Amino Acids, XIV; (±)-Pipecolic Acid Derivatives, IV[1]:

An Efficient Synthetic Method for the Preparation of (±)-Baikiain and its Derivatives

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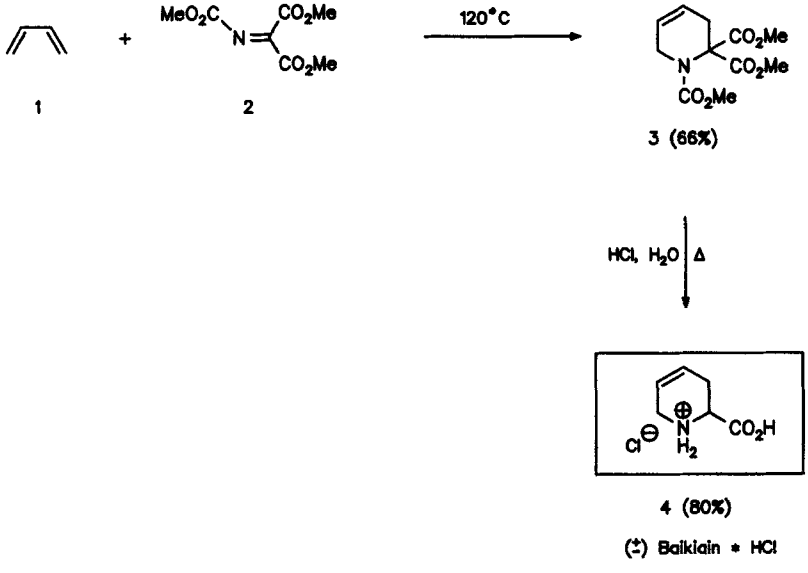
[4+2] Cycloaddition of the highly electrophilic imine **2** to 1,3-butadiene (**1**) furnished the Diels-Alder product **3**. Hydrolysis of the geminal diester provided (±)-Baikiain hydrochloride (**4**). Cis-Hydroxylation of the double bond of **3** afforded **8**. The trans product 9 was prepared via ring opening of the epoxide **5**. The regioselective hydroboration/oxidation of **3** provided **7** which was oxidized to **11**. Halolactonization of the *N*-tosyl derivative **12** of Baikiain furnished after functional group transformation the 2-hydroxymethyl-piperidine-4-ol **15**.

Aminosäuren, 14. Mitt.; (±)-Pipecolinsäure-Derivate, 4. Mitt.: Eine leistungsfähige Synthese für (±)-Baikiain und seine Derivate

[4+2] Cycloaddition des stark elektrophilen Imins **2** mit 1,3-Butadien (**1**) lieferte das *Diels-Alder* Produkt **3**. Durch Hydrolyse erhielt man racemisches Baikiainhydrochlorid (**4**). Die *cis*-Dihydroxyverbindung **8** konnte aus **3** durch Osmiumtetroxid-Oxidation gewonnen werden. Die dazu diastereomere *trans*-Verbindung **9** wurde durch Ringöffnung des Epoxids **5** erhalten. **3** wurde durch Hydroborierung und anschließende Oxidation in **11** umgewandelt. Die Halolactonisierung von **12** lieferte nach Enthalogenierung **14**, das zu **15** reduziert wurde.

S-Baikiain (*S*-**4**) (L-4,5-Didehydropipecolic acid) was isolated for the first time from the heartwood of *Baikiaea plurijuga* (Rhodesian teak)[2a] and later from the red algae *Serraticardia maxima*[2b]. The stereoselective synthesis of substituted pipecolic acids is a subject of current investigations[3]. *Hanson* has shown that (±)-Baikiain could easily transformed to pipecolic acid derivatives by iodolactonization procedure. Synthesis of (±)- Baikiain was accomplished employing an eight step reaction sequence starting from 1,4-dichloro-2-butyne in an overall yield of about 6%[2c]. Later on *Burgstahler* and *Aiman* showed that **4** could be prepared in 29% overall yield starting with *cis*-1,4-dichloro-2-butene[2d].

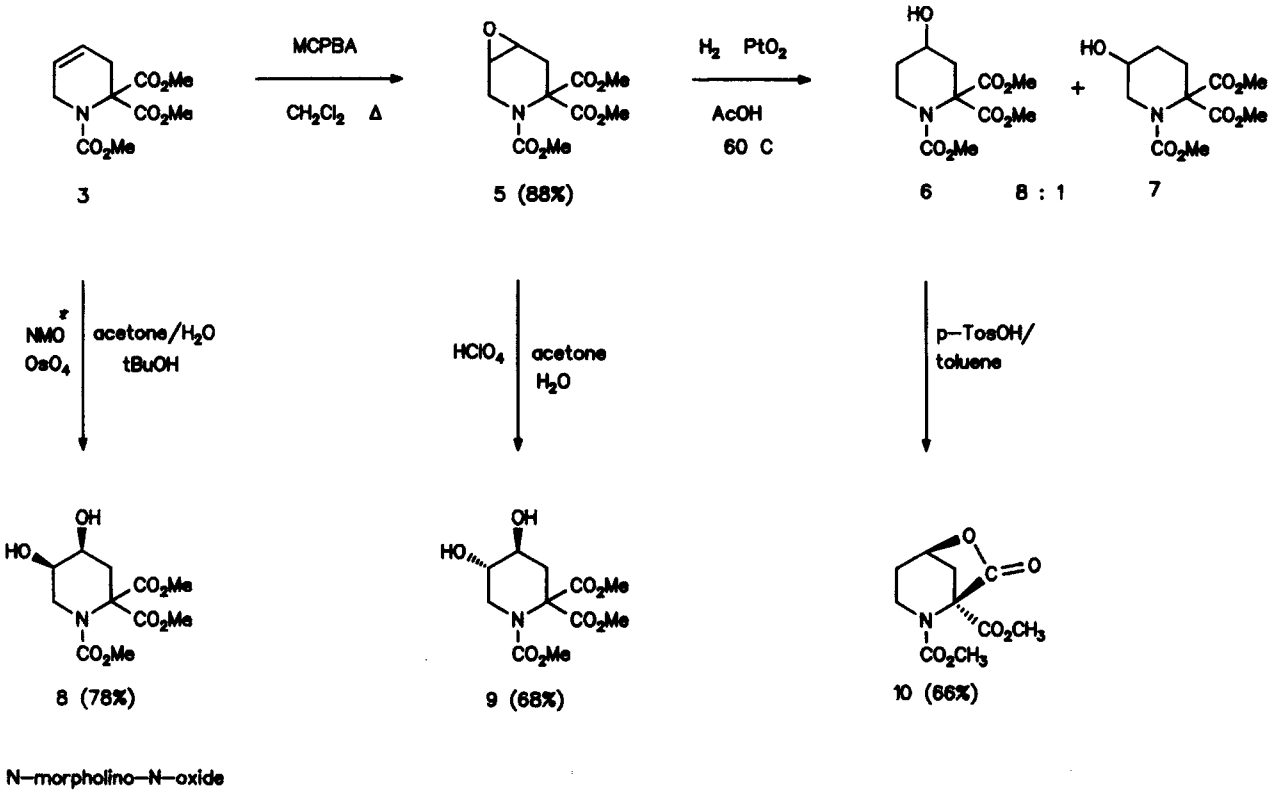
With the knowledge that the latter compound has considerable carcenogenicity we envisiged a synthesis of **4**, starting with the readily available imine **2** and 1,3-butadiene (**1**) in a hetero-*Diels-Alder* reaction. In part 1 of this serie[3g] we have shown that **2**[3g] and derivatives thereof were excellent dieneophiles for siloxy-1,3-butadienes in the [4+2] cycloaddition. Here we show that this is also true for 1,3-butadiene when heated together with **2** in a sealed tube. The cycloadduct **3** was isolated in 66% yield. Contrary to our former results, formation of ring open product was not detected[3g]. **3** could be smoothly hydrolized with concomitant decarboxylation to (±)-Baikiain hydrochloride **4** in an overall yield of 53% starting from **2**.



1 2 3 (66%) 4 (80%) (±) Baikiain • HCl

Scheme 1

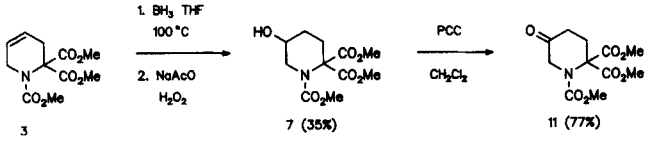
  0365-6233/93/0505-0297 $ 5.00 + .25/0



Scheme 2

This reaction sequence is suitable for large scale preparation of **4**. Moreover, **3** is an interesting building block for the synthesis of pipecolic acid derivatives. Epoxidation furnished **5** in high yield, which upon treatment with perchloric acid[4] provided **9** in moderate yield. On the other hand *cis*-dihydroxylation of **3** with OsO_4 yielded **8**.

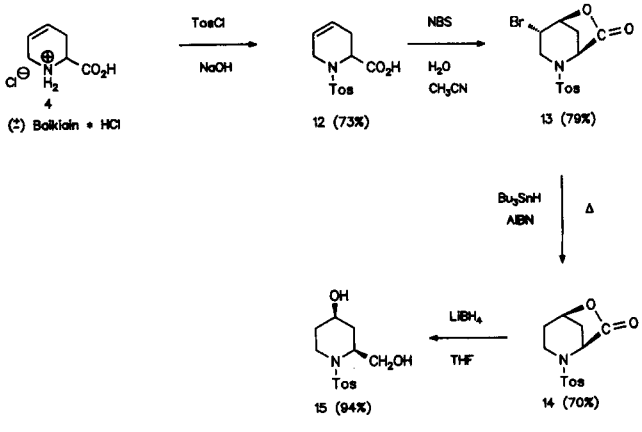
Catalytic hydrogenation of **5** with PtO_2/acetic acid gave a mixture of regioisomers **6** and **7** in a ratio of 8:1. As we have shown in a similar case[3g] facile lactonization occurred when **6** was heated with catalytic amounts of *p*-toluenesulfonic acid, furnishing **10** in 66% yield. Structural proof for **7** was accomplished by hydroboration of **3** (B_2H_6/THF) and oxidative workup with H_2O_2/NaOH.



Scheme 3

Surprisingly **7** was the only detectable regioisomer albeit in low yield (35%). **7** was oxidized with pyridinium chlorochromate to **11**, whose analytical data could be compared with the 4-oxo regioisomer, which was prepared by Aza-*Diels-Alder* reaction from **2** and 2-trimethylsiloxy-1,3-butadiene[3g]. In contrast (±)-methyl *N*-carbobenzoxy-baikiain-carboxylate gave after hydroboration and oxidative workup *trans* 4- and 5-hydroxypipecolic acid in a ratio of 28:72[5].

The regiospecifity of the hydroboration of **3** can be rationalized by the steric demand of the ester functionalities. Diborane attack at the double bond in 4-position is severely hindered by 1,3 interaction.- Tosylation of **4** produced crystalline **12**[6], which was converted by NBS to the bromolactonization product **13**[6]. Reductive debromination to the lactone **14** was accomplished with tributyl tin hydride/AIBN[7] in refluxing benzene. **14** was reduced with $LiBH_4$ in THF to **15**. As we have shown these two compounds were also synthesized by Aza-*Diels-Alder* reaction from *cis* and trans *4*-hydroxypipecolic acid[3g].



Scheme 4

We thank the Fonds der Chemischen Industrie for financial support and Mrs. *A. Betz* for the preparation of starting materials.

Experimental Part

General methods: ref. 3g

Dimethyl N-methoxycarbonyl-1,2,3,6-tetrahydropyridine-2,2-dicarboxylate (**3**)

In a glass vessel imine **2** (4.20 g, 20.67 mmol) and liquid **1** (3.41 g, 63.04 mmol) were mixed under N_2 at -20°C. The mixture was heated to 100°C for 30 min and then to 120° C for 6 h. After cooling the remaining oil was concentrated under reduced pressure and chromatographed on silica gel with $CHCl_3$/EtOAc 9+1. The solvent was evaporated and the oil crystallized. Recrystallization from ligroin/EtAc provided colorless crystals.- Yield 3.52 g (66%).- m.p. 81°C.- R_F = 0.44 ($CHCl_3$/EtOAc 9+1).- $C_{11}H_{15}NO_6$ (257.3) Calcd. C 51.4 H 5.88 N 5.4 Found C 51.3 H 6.06 N 5.2.- IR (KBr): 3060-2850; 1755; 1745 (C=O ester); 1710 (C=O); 1445; 1440; 1345; 1300; 1270; 1260; 1230; 1215; 1080; 1060; 1005; 960; 780; 730; 715 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.88 (2H, m, H-3), 3.76 (3H, s, OCH_3 urethane), 3.80 (6H, s, OCH_3 2x ester), 3.97 (2H, $J_{5,6}$ = 2.3 Hz, H-6), 5.65-5.78 (2H, m, H-5, H-4).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.16 (C-3), 43.99 (C-6), 53.11 (OCH_3 urethane + 2x ester), 67.06 (C-2), 121.51; 123.49 (C-4, C-5), 157.47 ($\underline{C}O_2CH_3$), 168.92 ($\underline{C}O_2CH_3$ 2x ester).

1,2,3,6-Tetrahydropyridine-2-carboxylic acid hydrochloride (**4**) *(Baikiain hydrochloride)*

3 (1.00 g, 3.89 mmol) war refluxed with acetic acid (10 ml) and conc. HCl (6 ml) for 12 h. The solvent was evaporated under reduced pressure and the residue triturated with acetone. The crystalline material was isolated by suction and dried.- Yield 508 mg (80%).- m.p. 260°C (ref.[2d]: 262-264°C).- $C_6H_{10}ClNO_2$ (163.6) Calcd. C 44.1 H 6.16 N 8.6 Found C 44.4 H 6.38 N 8.4.- IR (KBr): 3200-2600; 1745 (C=O); 1570; 1430; 1420; 1395; 1375; 1255; 1205; 1190; 1070; 935; 830; 770; 730; 680 cm^{-1}.- ^{1}H-NMR ([D_4]MeOH): δ (ppm) = 2.56 (1H, m, H_a-3), 2.77 (1H, m, H_e-3), 3.80 (2H, m, H-6), 4.19 (1H, dd, $J_{2a,3a}$ = 10.4 Hz, $J_{2a,3e}$ = 5.6 Hz, H_a-2), 5.83 (1H, m, H-5), 6.01 (1H, m, H-4).- ^{13}C-NMR ([D_4]MeOH): δ (ppm) = 25.94 (C-3), 42.91 (C-6), 54.21 (C-2), 121.10, 125.43 (C-4, C-5), 171.55 ($\underline{C}O_2D$).

Dimethyl 4,5-epoxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**5**)

A solution of **3** (600 mg, 2.33 mmol) in CH_2Cl_2 (20 ml) with MCPBA 55% (880 mg, 2.80 mmol) was refluxed for 24 h. The solution was brought to ambient temp. and treated with 0.5 N $Na_2S_2O_3$ (10 ml) and Na_2CO_3 solution (10 ml) with stirring. The mixture was extracted with CH_2Cl_2 (3x). The combined org. layers were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was recrystallized from hexane/EtOAc (3+1).- Yield 560 mg (88%), colorless crystals.- m.p. 106-107°C.- R_F = 0.67 ($CHCl_3$/MeOH 9+1).- $C_{11}H_{15}NO_7$ (273.2) Calcd. C 48.4 H 5.53 N 5.1 Found C 48.6 H 5.78 N 4.9.- IR (KBr): 3030-2840; 1745-1730 (C=O ester); 1700 (C=O urethane); 1440; 1380; 1325; 1295; 1260; 1240; 1200; 1180; 1145; 1060; 1040; 1035; 990; 930; 820; 795; 770; 735 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.63 (1H, d, $J_{3a,3e}$ = 14.7 Hz, H-3), 3.07 (1H, dd, $J_{3a,3e}$ = 14.7 Hz, $J_{3,4e}$ = 3.1 Hz, H-3), 3.27-3.37 (2H, m, H-4, H-5), 3.74 (3H, s, OCH_3 urethane), 3.78, 3.81 (6H, s, OCH_3 2x ester), 3.92 (2H, m, H-6).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.23 (C-3), 41.98 (C-6), 48.86 (C-4, C-5), 52.96, 53.26 (OCH_3 urethane + 2x ester), 65.53 (C-2), 157.04 ($\underline{C}O_2CH_3$ urethane), 168.38, 168.85 ($\underline{C}O_2CH_3$ 2x ester).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 31.80 (C-3), 41.56 (C-6), 48.24, 48.44 (C-4, C-5), 52.50, 52.73, 52.99 (OCH_3 urethane + 2x ester), 65.03 (C-2), 156.19 ($\underline{C}O_2CH_3$ urethane), 167.76, 168.14 ($\underline{C}O_2CH_3$ 2x ester).

Dimethyl 4-hydroxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**6**)*

5 (500 mg, 1.83 mmol) was hydrogenated in acetic acid (5 ml) over PtO_2 (50 mg) under pressure (30 bar) for 14 h at 60°C. After filtration and evaporation of the solvent the ratio of **6**:**7** was determined by ^{1}H-NMR-spectroscopy as 8:1. The oily residue was crystallized by trituration with diisopropyl ether at -30°C. Yield 352 mg (70%).- m.p. 104-105°C (hexane/EtOAc 2+1).- $C_{11}H_{17}NO_7$ (275.3) Calcd. C 48.0 H 6.23 N 5.1 Found C 48.2 H 6.43 N 5.1.- IR (KBr): 3555; 3450 (OH); 3010-2860; 1740 (C=O ester); 1690 (C=O urethane); 1455; 1450; 1370; 1260; 1230; 1225; 1205; 1110; 1070; 805; 780; 735 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.60-1.77 (2H, m, H_a-5, OH), 1.84-1.96 (1H, m, H_e-5), 2.33 (1H, dd, $J_{3a,3c}$ = 13.4 Hz, $J_{3a,4a}$ = 7.4 Hz, H_a-3), 2.48 (1H, dd, $J_{3a,3e}$ = 13.4 Hz, $J_{3e,4a}$ = 2.3 Hz, H_e-3), 3.36 (1H, ddd, $J_{6a,6e}$ = 13.3 Hz, $J_{5a,6a}$ = 7.9 Hz, $J_{5e,6a}$ = 4.4 Hz, H_a-6), 3.66-3.92 (2H, m, H_e-6, H_a-4), 3.74 (3H, s, OCH_3 urethane), 3.81 (6H, s, OCH_3 2x ester).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 31.30 (C-5), 39.25 (c-3), 39.59 (C-6), 52.80, 52.87, 52.91 (OCH_3 urethane + 2x ester), 63.38 (C-4), 67.66 (C-2), 157.40 ($\underline{C}O_2CH_3$ urethane), 168.75 ($\underline{C}O_2CH_3$ 2x ester).- MS: m/z = 275 ($M^{+\cdot}$, 2.2%), 257 (0.3), 243 (0.6), 216 (100), 199 (5), 184 (36), 172 (17), 160 (44), 156 (13), 152 (45), 140 (7), 128 (44), 100 (12), 94 (6), 68 (11), 59 (17).

* **6** was also prepared from Dimethyl *N*-Methoxycarbonyl-4-oxo-piperidine-2,2-dicarboxylate (see ref.[3g])

Dimethyl 5-hydroxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**7**)

In a glass vessel to **3** (100 mg, 389 µmol) in THF (5 ml) borane (0.50 ml, 500 µmol of 1M borane solution in THF) was added under N_2. This solution was heated for 12 h to 100°C. After cooling the mixture with 30% H_2O_2 (3 ml), H_2O (10 ml) and sodium acetate (1 g) was heated for 2 h at 50°C. The mixture was extracted with CH_2Cl_2 (5x). The combined org. layers were dried and evaporated. The oily residue was chromatographed on silica gel with $CHCl_3$/EtOAc 8+2. After evaporation of the solvent **7** crystallized at -30°C. Yield 37 mg (35%), colorless crystals.- R_F = 0.06 ($CHCl_3$/EtOAc 9+1).- m.p. 90°C (ligroin/Etac 2+1).- $C_{11}H_{17}NO_7$ (275.3) Calcd. C 48.0 H 6.23 N 5.1 Found C 47.6 H 6.40 N 5.0.- IR (KBr): 3530; 3460 (OH); 3040-2840; 1755; 1735 (C=O ester); 1685 (C=O urethane); 1450; 1380; 1295; 1260; 1235; 1200; 1175; 1090: 1050; 1020; 925; 785; 730 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.48 (1H, m, H_a-4), 1.78 (1H, m, H_e-4), 2.18 (1H, m, H_e-3), 2.51 (1H, ddd, $J_{3a,3e}$ = 13.2 Hz, $J_{3a,4a}$ = 7.1 Hz, $J_{3a,4e}$ = 3.9 Hz, H_a-3), 2.58 (1H, s, OH), 3.23 (1H, dd, $J_{6a,6e}$ = 13.3 Hz, $J_{5a,6a}$ = 7.2 Hz, H_a-6), 3.64 (1H, dd, $J_{6a,6e}$ = 13.3 Hz, $J_{5a,6e}$ = 3.6 Hz, H_e-6), 3.74 (3H, s, OCH_3 urethane), 3.81-3.88 (7H, m, OCH_3 2x ester, H_a-5).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.52 (C-3, C-4), 49.33 (C-6), 53.16, 53.30 (OCH_3 urethane + 2x ester), 64.24 (C-5), 68.78 (C-2), 157.77 ($\underline{C}O_2CH_3$ urethane), 168.90 ($\underline{C}O_2CH_3$ 2x ester).- ^{13}C-NMR ([D_4]MeOH): δ (ppm) = 29.62, 30.16 (C-3, C-4), 50.46 (C-6), 53.48, 53.79 (OCH_3 urethane + 2x ester), 65.22 (C-5), 70.31 (C-2), 159.33 ($\underline{C}O_2CH_3$ urethane), 170.10, 170.55 ($\underline{C}O_2CH_3$ 2x ester).- MS: m/z = 275 ($M^{+\cdot}$, 0.1%), 257 (3.2), 243 (1.3), 216 (100), 199 (13), 184 (53), 172 (1.2), 160 (1.2), 156 (5), 152 (5), 141 (5), 140 (6), 128 (4), 114 (13), 112 (16), 100 (4), 96 (14), 94 (22), 68 (12), 59 (17).

Dimethyl cis-4,5-dihydroxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**8**)

To N-methylmorpholine-*N*-oxide (210 mg, 1.55 mmol) dissolved in acetone/H_2O 1:1 (5 ml) was added first OsO_4 (20 mg, 79 µmol) in *t*-butanol (4 ml) at ambient temp. and then **3** (200 mg, 777 µmol) with stirring. After 21 h the reaction was quenched with $NaHSO_3$ solution (2.0 mmol) and extracted with CH_2Cl_2 (5x). The combined org. layers were dried (Na_2SO_4) and evaporated. The residue was triturated with ether and recrystallized from hexane/EtOAc 1+1. Yield 177 mg (78%) colorless crystals.- m.p. 120°C.- $C_{11}H_{17}NO_8$ (291.3) Calcd. C 45.4 H 5.88 N 4.8 Found C 45.6 H 6.09 N 4.8.- IR (KBr): 3500; 3445 (OH); 3040-2900; 1760; 1720 (C=O ester); 1690 (C=O urethane); 1450; 1375; 1305; 1230; 1210; 1090; 1040; 925; 780; 740 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.33 (1H, dd, $J_{3a,3e}$ = 13.7

Hz, $J_{3e,4a}$ = 2.3 Hz, H_e-3), 2.65 (1H, dd, $J_{3a,3e}$ = 13.7 Hz, $J_{3a,4a}$ = 7.2 Hz, H_a-3), 2.89 (2H, s, 2x OH), 3.56 (2H, m, H-6), 3.74 (3H, s, OCH_3 urethane), 3.81 (6H, s, OCH_3 2x ester), 3.85 (2H, m, H_a-4, H_e-5).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 35.45 (C-3), 45.07 (C-6), 53.20, 53.35, 53.44 (OCH_3, 2x ester + urethane), 66.06, 66.72 (C-4, C-5), 67.00 (C-2), 157.71 ($\underline{C}O_2CH_3$ urethane), 168.79, 168.93 ($\underline{C}O_2CH_3$ 2x ester).

Dimethyl trans-4,5-dihydroxy-N-methoxycarbonyl-piperidine-2,2-dicarboxylate (**9**)

To a solution of **5** (100 mg, 366 µmol) in acetone (4 ml) was added a mixture of $HClO_4$ (70%) (0.25 g)[4a,b]. The reaction was monitored by TLC. After 6 h the reaction was treated with NaCl-solution and the org. material was extracted with CH_2Cl_2 (5x). The combined extracts were dried, evaporated and the oily residue was triturated with EtOAc/pentane under cooling. Yield 73 mg (68%), colorless crystals.- m.p. 120°C (EtOAc/hexane 1+1).- $C_{11}H_{17}NO_8$ (291.3) Calcd. C 45.4 H 5.88 N 4.8 Found C 45.1 H 5.85 N 4.8.- IR (KBr): 3480; 3400 (OH); 3020-2890; 1755-1710 (C=O ester, urethane); 1440; 1360; 1250; 1220; 1100; 1080; 925; 775 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.15 (1H, dd, $J_{3a,3e}$ = 13.4 Hz, $J_{3a,4a}$ = 9.9 Hz, H_a-3), 2.58 (1H, dd, $J_{3a,3e}$ = 13.4 Hz, $J_{3e,4a}$ = 3.7 Hz, H_e-3), 2.96 (1H, dd, $J_{6a,6e}$ = 13.1 Hz, $J_{5a,6a}$ = 8.8 Hz, H_a-6), 2.99 (2H, s, 2x OH), 3.47 (1H, m, H_a-4), 3.65 (1H, m, H_a-5), 3.74 (3H, s, OCH_3 urethane), 3.80, 3.84 (6H, s+s, OCH_3 2x ester), 4.04 (1H, dd, $J_{6a,6e}$ = 13.1 Hz, $J_{5a,6e}$ = 4.3 Hz, H_e-6).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = = 36.76 (C-3), 46.81 (C-6), 53.32, 53.43, 53.51 (OCH_3, 2x ester + urethane), 68.66 (C-2), 69.51, 69.85 (c-4, C-5), 157.42 ($\underline{C}O_2CH_3$, urethane), 168.57 ($\underline{C}O_2CH_3$, 2x ester).

Methyl N-methoxycarbonyl-7-oxo-6-oxa-2-azabicyclo[3.2.1]octane-1-carboxyate (**10**)

6 (175 mg, 636 µmol) was heated with *p*-toluenesulfonic acid (70 mg) in toluene (5 ml) for 30 min. to 100°C. The solvent was evaporated and the residue was chromatographed on silica gel ($CHCl_3$/EtOAc 9+1). After evaporation the residue crystallized at -30°C. Yield 102 mg (66%), colorless crystals.- R_F = 0.19 ($CHCl_3$/EtOAc 9+1). m.p.: 111°C (hexane/EtOAc 2+1).- $C_{10}H_{13}NO_6$ (243.2) Calcd. C 49.4 H 5.39 N 5.8 Found C 49.1 H 5.32 N 5.7.- IR (KBr): 3020-2850; 1795 (C=O lactone); 1745 (C=O ester); 1690 (C=O urethane); 1460; 1450; 1390; 1325; 1260; 1215; 1150; 1080; 1065; 1040; 1000; 970 cm^{-1}.- *) ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.80-2.15 (2H, m, H_a-5, H_e-5), 2.37 (1H, d, $J_{3a,3e}$ = 12.6 Hz, H_a-3), 2.86 (1H, ddd, $J_{3a,3e}$ = 12.6 Hz, $J_{3e,4e}$ = 5.8 Hz, $J_{3e,5e}$ = 1.3 Hz, H_e-3), 3.62 (1H, m, H_a-6), 3.74 (3H, s, OCH_3 urethane), 3.85 (3H, s, OCH_3 ester), 4.08 (1H, ddd, $J_{6a,6e}$ = 14.7 Hz, $J_{5a,6e}$ = 6.1 Hz, $J_{5e,6e}$ = 3.9 Hz, H_e-6), 5.06 (1H, ddd, $J_{3e,4e}$ = 5.8 Hz, $J_{4e,5a}$ = 2.4 Hz, H_e-4).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 29.22 (C-5), 38.28 (C-3), 40.40 (C-6), 53.03, 53.44 (OCH_3 urethane + ester), 65.63 (C-2), 75.45 (C-2), 155.59 (CO_2CH_3 urethane), 166.03 (CO_2 lactone), 168.84 ($\underline{C}O_2CH_3$ ester).

*) Atom numbering refers to the piperidine-ring system (see also **13**, **14**)

Dimethyl N-methoxycarbonyl-5-oxo-piperidine-2,2-dicarboxylate (**11**)

To a solution of **7** (30 mg, 109 µmol) in CH_2Cl_2 (5 ml) was added pyridinium chlorochromate (120 mg, 557 µmol) at room temp.. After 2.5 h, ether (10 ml) was added and the org. layer decanted. The residue was washed with ether (2x) and the combined org. phases were evaporated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/EtOAc 9+1. Yield 23 mg (77%).- R_F = 0.19 ($CHCl_3$/EtOAc 9+1).- m.p. 85°C (hexane/EtOAc 4+1).- $C_{11}H_{15}NO_7$ (273.2).- IR (KBr): 3050-2880; 1755 (C=O ester); 1735 (C=O ketone); 1710 (C=O urethane); 1450; 1440; 1385; 1310; 1260; 1235; 1215; 1205; 1050; 785 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.44-2.62 (4H, m, H-3, H-4), 3.76 (3H, s, OCH_3 urethane), 3.84 (6H, s, 2x OCH_3 ester), 4.12 (2H, s, H-6).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.97 (C-3), 34.64 (C-4), 45.44 (C-3), 52.03 (C-6), 53.35, 53.52 (OCH_3, 2x ester + urethane), 66.58 (C-2), 155.93 ($\underline{C}O_2CH_3$ urethane), 168.73 (2x $\underline{C}O_2CH_3$ ester), 204.18 (C-5).

N-Tosyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid (**12**) *(N-Tosyl-baikiain)*

To a solution of **4** (500 mg, 3.06 mmol) in H_2O (10 ml) 1N NaOH (4.6 ml, 9.20 mmol) and tosylchloride (875 mg, 4.59 mmol) were added with stirring. After 5 h at room temp. tosylchloride (191 mg, 1.00 mmol) and 2N NaOH (0.5 ml, 1.00 mmol) were added again. After 12 h the mixture was diluted with 2N NaOH and extracted with ether (3x). To the aqueous phase was added dil. HCl until pH 1. Extraction with CH_2Cl_2 (5x), drying and evaporation yielded colorless crystals. Yield 626 mg (73%).- m.p. 115-116°C (EtOH/H_2O 1+1), (ref.[6]: oil!).- $C_{13}H_{15}NO_4S$ (281.3) Calcd. C 55.5 H 5.37 N 5.0 Found C 55.8 H 5.55 N 5.0.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.41 (3H, s, CH_3), 2.54 (2H, m, H-3), 3.84 (1H, m, $J_{6a,6e}$ = 17.5 Hz, H-6), 4.03 (1H, m, $J_{6a,6e}$ = 17.5 Hz, H-6), 4.88 (1H, t, $J_{2e,3a} \approx J_{2e,3e}$ = 4.2 Hz, H_e-2), 5.68 (2H, m, H-5, H-4), 7.27 (2H, d, J = 8.3 Hz, H arom.), 7.67 (2H, d, J = 8.3 Hz, H arom.), 11.04 (1H, s, CO_2H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.44 (CH_3), 27.33 (C-3), 41.92 (C-6), 52.25 (C-2), 122.04, 123.47 (C-4, C-5), 127.10, 129.46, 136.12, 143.53 (C arom.), 176.62 ($\underline{C}O_2H$).

4-anti-4-Brom-N-tosyl-6-oxa-2-azabicyclo[3.2.1]octane-7-one (**13**)

To a solution of NBS (70 mg, 393 µmol) in H_2O was added a solution of **12** (100 mg, 355 µmol) in acetonitrile (5 ml)[6] with stirring. After 5 min **13** separated. After 4 h **13** was isolated by suction, washed with water and recrystallized from methanol. Yield 101 mg (79%).- R_F = 0.42 (petrol-ether/EtOAc 2+1).- m.p. 175°C (MeOH), (ref.[6]: 179-181°C).- $C_{13}H_{14}BrNO_4S$ (360.2) Calcd. C 43.3 H 3.92 N 3.9 Found C 43.1 H 3.80 N 3.8.- IR (KBr): 3100-2820; 1800 (C=O lactone); 1595; 1495; 1465; 1445; 1350; 1245; 1170; 1145; 1095; 1010; 960; 950; 815; 680 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.29 (1H, td, $J_{3a,3e}$ = 12.8 Hz, $J_{2e,3e} \approx J_{3e,4e} \approx$ 4-5 Hz, H_e-3), 2.43 (3H, s, CH_3), 2.94 (1H, d, $J_{3a,3e}$ = 12.8 Hz, H_a-3), 3.37 (1H, dd, $J_{6a,6e}$ = 14.5 Hz, $J_{5e,6e}$ = 4.2 Hz, H_e-6), 4.05 (1H, d, $J_{6a,6e}$ = 14.5 Hz, H_a-6), 4.28 (1H, t, $J_{4e,5e} \approx J_{5e,6e} \approx$ 4-5 Hz, H_e-5), 4.62 (1H, d, $J_{2e,3e} \approx$ 4.4 Hz, H_e-2), 4.85 (1H, t, $J_{3e,4e} \approx J_{4e,5e} \approx$ 4-5 Hz, H_e-4), 7.33 (2H, d, J = 8.3 Hz, H arom.), 7.71 (2H, d, J = 8.3 Hz, H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.59 (CH_3), 32.96 (C-3), 40.92 (C-5), 48.29 (C-6), 55.07 (C-2), 77.91 (C-4), 127.91, 129.80, 134.01, 144.53 (C arom.), 169.78 (CO_2 lactone).

2-Tosyl-6-oxa-2-azabicyclo[3.2.1]octane-7-one (**14**)

A mixture of **13** (80 mg, 222 µmol) tributyl tin hydride (130 mg, 447 µmol) and AIBN (7 mg, 43 µmol) was refluxed in benzene (5 ml) for 90 min under N_2. After evaporation of the solvent the crystalline residue was dissolved and "filtered" over silica gel (petrol ether/etOAc 2+1). After evaporation of the solvent the residue was recrystallized from hexane/EtOAc 3+1. Yield 44 mg (70%).- R_F = 0.78 ($CHCl_3$/MeOH 9+1).- m.p. 145°C.- $C_{13}H_{15}NO_4S$ (281.3) Calcd. C 55.5 H 5.37 N 5.0 Found C 55.8 H 5.51 N 4.9.- IR (KBr): 3020-2860; 1790 (C=O lactone); 1595; 1450; 1350; 1335; 1160; 1145; 965; 940; 705; 695; 670 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.05 (2H, m, H-5), 2.13 (1H, dd, $J_{3a,3e}$ = 14.1 Hz, $J_{3a,4e}$ = 2.1 Hz, H_a-3), 2.34 (1H, m, H_e-3), 2.43 (3H, s, CH_3), 2.80 (1H, ddd, $J_{6a,6e}$ = 12.2 Hz, $J_{5a,6a}$ = 10.3 Hz, $J_{5e,6a}$ = 6.1 Hz, H_a-6), 3.87 (1H, m, H_e-6), 4.60 (1H, d, $J_{2e,3e}$ = 4.3 Hz, H_e-2), 4.90 (1H, m, H_e-4), 7.33 (2H, d, J = 8.2 Hz, H arom.), 7.74 (2H, d, J = 8.2 Hz, H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.57 (CH_3), 28.49 (C-5), 37.40 (C-3), 40.32 (C-6), 55.26 (C-2), 76.21 (C-4), 128.07, 129.62, 133.91, 144.22 (C arom.), 170.97 (CO_2 lactone).- MS: m/z = 281 ($M^{+\cdot}$, 8%), 237 (76), 155 (35), 106 (11), 98 (11), 91 (97), 82 (100), 65 (37).

cis-2-Hydroxymethyl-N-tosyl-piperidine-4-ol (**15**)

To a solution of **14** (40 mg, 142 µmol) in THF (5 ml) was added $LiBH_4$ (10 mg, 459 µmol) under N_2 at room temp. with stirring. After 1 h the mixture was acidified with dil. HCl and extracted with CH_2Cl_2 (5x). The combined org. layers were dried and evaporated. The residue was recrystallized from hexane/EtOAc 1+1. Yield 38 mg (94%).- R_F = 0.22 ($CHCl_3$/MeOH 9+1).- m.p. 110°C.- $C_{13}H_{19}NO_4S$ (285.4) Calcd. C 54.7 H 6.71 N 4.9 Found C 55.1 H 6.62 N 4.7.- IR (KBr): 3170 (OH); 3020-2840; 1595; 1490; 1460; 1335; 1315; 1150; 1110; 945; 835; 810; 685 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.54 (2H, m, H-5), 1.77 (2H, m, H-3), 2.43 (3H, s, CH_3), 2.83 (2H, s, 2x OH), 3.50-4.10 (6H, m, H-6, CH_2O, H-2, H-4), 7.30 (2H, d, J = 8.1 Hz, H arom.), 7.74 (2H, d, J = 8.1 Hz, H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 21.51 (CH_3), 31.41 (C-5), 32.92 (C-3), 37.37 (C-6), 52.90 (C-2), 62.88 (C-4), 64.97 (CH_2OH), 126.96, 129.80, 138.01, 143.32 (C arom.).

References

1 Part III: C. Herdeis, W. Engel, *Tetrahedron: Asymmetry* **1991**, *10*, 945-948.

2 a. F. E. King, T. J. King, A. J. Warwick, *J. Chem. Soc.* **1950**, 3590-3597.- b. Y. Hasegawa, H. Hashimoto, M. Maeda, *Agric. Biol. Chem.* **1980**, *44*, 2725-2728.- c. N. A. Dobson, R. A. Raphael, *J. Chem. Soc.* **1958**, 3642-3647.- d. A. W. Burgstahler, C. E. Aiman, *J. Org. Chem.* **1960**, *25*, 489-492.

3 a. P. D. Bailey, G. R. Brown, F. Korber, A. Reid, R. D. Wilson, *Tetrahedron: Asymmetry* **1991**, *2*, 1263-1282.- b. G. J. Hanson, M. A. Russel, *Tetrahedron Lett.* **1989**, *30*, 5751-5754.- c. D. Ben-Ishai, S. Hirsch, *Tetrahedron*, **1988**, *44*, 5441-5449.- d. S. R. Angle, D. O. Arnaiz, *Tetrahedron Lett.* **1989**, *30*, 515-518.- e. H. Rapoport, R. C. Roemmele, *J. Org. Chem.* **1989**, *54*, 1866-1875.- f. see ref.[1].- g. C. Herdeis, W. Engel, *Arch. Pharm. (Weinheim)* **1992**, *325*, 411-417.- h. C. Agami, F. Couty, *Synlett*, **1990**, 731-732.- i. P. M. Esch, H. Hiemstra, W. N. Speckamp, *Tetrahedron Lett.* **1990**, *31*, 759-762.- k. A. J. Hutchison, M. Williams, C. Angst, R. de Jesus, L. Blanchard, H. R. Jackson, E. J. Wilusz, D. E. Murphy, P. S. Bernard, J. Schneider, T. Campell, W. Guida, M. A. Sills, *J. Med. Chem.* **1989**, *32*, 2171-2199.

4 a. C. R. Poppelstone, A. M. Unrau, *Can. J. Chem.* **1973**, *51*, 1223-1227.- b. R. Takasaki, *Chem. Pharm. Bull.* **1962**, *10*, 445-449.

5 B. Witkop, Y. Fujita, F. Irreverre, *J. Am. Chem. Soc.* **1964**, *86*, 1844-1846.

6 **12** is described as an oil which could not be crystallized: B. Witkop, N. Izumiya, J. E. Francis, A. V. Robertson, *J. Am. Chem. Soc.* **1962**, *84*, 1702-1709.

7 W. P. Neumann, *Synthesis* **1987**, 665-683.

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