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Synthesis and Stereostructure of 3-Amino-5- and -6-hydroxybicyclo[2.2.1]heptane-2-carboxylic Acid Diastereomers

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Summary. *All-endo*-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid and two epimers of 3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid were prepared *via* 1,3-oxazine or γ-lactone intermediates by the stereoselective functionalization of *endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid derivatives. Their structures were proved by IR and NMR spectroscopy, with the use of HMQC, HMBC, DEPT, and DIFFN*O*E techniques.

Keywords. Amino acids; Heterocycles; IR spectroscopy; NMR spectroscopy; Cyclization.

Introduction

During the past decade considerable attention has been directed towards the synthesis of hydroxy-β-amino acids [1–6]. These compounds constitute an important class of amino acids, because of their occurrence in many biologically relevant compounds, including Paclitaxel (Taxol) and Docetaxel (Taxotere), which are among the most effective chemotherapeutic agents [7, 8]. The alicyclic hydroxy-β-amino acids can be used as building blocks for the preparation of modified analogues of biologically active peptides [9, 10]. Hydroxylated alicyclic β-amino acids and their derivatives can be widely used for the synthesis of various heterocyclic compounds [11–17]. Our present aim was the synthesis and structure analysis of the title hydroxylated alicyclic β-amino acids.

Results and Discussion

The key step in the synthesis of *all-endo*-3-amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**4**) was the stereoselective iodolactonization [15] of *N-Boc*-

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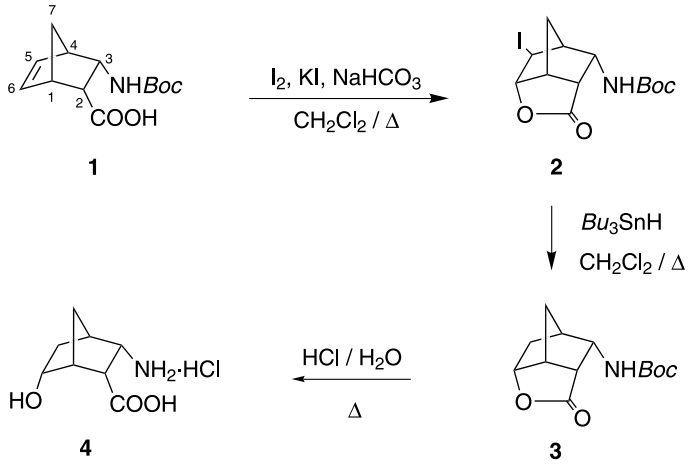
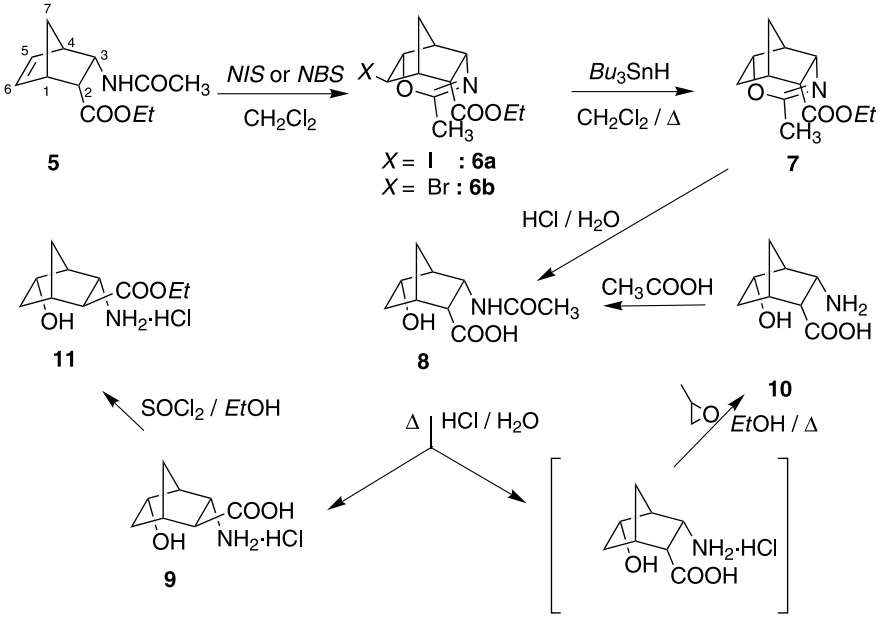


Scheme 1

endo-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**1**). The iodolactonization was performed under two-phase conditions, furnishing iodolactone **2**, which was reduced with Bu_3SnH to give lactone **3**. The *N-Boc* lactone was converted to the *all-endo* isomer of hydroxy-amino acid **4** by acidic hydrolysis (Scheme 1).

When *N*-acetylamino ester **5** was reacted with *N*-iodosuccinimide [16] (*NIS*) or *N*-bromosuccinimide (*NBS*) a tricyclic 1,3-iodo- or -bromooxazine derivative (**6a** or **6b**) was obtained stereoselectively. When dehalogenated with Bu_3SnH under an argon atmosphere, **6a** or **6b** yielded **7**. The hydrolysis of oxazine **7** with dilute



Scheme 2

hydrochloric acid at room temperature gave *N*-acetyl-hydroxy amino acid **8**. When **8** was boiled in acidic solution, *endo* → *exo* isomerization took place and the forced conditions resulted in 3,5-di-*endo*-2-*exo*-3-amino-5-hydroxybicyclo[2.2.1] heptane-2-carboxylic acid hydrochloride (**9**) as the main product. The mother liquor was treated with a large excess of propylene oxide and, after fractional crystallisation, compound **10** was isolated as a diastereomerically enriched (8:2) mixture (Scheme 2). The correct configurations of hydroxylated amino acids **9**

Table 1. Characteristic IR frequencies[a] and ^{1}H NMR data[b] for compounds **2**–**5**, **7**–**9**, and **11**[c]

Compound	Amide-I band[d]	νC=O band[e]	CH_3 s(9H)[f]	CH_3 *t*(3H)[g]	CH_2 *qa*(2H)[g]	NH broad[h]
2	1688	1788	1.44	–	–	4.15[r]
3	1693	1775	1.42	–	–	4.81[r]
4	–	1763	–	–	–	4.67
5	1654	1730	1.86	1.20	4.04	6.4
7	1676	1733	1.86	1.24	4.10	–
8	1680	1732	2.35	–	–	12.9
9	–	1714	–	–	–	∼12.6
11	–	1732	–	1.21	4.10	∼7.9

Compound	Norbornane/ene moiety						
	H–1[i]	H–2[k]	H–3′[l]	H–4′[m]	H–5[n]	H–6[o]	CH_2(7)[p]
2	3.24	2.80	4.15[r]	2.90	∼4.9	5.17	1.94, 2.34
3	3.24	2.78	4.11	2.56	∼1.75	4.81[r]	1.58, 1.73
4	3.40	2.95	3.82	2.63	1.82, 1.90	5.01	1.70, 1.77
5	3.10[r]	3.13	4.72	3.10[r]	6.14	6.27	1.35, 1.45
7	2.08	3.02	4.03	2.35	4.55	2.02, 2.19	1.41, 1.48
8	∼2.45[r]	3.25	4.24	∼2.45[r]	5.21	1.75, 2.20	1.53, 1.64
9	2.36	2.54[r]	3.76	2.52[r]	4.35	1.22, 2.05	1.26, 1.33
11	2.35	2.59	3.77	2.54	4.35	1.23, 2.07	1.27, 1.33

[a] In KBr discs (cm^{-1}); further bands, νOH band: ∼3345 (**9**), 3460 (**11**), νNH band: ∼3230 (**2**), 3247 (**3**), 3318 (**5**), coalesced νOH (acidic & alcoholic) and/or νN^+H_3 bands: 3250–2250 (**4**), 3600–3250 (**8**), 3500–2500 (**9**, **11**), νC–O: 1014 (**2**), 1167 (**3**), 1108 (**4**), 1182 and 1047 (**5**), 1184 and 1060 (**7**), 1185 and 1155 (**11**); [b] in $CDCl_3$ solution (D_2O for **4** and *DMSO*-d_6 for **8**, **9**, and **11**) at 500 MHz; chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz; [c] assignments were supported by HMQC (except for **2**), for **5**, **7**, **9**, and **11** by HMBC, and for **8** and **11** also by DIFFN*O*E measurements; [d] urethane group (**2**, **3**), νC=N band (**7**); [e] COOH (**1**, **4**, **8**, and **9**), lactone (**2** and **3**), COOEt (**5**, **7**, and **11**); [f] 3H (**5**, **7**, and **8**); [g] ethyl group, *J*: 7.1; [h] Intensity 1H (**2**, **3**, **5**, and **9**), 2H (**8**), coalesced signal of the acidic protons and the solvent (**4**), or the amide-NH and COOH (**8**), or the OH and NH_3^+ groups (**11**), *d* (*J*: 6.5, **5**); [i] ∼*t* (**2**, **4**, and **7**), ∼*s* (**9**) with coalesced lines, *t* (*J*: 4.7 for **3**), *d* (*J*: 4.5 for **11**); [k] *dd*, *J*: 10.3 and 4.7 (**2**–**4**), ∼*dd* (**5**), *ddd* (**7**), *td* (**8**) with coalesced lines, *d*, *J*: 4.3 (**9**), 5.1 (**11**); [l] broad *m* (**2**), ∼*t*(**3**), ∼*d*, *J*: 9.3 (**4**), 4.3 (**9**), *dt*, *J*: 8.9 ad 3.5 (**5**), *m* (**7**, **8**, and **11**); [m] signals with coalesced lines, *m* (**2**, **5**, and **8**), ∼*s* (**3**, **4**, and **9**), ∼ *t* (**7** and **11**); [n] broad *m* (1H) for **2** and **7**–**9**, *dd*, *J*: 5.6 and 2.9 (**5**), *m* (2H) for **3**, 2 × *m* (2 × 1H) for **4**, *m* for **11**; [o] *d* (1H), *J*: 5.0 (**2**), *m* (2H, **3**), *t* (1H), *J*: 6.3 (**4**), *dd* (1H), *J*: 5.6 and 3.0 (**5**), 2 × *m* (2 × 1H, **7**–**9**, and **11**); [p] *AB*-type multiplet, 2 × *d* (2 × 1H), *J*: 11.8 (**2** and **4**), 11.2 (**3**), 9.0 (**5**), 10.8 (**7** and **8**), ∼10 (**9**), 11.5 (**11**), further split by long-range couplings of downfield/upfield *d* to *td*′ (**2**/**7**), both doublets to *dd* (**9**) and downfield *d* to *m* (**7** and **8**), respectively; [r] overlapping signals

and **10** were proved indirectly. The stereostructures of **8** and **11** being demonstrated using the DIFFN*O*E technique and also by chemical transformation: esterification of **9** led to hydroxylated amino ester **11**, whereas after acetic acid treatment **10** gave an *N*-acetyl derivative. The NMR spectrum of the resulted compound was identical with that of *all-endo*-3-acetylamino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid (**8**).

The constitutions and stereostructure of the new compounds **2**–**5** and **7**–**11** were determined by IR, ^{1}H, and ^{13}C NMR spectroscopy. The spectral data are self-explanatory; only a few additional remarks are necessary. It should be noted that, for easier comparison of analogous spectral data, the numbering of **1** given in Scheme 1 will be used for all compounds in this section and also in the experimental part.

1) The di-*endo* arrangement of the 2,3-substituents in **2**–**5**, **7**, and **8** follows from our ''splitting rule'' [17, 18]. In consequence of the dihedral angles of *ca*. 90°, the 1,2- and 3,4-vicinal H,H-couplings do not cause double spliting of the H–2 and H–3 signals in the di-*exo* compounds, whereas these couplings lead to a well-detectable split by 2–4 Hz in the case of the di-*endo* anellated molecules,

Table 2. ^{13}C NMR chemical shifts[a] of compounds **2**–**5**, **7**–**9**, and **11**[b]

Compound	CH_3[c]	CH_2	C_{quat} or CH_3[d]	OC=O[e]	C=O[f] or C=N
2	28.7	–	81.0	176.6	155.8
3	28.7	–	80.4	178.1	155.9
4	–	–	–	179.9	–
5	14.5	60.9	23.8	173.8	170.1
7	14.7	60.3	21.9	172.2	156.6
8	–	–	19.9	172.0	171.1
9	–	–	–	174.8	–
11	14.9	61.5	–	173.5	–

	Norbornane/ene moiety[g]						
Compound	C–1	C–2	C–3	C–4	C–5	C–6	CH_2(7)
2	51.4	41.8	54.6	48.2	24.5	89.6	35.6
3	47.8	43.4	54.1	40.7	32.5	81.1	35.6
4	48.4	42.1	53.9	39.7	31.1	83.1	35.3
5	47.6[h]	47.7[h]	52.5	47.4[h]	134.3	137.6	48.0
7	34.5	50.1	50.3	36.8	73.4	33.2	37.9
8	34.7[h]	48.9	46.1	36.9[h]	79.3	32.6	36.1
9	42.7	51.3	54.7	43.3	72.6	40.2	35.2
11	42.8	51.2	54.8	43.3	72.5	40.1	35.2

[a] In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz, solvent: $CDCl_3$ (for **4** D_2O, for **8**, **9**, and **11** *DMSO*-d_6); [b] assignments were supported by DEPT, HMQC (except for **2**), and for **5**, **7**, **9**, and **11** also by HMBC measurements; [c] *t*-butyl (**2**, **3**) or ethyl (**5**, **7**, and **11**); [d] quaternary carbon (*t*-butyl, **2** and **3**), methyl (acetyl, **5** and **8** or oxazoline **7**); [e] lactone (**2**, **3**), carboxyl (**4**, **8**, and **9**), ester (**5**, **7**, and **11**); [f] carbamoyl (**2**, **3**), amide (**5**, **8**), C=N for **7**; [g] for the numbering used in tables and in the spectroscopic part of the text, see **1** (Scheme 1); [h] interchangeable assignments

where the dihedral angles are *ca*. 30°. Hence, as a consequence of the H–2, H–3 interaction, H–2 and H–3 exhibit doublets in the di-*exo* derivatives and double doublet signals in the di-*endo* analogues. The H–2,3 coupling results in a 7–11 Hz split due to the dihedral angle of 0° for the di-*endo* and di-*exo* anellated compounds [17], while this coupling constant is expected to be smaller (*ca*. 4–6 Hz) for *exo–endo* derivatives [19], where the dihedral angle is *ca.* 109°. Thus, the *dd* (**2**–**4**), *dt* (**5**), *ddd* (**7**), or *td* (**8**) split of the H–2 (**2**–**5**) or H–3 (**7**, **8**) signal confirms the 2,3-di-*endo* configuration. Higher than *dd* splits are due to couplings with the NH (**5**) or H–7 (*exo*) (**7**, **8**). The similar ^{13}C NMR chemical shifts in **3** and **4** demonstrate the unaltered *all-endo* orientation of the three substituents in **4** as compared with **3**.

In the ^{1}H NMR spectrum of **9**, the H–2 and H–3 signals are doublets, split by 4.3 Hz, and consequently this molecule must have the *endo–exo* configuration. In accordance, the C–1 and C–4 chemical shifts in **9** are dramatically higher (by 8.0 and 8.6 ppm) because of the absence of a field effect [20] causing opposite shifts to those in **8**, due to very strong hindrance between the three *endo* substituents. Hence, during the acidic hydrolysis of **8**, *endo* → *exo* isomerisation occurred, probably in position **2**, *via* the enolic form of the carboxyl group.

The practically identical ^{13}C NMR chemical shifts of **9** and **11** confirm analogous stereostructures for these molecules. For **11**, DIFFN*O*E measurements unambiguously proved the 2-*exo*-3-*endo* configuration. On saturation of the H–2 doublet (at 2.59 ppm), for example the H–6(*exo*) signal (at 1.24 ppm) responded, while for the H–7(*endo*) signal an intensity enhancement was not observed. The DIFFN*O*E measurements together with the HMQC and HMBC spectra also furnished proof of the assignments.

2) In the ^{13}C NMR spectrum of **2** the very characteristic upfield-shifted line of iodo-substituted carbon (C–5) [20] appears at 24.5 ppm. The β-effect of the iodo substituent [20] is revealed in a downfield shift by 7.5 and 8.5 ppm of the C–4 and C–6 lines as compared with **3**. An anisotropic neighbouring deshielding effect of the iodine atom is also observable on the H–7 signals in the ^{1}H NMR spectrum, which are downfield-shifted in **2** (by 0.36 and 0.61 ppm) as compared with **3**. This supports the *ab ovo* more probable *exo* position of the iodine atom [to avoid the steric interaction between 2(*endo*)-I and O–4(*endo*)].
3) The ^{1}H NMR signal (a singlet of 9H intensity) of the methyl group and its carbon line in ^{13}C NMR spectrum, together with the line of the quaternary carbon atom, are proof of the presence of the *t-But* group in **2** and **3**.
4) The position of the hydroxy group in **4** follows from the structures of **2** and **3** containing a γ-lactone ring, the presence of which is proven by the high IR carbonyl frequency [23] (1788 and 1775 cm^{-1} in **2** and **3**).
5) In the spectra of **5**, **7**, and **11** all the IR, ^{1}H, and ^{13}C NMR signals of the COO*Et* group appear and the rigid structure of **7** results in a series of long-range couplings, which lead to higher multiplicities of all signals observed in this case only in the ^{1}H NMR spectrum.
6) The downfield shift of the methyl (*Ac*) signal (by 0.49 ppm) in the ^{1}H NMR spectrum of **8** relative to **5** is noteworthy; this is caused by the anisotropic effect [20] of the *endo*-OH group.

Experimental

Melting points were determined on a Kofler micro melting point apparatus. Elemental analyses were conducted with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyser; the results were found to be in good agreement (±0.2%) with the calculated values. Merck Kieselgel $60F_{254}$ plates were used for TLC: the eluent was toluene:*Me*OH = 4:1. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and *TMS* as internal standard. DEPT spectra were run in a standard manner, using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down". The HMQC and HMBC spectra were obtained by using the standard Bruker pulse programs.

(1S,2R*,3S*,4R*)-3-tert-Butoxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid* (**1**) [22]

To a solution of 3.1 g 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (20 mmol) [23] in 60 cm^3 of a 2:1 dioxane:H_2O mixture 20 cm^3 1 *M* NaOH were added. The solution was cooled to 0°C in an ice bath and di-*tert*-butyl dicarbonate was added slowly. The mixture was stirred at 0°C for 30 min and then warmed to room temperature and stirred for 4 h. The solvent was concentrated to 20 cm^3 on a rotatory evaporator, the *pH* was then adjusted to 2.5 with 10% H_2SO_4, and the resulting solution was extracted with *Et*O*Ac* (3×50 cm^3). The combined extracts were dried (Na_2SO_4), and evaporated, to give **1** as a white solid, which was recrystallized from iPr_2O. Yield 3.59 g (75%); mp 183–187°C (Ref. [24] 126–127°C).

(1S,2S*,3S*,6R*,7R*,9S*)-9-tert-Butoxycarbonylamino-2-iodo-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one* (**2**, $C_{13}H_{18}INO_4$)

To a solution of 2.25 g **1** (11.5 mmol) in 100 cm^3 CH_2Cl_2, 70 cm^3 $NaHCO_3$ solution (0.5 *N*), 11.62 g KI (70 mmol), and 5.84 g I_2 (23 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 20 h and then poured into 50 cm^3 10% aqueous $Na_2S_2O_3$ solution. The reaction mixture was extracted with 3×20 cm^3 CH_2Cl_2 and the combined extract was washed with 20 cm^3 brine, dried (Na_2SO_4), and evaporated. The residue was recrystallized from iPr_2O. Yield 3.66 g (84%); mp 183–187°C.

(1R,3R*,6R*,7R*,9S*)-9-tert-Butoxycarbonylamino-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one* (**3**, $C_{13}H_{19}NO_4$)

Bu_3SnH (4.8 cm^3, 18 mmol) was added to a solution of 4.41 g iodolactone **2** (9 mmol) in 65 cm^3 dry CH_2Cl_2 under Ar. After stirring for 20 h, at 40°C, the solvent was evaporated and the residue was crystallized from *n*-hexane, and recrystallized from iPr_2O-*Et*O*Ac*. Yield 1.26 g (55%); mp 145–150°C.

(1R,2R*,3S*,4R*,6R*)-3-Amino-6-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride* (**4**, $C_8H_{14}ClNO_3$)

Compound **3** (1.01 g, 4 mmol) was dissolved in 20 cm^3 aqueous HCl (20%) and the solution was stirred at room temperature for 10 h. The solvent was next evaporated and the residue was recrystallized from H_2O-acetone. Yield 0.70 g (84%); mp 220–222°C.

Ethyl (1S,2R*,3S*,4R*)-3-acetylaminobicyclo[2.2.1]hept-5-ene-2-carboxylate* (**5**, $C_{12}H_{17}NO_3$)

To a suspension of 2.17 g ethyl 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate hydrochloride [25] (10 mmol) in 40 cm^3 toluene, 2.04 g triethylamine (20 mmol), and 0.94 g acetyl chloride (12 mmol) were added and the reaction mixture was stirred at room temperature for 2 h, and then washed with 2×10 cm^3 H_2O. The aqueous layer was extracted with 3×20 cm^3 *Et*O*Ac*. The combined organic layer

was dried (Na_2SO_4) and evaporated. The residue was recrystallized from *n*-hexane-iPr_2O. Yield 1.67 g (75%); mp 64–67°C.

Ethyl (1R,2R*,3R*,7S*,8R*,10R*)-2-iodo-5-methyl-4-oxa-6-azatricyclo[5.2.1.0^{3,8}]dec-5-ene-10-carboxylate* (**6a**, $C_{12}H_{16}INO_3$) *and Ethyl(1R*,2R*,3R*,7S*,8R*,10R*)-2-bromo-5-methyl-4-oxa-6-azatricyclo[5.2.1.0^{3,8}]dec-5-ene-10-carboxylate* (**6b**, $C_{12}H_{16}BrNO_3$)
A solution of 1.67 g **5** (7.5 mmol) in 80 cm^3 CH_2Cl_2 was treated with 1.68 g *N*-iodosuccinimide (7.5 mmol) or 1.34 g *NBS* (7.5 mmol) and subsequently stirred for 14 h at room temperature. When the reaction was completed, the mixture was washed with 3×10 cm^3 10% NaOH solution. The aqueous solution was extracted with 3×40 cm^3 CH_2Cl_2, the organic phase was dried (Na_2SO_4), and evaporated. The oily products (**6a**: 1.92 g (73%); **6b**: 2.07 g (91%)) were sensitive to air; they were therefore used without purification in the next step.

Ethyl (1S,3S*,7S*,8S*,10R*)-5-methyl-4-oxa-6-azatricyclo[5.2.1.0^{3,8}]dec-5-ene-10-carboxylate* (**7**, $C_{12}H_{17}NO_3$)
Bu_3SnH (2.9 cm^3, 11 mmol) was added to a solution of iodo- or bromooxazine **6a** or **6b** (5.5 mmol) in 65 cm^3 dry CH_2Cl_2 under Ar. After stirring for 20 h at 40°C, the solvent was evaporated and the residue was purified by column chromatography on silica gel (*n*-hexane:*Et*O*Ac* = 10:1) to afford **7** as an oil (0.82 g (67%) from **6a**; and 0.84 g (69%) from **6b**).

(1S,2R*,3S*,4S*,5R*)-3-Acetylamino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid* (**8**, $C_{10}H_{15}NO_4$)
A solution of 0.67 g **7** (3 mmol) in 20 cm^3 20% aq. HCl was stirred for 2 h. The solvent was then evaporated to afford crude **8**, which was recrystallized from H_2O-acetone. Yield 0.51 g (80%); mp 225–235°C (dec).

(1S,2S*,3S*,4S*,5R*)-3-Amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride* (**9**, $C_8H_{14}ClNO_3$)
A solution of 0.4 g **8** (1.8 mmol) in 20 cm^3 20% aq. HCl was refluxed for 30 h. The solvent was then evaporated to afford crude **9**, which was recrystallized from *Et*OH-Et_2O. Yield 0.21 g (55%); mp 240–245°C (dec).

(1S,2R*,3S*,4S*,5R*)-3-Amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylic acid* (**10**, $C_8H_{13}NO_3$)
The mother liquor of **9** was evaporated and the residue was dissolved in dry *Et*OH. To this solution, 10 equivalents of propylene oxide were added. After stirring and refluxing for 2 h the mixture was evaporated to afford a mixture of **10**:**9** = 8:2 as solid crystals. Yield 0.1 g (32%); mp 230–235°C (dec).

Ethyl (1S,2R*,3S*,4S*,5R*)-3-amino-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate hydrochloride* (**11**, $C_{10}H_{18}ClNO_3$)
Thionyl chloride (0.5 cm^3, 7 mmol) was added dropwise with stirring to 5 cm^3 dry *Et*OH at −15°C. To this mixture 0.21 g **9** (1 mmol) were added in one portion, which was then stirred for 30 min at 0°C. After standing for 3 h at room temperature, the mixture was refluxed for a further 1 h and then evaporated. The residue was recrystallized from *Et*OH-Et_2O. Yield 0.22 g (93%); mp 210–211°C.

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