Synthesis of Derivatives of the Optically Active β-Amino Acids from (+)-Car-2-ene

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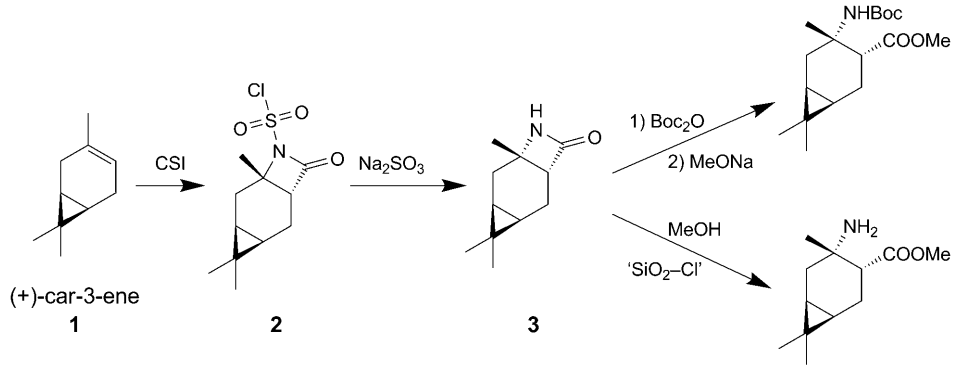
The reaction of (+)-car-2-ene (**4**) with chlorosulfonyl isocyanate (=sulfuryl chloride isocyanate; $ClSO_2NCO$) led to the tricyclic lactams **6** and **8** corresponding to the initial formation both of the tertiary carbenium and α-cyclopropylcarbenium ions (*Scheme 2*). A number of optically active derivatives of β-amino acids which are promising compounds for further use in asymmetric synthesis were synthesized from the lactams (see **16**, **17**, and **19**–**21** in *Scheme 3*).

Introduction. – In recent decades, optically active monoterpenes have often been considered as substrates for the synthesis of chiral reagents and as unique synthons in asymmetric synthesis [1]. Among the optically active monoterpenes used in stereoselective synthesis, car-3-enes and car-2-enes play an important role [2]; in particular, their N-derivatives are widely used. The chiral carenes containing N-atoms can be obtained by various methods, namely, by reactions involving organoboranes [3], reactions of car-3-ene with nitrosyl chloride [4], reactions of car-3-ene epoxide with amines [5–7] or sodium azide [8], by allyl amination of car-2-ene with selenium diimide [9], or by other methods. The reaction of monoterpenes with chlorosulfonyl isocyanate (=sulfuryl chloride isocyanate; CSI; $ClSO_2NCO$) is a convenient method for introducing both the amine and carbonyl functions into monoterpene molecules [10].

As is known [10][11], the reaction of (+)-car-3-ene (**1**) with CSI leads to the formation of compound **2** (*Scheme 1*), and reductive treatment of the latter furnishes bicyclic lactam **3** with a total yield of up to 76% after both steps. Methanolysis of **3** is possible after activation of the lactam group with the (*tert*-butoxy)carbonyl group [11], or by using 'silica chloride' as a catalyst, which can be prepared by the interaction of silica gel with $SOCl_2$ [12] (*Scheme 1*). At the same time, no data are currently available on the interaction of CSI with (+)-car-2-ene (**4**), which generally differs widely from (+)-car-3-ene (**1**) in its reactivity in reactions with electrophiles. The aim of the present work was the synthesis of derivatives of the optically active β-amino acids derived from commercially available (+)-car-2-ene (**4**).

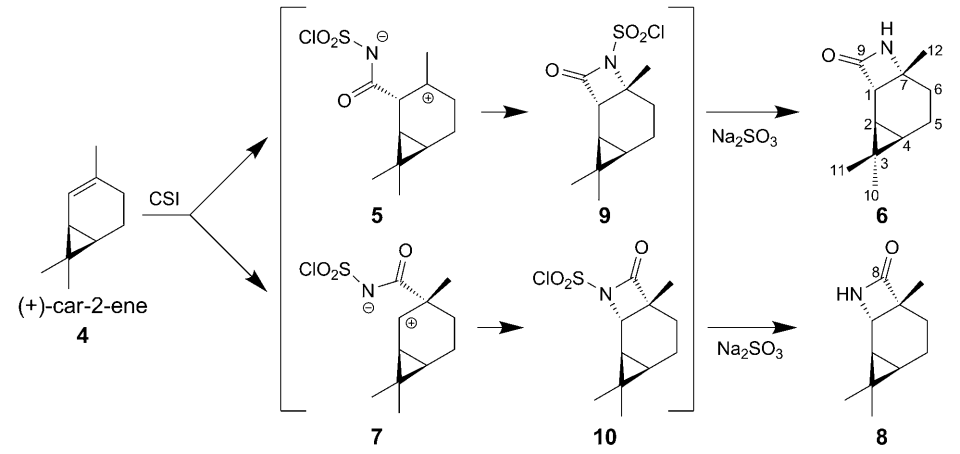
Results and Discussion. – We found that, according to its products, the reaction of (+)-car-2-ene (**4**) with CSI occurs by two routes, namely the formation of the tertiary carbenium ion **5** and the α-cyclopropylcarbenium ion **7** and, after treatment with Na_2SO_3, a mixture of the β-lactams **6** and **8** was isolated with a total yield of 79%

Scheme 1



(*Scheme 2*). The ratio **6**/**8** varied from 1:1.6 to 1:2.1 from run to run. In subsequent reactions, we used a 1:1.6 mixture of **6** and **8**. As in the case of (+)-car-3-ene (**1**), CSI was added exclusively on the side that is less sterically hindered, namely, *trans* to the cyclopropane ring.

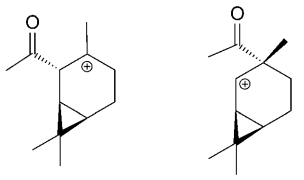
Scheme 2[1])



We performed calculations to determine the relative stability of the lactams **6** and **8**, as well as of the expected intermediates **9** and **10**. It appeared that **6** was slightly more stable than **8** (PBE/3z, $\Delta E = -1.4$ kcal/mol; B3LYP/6-311 + G*, $\Delta E = -1.0$ kcal/mol), although the product ratio suggested the opposite, and the precursor **9** was also more stable than its isomer **10** (PBE/3z, $\Delta E = -0.8$ kcal/mol; B3LYP/6-311 + G*, $\Delta E = -0.7$ kcal/mol). The carbenium ions **11** and **12** were used as models of the transition states/intermediates, and their relative stability was calculated. Cation **11**, which is a model for **5**, was less stable than **12** (PBE/3z, $\Delta E = 1.1$; B3LYP/6-311G*, $\Delta E = 3.8$), *i.e.*,

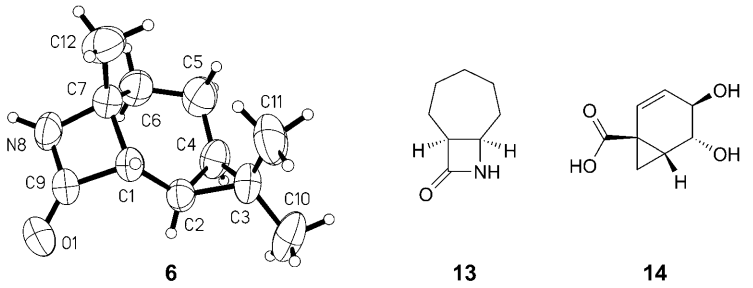
[1]) Arbitrary atom numberings; for systematic names, see *Exper. Part.*

it is assumed that the formation of **10** and, accordingly, lactam **8** is kinetically preferable, which explains the ratio of products **6** and **8** obtained in the experiment.



11 **12**

An attempt to separate lactams **6** and **8** by chromatography (silica gel) failed; the compounds could not be separated in pure form and significant amounts, although a tendency for separation was clearly observed. These compounds were ultimately separated by fractional recrystallization from hexane. The yield of pure lactam **6** was 47% based on its calculated content in the product mixture; the yield of lactam **8** was 28%. The structure of the products was elucidated by ^{1}H- and ^{13}C-NMR spectroscopy (*Table*) and confirmed by XRD data of lactam **6** (*Fig.*).



6 **13** **14**

Figure. *Structure of* **6**[1]) *and compounds with similar partial structures*

The four-membered ring of **6** is planar to an accuracy of ±0.023 Å; its bond lengths are close to the literature data, *e.g.*, for *cis*-8-azabicyclo[5.2.0]nonan-9-one (**13**) [13]. The six-membered ring has a screw-boat conformation similar to the one found for (1*S*,4*R*,5*R*,6*R*)-4,5-dihydroxybicyclo[4.1.0]hept-2-ene-1-carboxylic acid (**14**) [14]. In the crystal, the molecules of **6** are linked in a head-to-tail fashion by N(8)–H···O(1) H-bonds with the parameters N–H 0.99(3) and H···O 1.90(3) Å, and N–H···O 168(2)°. The molecular chains form layers parallel to the *ab* plane; the neighboring layers are rotated by 90°.

As in the case of (+)-car-3-ene (**1**) [11], attempts to achieve cleavage of the lactam ring in **6** and **8** with MeONa or HCl/Et_2O did not give the desired result, and the starting lactams remained unchanged in all cases.

At the same time, compound **15**, obtained by the reaction of lactam **8** with di(*tert*-butyl) dicarbonate (^{t}BuOC(=O)OC(=O)^{t}Bu; Boc_2O) in the presence of a catalytic amount of *N*,*N*-dimethylpyridin-4-amine (DMAP) (*Scheme 3*), readily underwent

Table. *^{13}C-NMR Data* (100.61 MHz, $CCl_4/CDCl_3$ 1:1) *of* **6**, **8**, *and* **15**–**21**. Chemical shifts in ppm[a]).

	6	**8**	**15**	**16**	**17**	**18**	**19**	**20**[b])[c])	**21**[b])
C(1)	51.6 (*d*)	51.6 (*d*)	54.8 (*d*)	51.5 (*d*)	53.5 (*d*)	51.4 (*d*)	47.9 (*d*)	49.7 (*d*)	41.5 (*d*)
C(2)	19.2 (*d*)	23.3 (*d*)	20.3 (*d*)	28.8 (*d*)	27.0 (*d*)	17.9 (*d*)	21.1 (*d*)	22.7 (*d*)	18 7 (*d*)
C(3)	17.9 (*s*)	16.9 (*s*)	16.9 (*s*)	18.0 (*s*)	18.5 (*s*)	17.5 (*s*)	18.1 (*s*)	16.9 (*s*)	17.9 (*s*)
C(4)	22.3 (*d*)	22.7 (*d*)	22.2 (*d*)	20.1 (*d*)	20.1 (*d*)	22.3 (*t*)	18.5 (*d*)	18.1 (*d*)	20.9 (*d*)
C(5)	17.9 (*t*)	15.4 (*t*)	15.4 (*t*)	16.5 (*t*)	16.3 (*t*)	16.6 (*t*)	15.8 (*t*)	16.3 (*t*)	15.5 (*t*)
C(6)	35.3 (*t*)	28.8 (*t*)	28.2 (*t*)	34.9 (*t*)	34.9 (*t*)	33.1 (*t*)	31.1 (*t*)	30.6 (*t*)	29.9 (*t*)
C(7)	53.1 (*s*)	52.0 (*s*)	50.3 (*s*)	46.0 (*s*)	44.6 (*s*)	58.0 (*s*)	51.3 (*s*)	49.9 (*s*)	53.9 (*s*)
C(8)		175.0 (*s*)	171.0 (*s*)	176.7 (*s*)	175.8 (*s*)				
C(9)	170.2 (*s*)					168.4 (*s*)	176.2 (*s*)	173.0 (*s*)	65.0 (*t*)
C(10)	27.6 (*q*)	28.1 (*q*)	28.0 (*q*)	28.7 (*q*)	28.3 (*q*)	27.2 (*q*)	28.7 (*q*)	29.3 (*q*)	29.1 (*q*)
C(11)	15.8 (*q*)	15.9 (*q*)	15.9 (*q*)	15.1 (*q*)	14.9 (*q*)	15.5 (*q*)	14.9 (*q*)	15.2 (*q*)	15.1 (*q*)
C(12)	24.6 (*q*)	18.7 (*q*)	18.4 (*q*)	23.1 (*q*)	23.2 (*q*)	22.0 (*q*)	24.7 (*q*)	24.7 (*q*)	23.0 (*q*)
C(13)			148.3 (*s*)	155.6 (*s*)	51.8 (*q*)	147.6 (*s*)	154.9 (*s*)	154.3 (*s*)	27.4 (*q*)
C(14)			82.6 (*s*)	78.5 (*s*)		82.5 (*s*)	78.3 (*s*)	76.5 (*s*)	
C(15)			28.1 (*q*)	28.5 (*q*)		28.0 (*q*)	28.3 (*q*)	28.3 (*q*)	
C(16)				51.4 (*q*)			51.8 (*q*)		

[a]) For the (arbitrary) atom numberings, see *Schemes 2* and *3* and the *Figure*. [b]) At 125.76 MHz. [c]) In (D_6)DMSO.

base-catalyzed methanolysis to give the substituted amino acid **16**. Acid-catalyzed deprotection of the amino group in **16** yielded the optically active β-amino acid ester **17**.

Similarly, from lactam **6**, we synthesized compound **18**, which was further subjected to base-catalyzed methanolysis. In contrast to amino ester **16**, its isomer **19** was readily hydrolyzed to the free acid **20** under the basic conditions and in the presence of even small amounts of H_2O. We obtained either a mixture of compounds **19** and **20** or only the substituted amino acid **20**, depending on the time of contact with H_2O.

Reduction of a mixture **19**/**20** with $LiAlH_4$ led to the formation of amino alcohol **21** in 60% yield based on the starting *N*-Boc-substituted β-lactam **18** (*Scheme 3*). A similar transformation was observed earlier [15] when a pinene-derived amido ester was reduced with $LiAlH_4$ to the (methylamino) alcohol.

Thus, we investigated for the first time the reaction of (+)-car-2-ene (**4**) with CSI and showed that the product mixture corresponded to the initial formation of the tertiary carbenium and α-cyclopropylcarbenium ions. The reactions of lactams **8** and **6** with Boc_2O and further methanolysis led to the optically active derivatives of β-amino acids (compounds **16**, **17**, and **19**–**21**). Due to the close position of the newly formed asymmetric centers to the cyclopropane ring, the chiral β-amino acids obtained in these reactions are promising compounds for further use in asymmetric synthesis. Indeed, as is known, the chiral ligands obtained from (+)-car-2-ene exceed by far (in asymmetric induction) the analogous ligands obtained from (+)-car-3-ene or α-pinene in syntheses of '*syn*'-aldols [16] and asymmetric allylboration [17].

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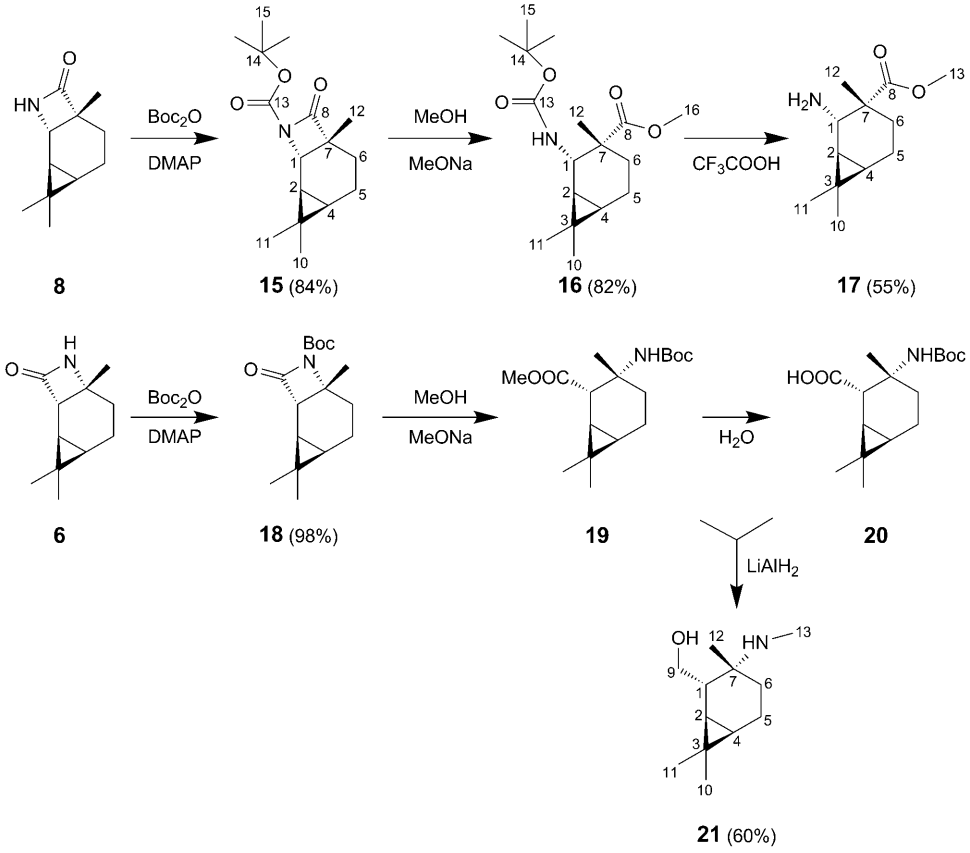
Scheme 3[1])



Experimental Part

1. *General.* $[\alpha]_D$: *Polamat-A* polarimeter; $CHCl_3$ solns. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500* (^1H: 500.13 MHz; ^{13}C: 125.76 MHz) and *AM-400* (^1H: 400.13 MHz; ^{13}C: 100.61 MHz) instruments; CCl_4/$CDCl_3$ 1:1 and (D_6)DMSO solns.; $CHCl_3$ was used as internal standard (δ(H) 7.24; δ(C) 76.90) or DMSO (δ(H) 2.50; δ(C) 39.50); δ in ppm, J in Hz; assignments based on geminal- and vicinal-proton J in ^1H,^1H double-resonance spectra, on ^{13}C-NMR spectra recorded with proton off-resonance saturation, on ^{13}C,^1H-2D-COSY (^1J(C,H) 135 Hz), and on ^{13}C,^1H-1D-LRJMD (J(C,H) 10 Hz) spectra. HR-MS: *Finnigan MAT-8200* instrument; in m/z.

Single-crystal X-ray structure determination: *Bruker P4* diffractometer with graphite-monochromated MoK_α (λ 0.71073 Å) radiation and ω data collection. The DTF calculations with the PBE functional were carried out with the PRIRODA program [18], and calculations with the B3LYP functional were carried out with the GAMESS program [19].

2. *Reaction of (+)-Car-2-ene* (**4**) *with Chlorosulfonyl Isocyanate (CSI).* CSI (1.044 g) was added to a soln. of **4** (1.000 g; *Fluka*; $[\alpha]_D^{20} = 88.6$ ($c = 1$, EtOH), ee > 99.5% (chiral GLC/MS)) in dry Et_2O (20 ml) at 0°. The mixture was stirred for 7 h at 0°. Then, a soln. of Na_2SO_3 (3 g) in H_2O (21 ml) was carefully added dropwise, while stirring and cooling the mixture; the pH was maintained at 7–8 by gradually adding a 20% KOH soln. in H_2O. The mixture was stirred for 2.5 h at r.t. Then, the aq. phase was

extracted with Et_2O, the combined org. phase dried ($MgSO_4$), and the solvent distilled off: **6**/**8** 1:1.6 (1.038 g, 79%). Fractional recrystallization of **6**/**8** from hexane gave **6** (0.187 g, 47%) and **8** (0.182 g, 28%) (yields based on the calculated contents in the product mixture).

(1S,2R,4R,7R)-3,3,7-Trimethyl-8-azatricyclo[5.2.0.0^{2,4}]nonan-9-one (**6**): M.p. 160–162°. $[\alpha]_{580}^{20} = -32.4$ ($c = 1.8$, $CHCl_3$). ^{1}H-NMR[1]): 0.81 (*s*, Me(11)); 1.06 (*s*, Me(10)); 1.27 (*s*, Me(12)); 0.74–0.94 (*m*, H_a–C(5), H–C(4), H–C(2)); 1.31 (*ddd*, *J*(6a,6e) = 13.0, *J*(6a,5a) = 13.0, *J*(6a,5e) = 4.0, H_a–C(6)); 1.72 (*ddd*, *J*(6e,6a) = 13.0, *J*(6e,5e) = 4.0, *J*(6e,5a) = 3.0, H_e–C(6)); 1.97–2.06 (*m*, H_e–C(5)); 2.61 (*d*, *J*(1,2) = 1.5, H–C(1)); 6.01 (br. *s*, NH). ^{13}C-NMR: *Table*. HR-MS: 136.1262 ($[M - CHNO]^+$, $C_{10}H_{16}^+$; calc. 136.1252).

(1S,2S,4R,7R)-3,3,7-Trimethyl-9-azatricyclo[5.2.0.0^{2,4}]nonan-8-one (**8**): M.p. 116–120°. $[\alpha]_{580}^{20} = -24.4$ ($c = 1.7$, $CHCl_3$). ^{1}H-NMR[1]): 0.84 (*s*, Me(11)); 1.04 (*s*, Me(10)); 1.16 (*s*, Me(12)); 0.63 (*d*, *J*(2,4) = 9.0, H–C(2)); 0.81–0.95 (*m*, H–C(5), H–C(4)); 1.41–1.50 (*m*, CH_2(6)); 1.88–1.98 (*m*, H′–C(5)); 3.16 (*s*, H–C(1)); 6.13 (br. *s*, NH). ^{13}C-NMR: *Table*. HR-MS: 136.1262 ($[M - CHNO]^+$, $C_{10}H_{16}^+$; calc. 136.1252).

Crystal Data of **6**: $C_{11}H_{17}NO$, M_r 179.26, crystal size $0.2 \times 0.4 \times 0.6$ mm; $a = b = 7.0157(7)$, $c = 43.888(6)$ Å, $V = 2160.2(4)$ Å^3, tetragonal, space group $P4_12_12$, $Z = 8$, $D_x = 1.102$ g cm^{-3}; $\mu(MoK_\alpha) = 0.070$ mm^{-1}, $\theta < 26°$; 2500 measured and 2136 independent ($R_{int} = 0.0222$) reflexions. The final indices are $R_1 = 0.0487$ for 1492 $I > 2\sigma(I)$, $wR_2 = 0.1320$, $S = 1.019$ for all I (186 parameters). Max. positive and max. negative electron density in the final *Fourier* synthesis are 0.111 and −0.110. The *Flack* absolute structure parameter is 0(3), so the absolute structure cannot be determined reliably. Intensity data were collected at 296(2) K and corrected for absorption by the integration method (transmission max–min: 0.987–0.961). The structure was solved by direct methods with SHELXS-97 [20] and refined by least-squares methods in the full-matrix anisotropic (isotropic for H-atoms) approximation with all F^2 and the SHELXL-97 program. H-Atoms were located from a difference *Fourier* map. CCDC-668951 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

3. *Reaction of* **8** *with Boc$_2$O*. Et_3N (20 µl), di(*tert*-butyl) dicarbonate (Boc_2O; 0.445 g), and cat. amounts of *N*,*N*-dimethylpyridin-4-amine were added to a soln. of **8** (0.182 g) in dry THF (3 ml). The mixture was stirred for 0.5 h at r.t. and refluxed for 2 h. The solvent was distilled off. The products were separated by CC (SiO_2 (8 g), AcOEt/hexane 0 → 100%): tert-*butyl (1S,2S,4R,7R)-3,3,7-trimethyl-8-oxo-9-azatricyclo[5.2.0.0^{2,4}]nonane-9-carboxylate* (**15**; 0.238 g, 84%). $[\alpha]_{580}^{20} = +20.3$ ($c = 7.2$, $CHCl_3$). ^{1}H-NMR[1]): 0.86 (*s*, Me(11)); 0.82–0.95 (*m*, 1 H–C(5), H–C(4)); 0.99 (*dd*, *J*(2,4) = 9, *J*(2,1) = 0.5, H–C(2)); 1.07 (*s*, Me(10)); 1.18 (*s*, Me(12)); 1.42–1.50 (*m*, CH_2(6)); 1.52 (*s*, *t*-Bu); 1.88–2.02 (*m*, 1 H–C(5)); 3.46 (*d*, *J*(1,2) = 0.5, H–C(1)). ^{13}C-NMR: *Table*. HR-MS: 223.1213 ($[M - C_4H_8]^+$, $C_{12}H_{17}NO_3^+$; calc. 223.1208).

4. *Methanolysis of* **15**. Cat. amounts of MeONa were added at r.t. to a soln. of **15** (0.361 g) in dry MeOH (10 ml). The mixture was stirred for 3 h, and the solvent was distilled off. Then, H_2O was added to the residue, the product extracted with $CHCl_3$ (3 × 5 ml), the extract dried ($MgSO_4$), and the solvent distilled off: *methyl (1S,2S,3R,6R)-2-{[(*tert*-butoxy)carbonyl]amino}-3,7,7-trimethylbicyclo[4.1.0]heptane-3-carboxylate* (**16**; 0.332 g, 83%). $[\alpha]_{580}^{20} = -56.0$ ($c = 6.8$, $CHCl_3$). ^{1}H-NMR[1]): 0.49 (*ddd*, *J*(4,2) = 9.2, *J*(4,5a) = 8.0, *J*(4,5e) = 1.2, H–C(4)); 0.64 (*dd*, *J*(2,4) = 9.2, *J*(2,1) = 5.0, H–C(2)); 0.97 (*s*, Me(10)); 0.99 (*s*, Me(11)); 0.92–1.06 (*m*, H_a–C(6)); 1.10 (*s*, Me(12)); 1.40 (*s*, *t*-Bu); 1.52 (*dddd*, *J*(5e,5a) = 15.0, *J*(5e,6a) = 7.5, *J*(5e,6e) = 1.2, *J*(5e,4) = 1.2, H_e–C(5)); 1.67 (*dddd*, *J*(5a,5e) = 15.0, *J*(5a,6a) = 12.0, *J*(5a,6e) = 8.0, *J*(5a,4) = 8.0, H_a–C(5)); 1.91 (*ddd*, *J*(6e,6a) = 14.0, *J*(6e,5a) = 8.0, *J*(6e,5e) = 1.2, H_e–C(6)); 3.15 (*dd*, *J*(1e,NH) = 10.3, *J*(1e,2) = 5.0, H_e–C(1)); 3.66 (*s*, MeO); 5.66 (*d*, *J*(NH,1e) = 10.3, NH). ^{13}C-NMR: *Table*. HR-MS: 311.2102 (M^+, $C_{17}H_{29}NO_4^+$; calc. 311.2096).

5. *Acidolysis of* **16**. CF_3COOH (0.3 ml) was added at 0° to a soln. of **16** (0.117 g) in dried CH_2Cl_2 (6 ml). The mixture was stirred at 0° for 2.5 h. Then it was neutralized with sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2, the extract dried ($MgSO_4$), the solvent distilled off, and the residue separated by CC (SiO_2 (4 g), AcOEt/hexane 0 → 100%): **16** (0.024 g). Subsequent elution with EtOH gave *methyl (1S,2S,3R,6R)-2-amino-3,7,7-trimethylbicyclo[4.1.0]heptane-3-carboxylate* (**17**; 0.035 g, 56% based on converted **16**). $[\alpha]_D^{24} = -21.2$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR[1]): 0.61 (*ddd*, *J*(4,2) = 9.3, *J*(4,5a) = 8.2, *J*(4,5e) = 1.2, H–C(4)); 0.8 (*dd*, *J*(2,4) = 9.3, *J*(2,1) = 5.0, H–C(2)); 0.89–1.00 (*s*, Me(11)); 0.95 (*m*, H_a–C(6));

1.01 (*s*, Me(10)); 1.27 (*s*, Me(12)); 1.53 (*dddd*, *J*(5e,5a) = 15.0, *J*(5e,6a) = 7.5, *J*(5e,6e) = 1.2, *J*(5e,4) = 1.2, H_e–C(5)); 1.79 (*dddd*, *J*(5a,5e) = 15.0, *J*(5a,6a) = 12.0, *J*(5a,6e) = 8.2, *J*(5a,4) = 8.2, H_a–C(5)); 1.97 (*ddd*, *J*(6e,6a) = 14.0, *J*(6e,5a) = 8.2, *J*(6e,5e) = 1.2, H_e–C(6)); 2.51 (*d*, *J*(1a,2) = 5.0, H_a–C(1)); 3.72 (*s*, MeO); 6.04 (br. *s*, NH_2). ^{13}C-NMR: *Table*. HR-MS: 211.1550 (M^+, $C_{12}H_{21}NO_2^+$; calc. 211.1571).

6. *Reaction of* **6** *with* Boc_2O. As described in *Exper. 3*, with Et_3N (20 µl), di(*tert*-butyl) dicarbonate (0.458 g), *N*,*N*-dimethylpyridin-4-amine, **6** (0.187 g), and THF (2 ml) (2.5 h at r.t. and reflux for 2 h). CC (SiO_2 (4.5 g), AcOEt/hexane 0 → 100%) gave tert-*butyl (1*S,*2*R,*4*R,*7*R*)-3,3,7-trimethyl-9-oxo-8-azatricyclo[5.2.0.0*^{2,4}*]nonane-8-carboxylate* (**18**; 0.285 g, 98%). $[\alpha]_D^{29} = +2.0$ ($c = 0.5$, $CHCl_3$). ^{1}H-NMR[1]): 0.77 (*s*, Me(11)); 1.01 (*s*, Me(10)); 1.38 (*s*, Me(12)); 1.47 (*s*, *t*-Bu); 0.65–0.76 (*m*, H_a–C(5)); 0.82–0.86 (*m*, H–C(2)); 0.83–0.93 (*m*, H–C(4)); 1.35 (*ddd*, *J*(6a,6e) = 13.0, *J*(6a,5a) = 13.0, *J*(6a,5e) = 4.0, H_a–C(6)); 1.92–2.02 (*m*, H_e–C(6), H_e–C(5)); 2.60 (*d*, *J*(1,2) = 2.0, H–C(1)). ^{13}C-NMR: *Table*. HR-MS: 136.1259 ([*M* – CNOBoc]$^+$, $C_{10}H_{16}^+$; calc. 136.1252).

7. *Methanolysis of* **18**. 7.1. Catalytic amounts of a MeOH soln. of MeONa were added at r.t. to a soln. of **18** (0.767 g) in dry MeOH (20 ml). The mixture was stirred for 3 h. The solvent was distilled off, and H_2O was added to the residue. The residue was washed with $CHCl_3$ (3 × 5 ml), and H_2O was distilled off to give **19**/**20** 1:1 (0.862 g, 100%).

7.2. Catalytic amounts of a soln. of MeONa were added at r.t. to a soln. of **18** (0.061 g) in dry MeOH (10 ml). The mixture was stirred for 3 h, and H_2O was added. The mixture was kept for 10 min at r.t., and the solvent and H_2O were distilled off. H_2O (10 ml) was added, and the pH of the soln. was adjusted to 3–4 with AcOH. The product was extracted with AcOEt (5 × 15 ml) and the solvent distilled off: **20** (0.067 g, 100%).

7.3. *Methyl (1*R,*2*S,*3*R,*6*R*)-3-{[(*tert-*Butoxy)carbonyl]amino}-3,7,7-trimethylbicyclo[4.1.0]heptane-2-carboxylate* (**19**): $[\alpha]_D^{23} = -34.7$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR[1]): 0.68 (*ddd*, *J*(6a,6e) = 14.0, *J*(6a,5a) = 12.0, *J*(6a,5e) = 6.8, H_a–C(6)); 0.70 (*dd*, *J*(4,2) = 9.0, *J*(4,5a) = 8.0, H–C(4)); 0.81 (*dd*, *J*(2,4) = 9.0, *J*(2,1) = 5.0, H–C(2)); 0.94 (*s*, Me(11)); 0.99 (*s*, Me(10)); 1.23 (*s*, Me(12)); 1.40 (*s*, *t*-Bu); 1.55 (*dd*, *J*(5e,5a) = 15.0, *J*(5e,6a) = 6.8, H_e–C(5)); 1.79 (*dddd*, *J*(5a,5e) = 15.0, *J*(5a,6a) = 12.0, *J*(5a,6e) = 8.0, *J*(5a,4) = 8.0, H_a–C(5)); 1.96 (*d*, *J*(1,2) = 5.0, H–C(1)); 2.45–2.58 (*m*, H_e–C(6)); 3.73 (*s*, MeO); 5.60 (br. *s*, NH). ^{13}C-NMR: *Table*. HR-MS: 311.2103 (M^+, $C_{17}H_{29}NO_4^+$; calc. 311.2091).

7.4. *(1*R,*2*S,*3*R,*6*R*)-3-{[(*tert-*Butoxy)carbonyl]amino}-3,7,7-trimethylbicyclo[4.1.0]heptane-2-carboxylic Acid* (**20**): $[\alpha]_D^{23} = -3.7$ ($c = 8.9$, 5% NaOH/H_2O). ^{1}H-NMR ((D$_6$)DMSO)[1]): 0.46 (*dd*, *J*(4,2) = 9.0, *J*(4,5a) = 8.0, H–C(4)); 0.58 (*ddd*, *J*(6a,6e) = 14.0, *J*(6a,5a) = 12.0, *J*(6a,5e) = 6.5, H_a–C(6)); 0.75 (*dd*, *J*(2,4) = 9.0, *J*(2,1) = 5.0, H–C(2)); 0.91 (*s*, Me(11)); 0.95 (*s*, Me(10)); 1.10 (*s*, Me(12)); 1.35 (*s*, *t*-Bu); 1.43 (*dd*, *J*(5e,5a) = 15.0, *J*(5e,6a) = 6.5, H_e–C(5)); 1.61 (*d*, *J*(1,2) = 5.0, H–C(1)); 1.57–1.67 (*m*, H_a–C(5)); 2.39 (*dd*, *J*(6e,6a) = 14.0, *J*(6e,5a) = 7.5, H_e–C(6)). ^{13}C-NMR: *Table*.

8. *Reduction of the Mixture* **19**/**20**. A suspension of $LiAlH_4$ (0.475 g) in dry THF (5 ml) was carefully added dropwise, while stirring and cooling the mixture to 0°, to a soln. of **19**/**20** (0.634 g; 1:1) in dry THF (20 ml). The mixture was boiled for 2 h. Then H_2O was added until H_2 ceased to evolve; the precipitate was filtered off and washed with Et_2O. The soln. was dried (Na_2SO_4): *(1*R,*2*S,*3*R,*6*R*)-3,7,7-trimethyl-3-(methylamino)bicyclo[4.1.0]heptane-2-methanol* (**21**; 0.239 g, 60% based on **18**). $[\alpha]_D^{23} = -15.8$ ($c = 0.9$, $CHCl_3$). ^{1}H-NMR[1]): 0.58–0.70 (*m*, H–C(2), H_a–C(6)); 0.88 (*s*, Me(11)); 0.85–0.94 (*m*, H–C(1), H–C(4)); 1.00 (*s*, Me(10)); 1.08 (*s*, Me(12)); 1.54–1.70 (*m*, CH_2(5), H_e–C(6)); 2.18 (*s*, Me(13)); 3.46 (*dd*, *J*(9,9′) = 10.8, *J*(9,1) = 2.0, H–C(9)); 4.21 (*dd*, *J*(9′,9) = 10.8, *J*(9′,1) = 2.4, H′–C(9)). ^{13}C-NMR: *Table*. HR-MS: 197.1768 (M^+, $C_{12}H_{23}NO^+$; calc. 197.1774).

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