2a** (2.35 g, 15.0 mmol) in CH_3OH (45 mL), NaN_3 (3.25 g, 50.0 mmol) and NH_4Cl (2.68 g, 50.0 mmol) were added. The mixture was refluxed for 6 h, cooled in a refrigerator (4°C) overnight and filtered. The filtrate was evaporated under reduced pressure and the residue was shaken with Et_2O (30 mL) and brine (30 mL). The organic layer was separated, dried ($MgSO_4$), and the solvent was then removed to give methyl *c*-4-azido-*t*-3-hydroxy-*r*-1-cyclohexanecarboxylate **4** as a light yellow oil. Yield was 2.75 g (13.8 mmol, 92%). A sample of **4** was purified by distillation (66–67°C/1 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (m, 1-H3), 3.65 (s, 3-CH_3), 3.32 (m, 1-H4), 2.89 (bs, 1-O*H*), 2.75 (m, 1-H1), 2.23 (m, 1-H2′), 2.00 (m, 1-H6′), 1.93 (m, 1-H5′), 1.63–1.45 (m, 3-H5, H6, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.69 (C7), 69.54 (C3), 64.51 (C4), 51.78 (*C*H_3), 38.09 (C1), 32.89 (C2), 25.74 (C5), 24.68 (C6).

3.4. *Preparation of methyl* c-*4-amino*-t-*3-hydroxy*-r-*1-cyclohexanecarboxylate* ***5***

A mixture of **4** (2.50 g, 12.6 mmol) and 10% palladium on carbon (90 mg) in methanol (100 mL) was stirred under hydrogen for 2 h. The mixture was filtered and concentrated under reduced pressure. The residual colorless oil crystallized slowly (2 days). After recrystallization from CH_3OH–Et_2O mixture small white crystals of **5** were obtained. Yield was 1.32 g (7.3 mmol, 61%). Mp: 63–65°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3-CH_3), 3.43 (ddd, J=11.0, 8.8, 4.3 Hz, 1-H3), 3.02 (bs, 3-NH_2, O*H*), 2.79 (ddddd, J=5.2, 4.8, 3.3, 2.7, 1.1, 1-H1), 2.56 (ddd, J=10.9, 8.8, 4.0, 1-H4), 2.35 (dddd, J=13.2, 4.3, 3.3, 2.2, 1-H2′), 2.10 (ddddd, J=13.7, 5.3, 3.6, 2.7, 2.2, 1-H6′), 1.83 (ddddd, J=13.1, 5.3, 3.9, 3.4, 1.1, 1-H5′), 1.53 (dddd, J=13.7, 12.9, 4.8, 3.4, 1-H6), 1.47 (ddd, J=13.2, 11.0, 5.2, 1-H2), 1.34 (dddd, J=13.1, 12.9, 10.9, 3.6, 1-H5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.05 (C7), 71.69 (C3), 56.03 (C4), 51.75 (*C*H_3), 39.21 (C1), 34.00 (C2), 30.31 (C5), 25.74 (C6). ESIMS (m/z, H_2O:MeOH:AcOH 1:1:0.05), 174.2 ($M+H^+$).

3.5. *Preparation of methyl* c-*4-(*tert-*butoxycarbonylamino)*-t-*3-hydroxy*-r-*1-cyclohexanecarboxylate* ***6***

To the solution of **5** (346 mg, 2.00 mmol) in acetone (15 mL), Boc_2O (572 mg, 2.60 mmol) and *N*,*N*-diisopropylethylamine (0.35 mL, 2.0 mmol) were added. The solution was stirred overnight at 26°C. The solvent was removed under reduced pressure affording a yellowish oil which was purified by LC (CH_3OH:$CHCl_3$ 5:95) and crystallization from Et_2O–hexane after which pure **6** was obtained as white crystals. Yield was 410 mg (75%). Mp: 79–80°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3-CH_3), 3.62 (ddd, J=9.2, 8.1, 4.0 Hz, 1-H3), 3.40 (ddd, J=9.2, 8.3, 3.7, 1-H4), 3.13 (bs, 1-O*H*), 2.78 (dddd, J=4.9, 4.9, 4.9, 4.9, 1-H1), 2.26 (dddd, J=13.6, 5.0, 4.1, 1.1, 1-H2′), 2.00–1.87 (m, 2-H6′, H5′), 1.66–1.54 (m, 2-H6, H2), 1.44 (s, 9-3CH_3, Boc; m, 1-H5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.12 (C7), 156.67 (*C*=O, Boc), 79.98 (C, Boc), 70.73 (C3), 54.66 (C4), 51.71 (*C*H_3), 38.18 (C1), 33.66 (C2), 28.32 (3*C*H_3, Boc),

27.18 (C5), 25.16 (C6). ESIMS (m/z, CH_3Cl:MeOH 1:1, 1×10^{-5} M NaCl) 296.2 (100%, $M+Na^+$), 569.4 (70%, $2M+Na^+$). Anal. calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.31; H, 8.40; N, 4.89.

3.6. *Preparation of methyl* cis-*4-(*tert-*butoxycarbonylamino)-3-oxo-1-cyclohexanecarboxylate* ***7***

To the solution of **6** (164 mg, 0.60 mmol) in DMF (4 mL) PDC[14] (1.352 g, 3.6 mmol) was added. The solution was stirred at 26°C for 24 h, diluted in water (25 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with 5% $CuSO_4$ aq. (10 mL) and dried ($MgSO_4$). After Et_2O evaporation, **7** was obtained as a colorless oil. Yield was 140 mg (86%). According to ^1H, ^{13}C NMR, and ESIMS this compound was pure. ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (d, J=6.0, 1-NH), 4.16 (ddd, J=12.2, 6.0, 6.0, 1-H4), 3.65 (s, 3-CH_3), 3.16 (dddd, J=6.6, 6.6, 2.3, 2.3, 1-H1), 2.79 (ddd, J=14.5, 2.3, 2.3, 1-H2′), 2.47 (ddd, J=14.5, 6.6, 1.1, 1-H2′; m, 1-H5′), 2.19 (dddd, J=14.3, 6.6, 3.1, 3.0, 1-H6′), 2.05 (dddd, J=14.3, 13.4, 3.1, 3.0, 12-H6, H2), 1.44 (s, 9-3CH_3, Boc; m 1-H5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.46 (C3), 173.89 (C7), 155.33 (*C*=O, Boc), 79.63 (C, Boc), 58.59 (C4), 52.08 (C8), 42.20 (C1), 41.25 (C2), 30.95 (C5), 28.23 (3*C*H_3, Boc), 25.92 (C6). ESIMS (m/z, CH_3Cl:MeOH 1:1, 1×10^{-5} M NaCl) 293.3 ($M+Na^+$).

3.7. *The X-ray structure and conformation in solution of* ***6***

$C_{13}H_{23}NO_5$, M_r=273.32 g mol^{-1}, white, crystal size 0.17×0.20×0.20 mm, a=23.404(5), b=6.7550(10), c=19.285(4) Å, β=99.60(3)°, V=3006.1(10) $Å^3$, T=293(2) K, monoclinic, C2/c, Z=8, D_c=1.208 g cm^{-3}, μ=0.766 mm^{-1}, extinction coefficient 0.0023(2) final R_1=0.046, wR_2=0.123, S=1.05 for 265 parameters and 2361 unique observed reflections with $I\geq2\sigma(I)$.

The crystals of **6** were grown from Et_2O–hexane solution. The measurements were done on a Kuma KM4 κ-axis diffractometer with graphite-monochromated Cu-Kα radiation (λ=1.54178 Å). No absorption correction was applied. The structure was solved by direct methods (program SHELXS97[16]). All hydrogen atoms were found from ΔF^2 syntheses. A full-matrix least-squares refinement (program SHELXL97[17]) of all the non-hydrogen atom coordinates with anisotropic displacement parameters and hydrogen atom coordinates with isotropic displacement parameters was performed.

The molecular structure of **6** (Fig. 3) indicates the chair conformation of the cyclohexane ring with two equatorial groups (-NHBoc and -OH) and one axial group (-CO_2CH_3). The analysis of the ^1H NMR spectrum suggests that the same conformation predominates in solution. The coupling constants of H3 and H4 signals (H3 $^3J_{3a,4a}$=9.2 Hz, $^3J_{3a,2a}$=8.1 Hz, $^3J_{3a,4e}$=4.0 Hz; H4 $^3J_{4a,3a}$=9.2 Hz, $^3J_{4a,5a}$=8.3 Hz, $^3J_{4a,5e}$=3.7 Hz) indicate their axial positions (two *anti*-periplanar and one *gauche* couplings), whereas the coupling constants of H1 signals, four small couplings (^3J=4.8, 4.8, 4.8, 4.8 Hz), indicate its equatorial position (Fig. 4). The *anti*-periplanar couplings of H3 and H4 are somewhat lower than expected from the Karplus relation. This may suggest a presence of some amount of other conformations in solution.

According to the literature data, the tendency to assume the conformation with the -CO_2CH_3 group in the axial position is also visible in the molecular structure of methyl *t*-3-(*tert*-butoxycarbonylamino)-*c*-4-hydroxy-*r*-1-cyclohexanecarboxylate, but in the molecular structure of methyl *c*-4-(*tert*-butoxycarbonylamino)-*c*-3-hydroxy-*r*-1-cyclohexanecarboxylate the -NHBoc group is in an axial position and the two remaining groups are in equatorial positions.[18]

Molecules of **6**, alternately both enantiomers, linked along the [010] direction of the crystal form linear chains via the OH···O and NH···O hydrogen bonds. There are no directional interactions between neighboring chains.

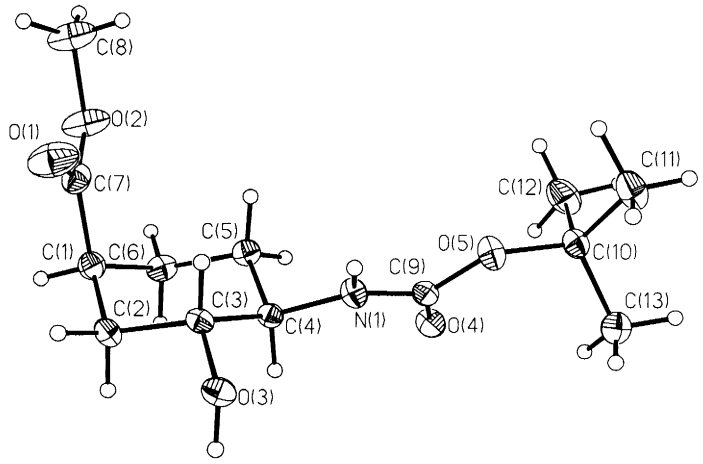


Fig. 3. ORTEP[19] drawing of the molecular structure of **6** (one of the enantiomers)

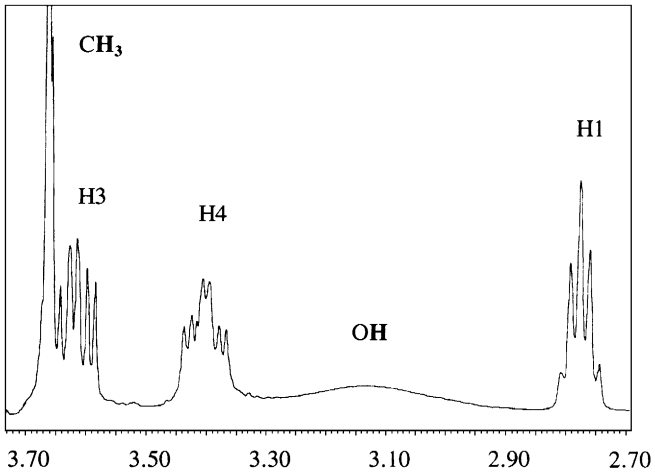


Fig. 4. The fragment of the ^{1}H NMR spectrum of **6** in $CDCl_3$ (300 MHz)

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