

Synthesis of Monocyclic and Bicyclic Imino Sugars

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Dedicated to Prof. W. Steglich on the occasion of his 70th birthday

Keywords: Aldol reactions / Amino acids / Enolates / Imino sugars / Inhibitors

A diastereoselective aldol reaction between the chelated alanine ester enolate **5** and the protected threose derivative **6**, followed by cyclization under Mitsunobu conditions, gave the pipercolinic acid derivative **9**. This compound could easily be converted into the versatile protected derivative **11**, which could be transformed in excellent yields either into the corresponding piperidine imino sugar **14** or into the unnatural

amino acid **17**. The imino alcohol **13**, an intermediate in the synthesis of imino sugar **14**, was also used in a straightforward approach to indolizidinone **19**, involving an intramolecular Horner–Emmons reaction for ring-closure.

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Introduction

Thanks to their structural relationship to carbohydrates, polyhydroxylated derivatives of monocyclic or bicyclic nitrogen-containing ring systems (imino sugars) are interesting substrates for the inhibition of various glycosidases.^[1] In this process, protonated imino sugars act as transition state analogues of these enzymes.^[2] Piperidine derivatives such as deoxynojirimycin (**1**)^[3] and isofagomine (**2**),^[4] and indolizidine derivatives such as castanospermine (**3**)^[5] and swainsonine (**4**),^[6] are specific inhibitors of glucosidases, mannosidases and fucosidases. This biological activity offers a promising approach to the treatment of diabetes,^[7] cancer^[8] and viral infections such as HIV^[9] and influenza.^[10] Some of the naturally occurring indolizidines interfere with the formation of metastases, others activate the immune system to fight against cancer cells. Swainsonine **4** is currently under investigation as a chemotherapeutic against cancer.^[11] In accordance with this biological importance, a vast amount of work has been dedicated to this area over the past few years.^[1–5,12]

Our group has a longstanding interest in the reactions of metal-chelated amino acid esters. These nucleophiles are capable of a number of highly selective reactions, such as Claisen rearrangements,^[13] aldol reactions^[14] and Pd-catalysed processes.^[15] Here we would like to report an efficient route which benefits from a diastereoselective aldol reaction to synthesize various imino sugar derivatives.

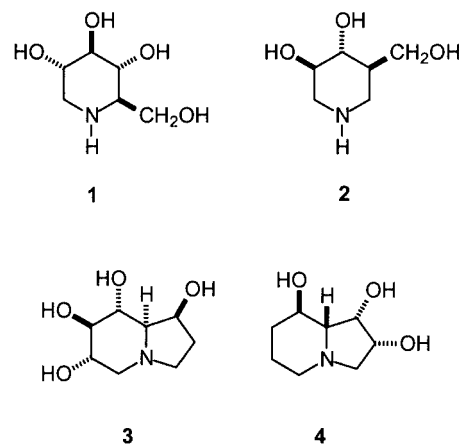
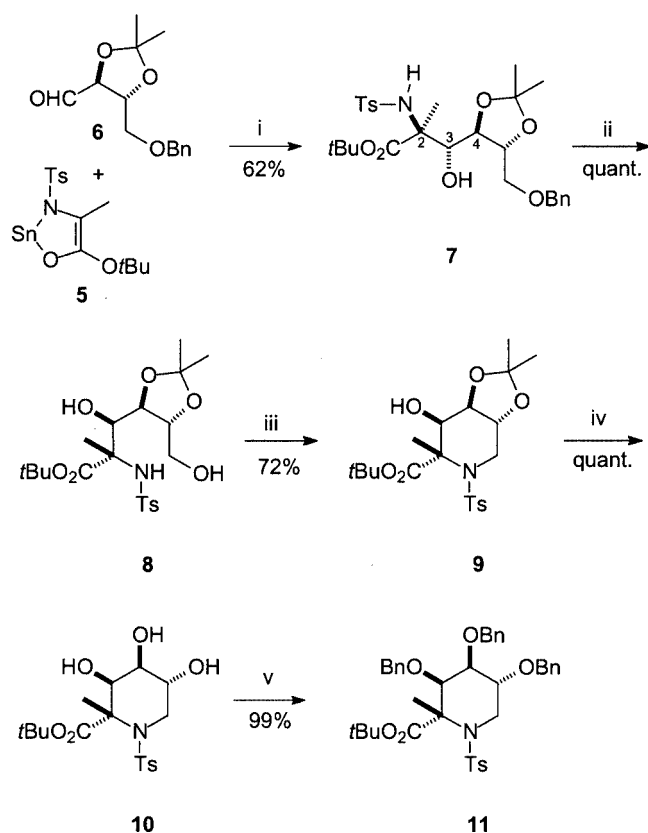


Figure 1. Examples of naturally occurring imino sugars

Results and Discussion

The aldol reaction between the metal-chelated *N*-protected alanine *tert*-butyl ester **5** and the protected threose derivative **6** provided a mixture of three diastereomers in an overall yield of 94% (Scheme 1).^[16] The desired 2,3-*anti*,3,4-*anti* isomer **7** could be isolated in 62% yield. After removal of the benzyl group,^[17] a cyclization under Mitsunobu conditions yielded the pipercolinic acid derivative **9** in 72% yield.^[16] As all attempts to remove the tosyl protecting group at this stage either resulted in low yields or failed completely, we decided to replace the potentially labile isopropylidene ketal with benzyl protecting groups. The cleavage was carried out in quantitative yield by use of catalytic amounts of the strong acidic ion-exchange resin Dowex 50WX8 in a methanol/water mixture. The resulting triol **10**

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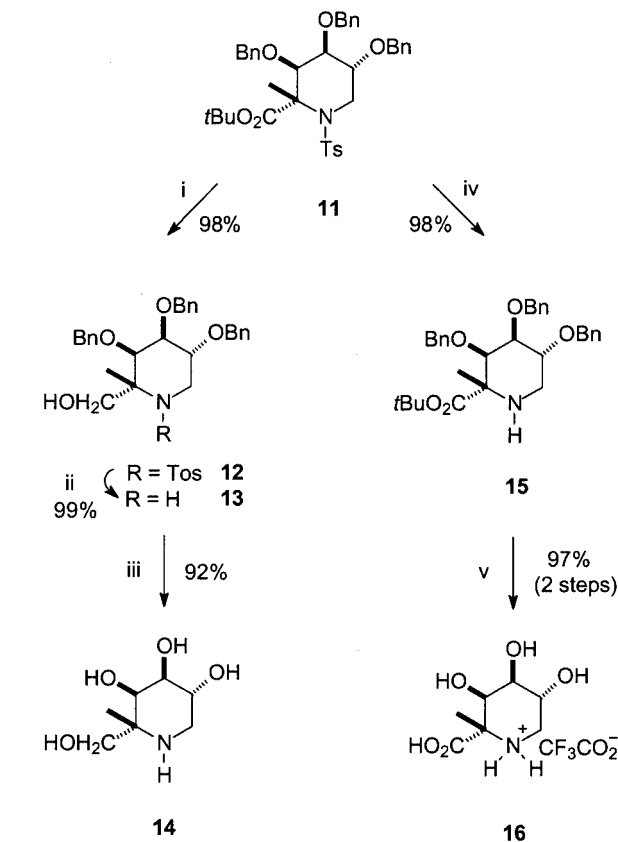


Scheme 1. Synthesis of precursors; conditions: i) -78°C , THF, ii) Pd/C, 3 bar H_2 , MeOH, room temp., iii) DEAD, PPh_3 , THF, room temp., iv) Dowex 50WX8, MeOH/ H_2O , v) NaH, BnBr, DMF, 0°C

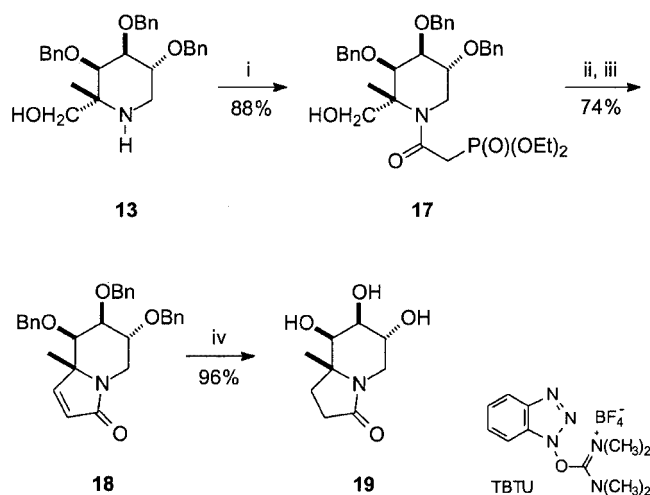
was perbenzylated with BnBr/NaH to give **11** in 99% yield.^[18]

By modifications of the pipecolic acid derivative **11** it was possible to obtain both a piperidine imino sugar **14** and an unnatural amino acid **16** in high yields (Scheme 2). The imino sugar **14** was accessible by reduction of the *tert*-butyl ester with LiAlH_4 , deprotection of the tosyl amide by titration with sodium naphthalide solution^[19] and cleavage of the benzyl ethers with $\text{H}_2/\text{Pd/C}$.^[17] The unnatural amino acid **16** could be obtained after removal of the tosyl protecting group and acidic cleavage of the *tert*-butyl ester in trifluoroacetic acid (TFA).^[20] The resulting salt was dissolved in THF and the Bn groups were removed under conditions identical to those above.

Furthermore, the imino alcohol **13** was transformed into the indolizidine derivative **19** in a three-step synthesis (Scheme 3). The first step was a TBTU-mediated [TBTU = *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate] coupling^[21] of **13** with diethyl phosphonoacetate.^[22] At 0 °C the reaction resulted in a mixture of amide and ester, but by lowering the temperature to −20 °C it was possible to obtain only the desired amide in 88% yield. The second reaction was a Dess–Martin oxidation of the primary hydroxy group and the third step involved an intramolecular Horner–Emmons reaction^[23] through the use of DBU, which yielded the indolizinone derivative **18** in 74% yield. After cleavage of the benzyl protecting



Scheme 2. Synthesis of piperidine derivatives **14** and **16**; conditions: i) LiAlH_4 , THF, room temp., 2 h, ii) sodium naphthalide, DME, -60°C , iii) Pd/C , 1 bar H_2 , THF, room temp., 3 d, iv) sodium naphthalide, DME, -60°C , v) 1. TFA, room temp., 2 h, 2. Pd/C , 1 bar H_2 , THF, room temp., 3 d



Scheme 3. Synthesis of indolizidinone **19**; conditions: i) (EtO)₂(O)PCH₂CO₂H, TBTU, NEt₃, CH₂Cl₂, -20 °C → room temp., ii) Dess–Martin periodinane, CH₂Cl₂, room temp., 8 h, iii) DBU, THF, room temp., 72 h, iv) Pd/C, 1 bar H₂, THF, room temp., 4 d

groups and simultaneous hydrogenation of the double bond, the indolizidinone **19** was isolated in 96% yield.

Conclusion

In conclusion, we have shown that polyhydroxylated pipecolic acid derivatives, which can be easily obtained through aldol reactions of chelated enolates and subsequent Mitsunobu cyclization, are valuable building blocks for a short and high-yielding approach to piperidine and indolizidine imino sugars. The transformation of the piperidine into an indolizidine framework involved a chemoselective coupling process followed by an intramolecular Horner–Emmons reaction.

Experimental Section

General Remarks: Most reactions were carried out under argon in oven-dried glassware (100 °C). All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane and dimethoxyethane (DME) from calcium hydride. Dowex 50WX8 was purchased from Aldrich. The starting materials and the products were purified by flash chromatography on silica gel (32–63 µm). Mixtures of ethyl acetate (EtOAc) and petroleum ether (PE, 40–60 °C) were generally used as eluents. TLC: commercially precoated Polygram® SIL-G/UV 254 plates (Macherey–Nagel). Viewing was accomplished with UV light and potassium permanganate solution. ¹H and ¹³C NMR: Bruker DRX 300, Bruker DRX 500, Bruker Avance 500 and Bruker Aspect 3000 spectrometers. Optical rotations were measured with a Perkin–Elmer PE 341 polarimeter.

tert-Butyl (2S,3R,4S,5R)-3,4,5-Trihydroxy-2-methyl-1-(p-toluenesulfonyl)piperidine-2-carboxylate (10): The pipecolic acid derivative **9**^[16] (970 mg, 2.20 mmol) was dissolved in methanol/water (40 mL, 1:1). A spatula of the strong acidic ion exchange resin Dowex 50WX8 was added and the mixture was shaken at room temperature for 10 h. After filtration, the solvent was evaporated in vacuo. In order to remove traces of water, the residue was dissolved in THF and the solvents were evaporated. The triol **10** (881 mg, 2.20 mmol, quantitative yield) was obtained as a colourless oil. $[\alpha]_D^{20} = -20.5$ ($c = 0.8$, CHCl₃). ¹H NMR (300 MHz, CDCl₃): $\delta = 1.40$ (s, 9 H), 1.64 (s, 3 H), 2.38 (s, 3 H), 2.87 (dd, $J = 13.8, 9.8$ Hz, 1 H), 3.12 (br. s, 3 H), 3.55 (dd, $J = 8.8, 2.9$ Hz, 1 H), 3.85 (m, 1 H), 4.06–4.13 (m, 2 H), 7.25 (d, $J = 8.3$ Hz, 2 H), 7.76 (d, $J = 8.3$ Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 20.5, 21.3, 27.5, 48.2, 67.6, 68.6, 73.4, 73.5, 82.9, 127.1, 129.3, 138.6, 143.2, 170.4$ ppm. C₁₈H₂₇NO₇S (401.48): calcd. C 53.85, H 6.78, N 3.49; found C 53.96, H 7.12, N 3.30. HRMS: calcd. for C₁₈H₂₈NO₇S [M + H]⁺ 402.1583; found 402.1579.

tert-Butyl (2S,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methyl-1-(p-toluenesulfonyl)piperidine-2-carboxylate (11): The triol **10** (881 mg, 2.20 mmol) and catalytic amounts of tetra-*n*-butylammonium iodide were dissolved in DMF (15 mL). The solution was cooled to 0 °C, and NaH (264 mg, 11.0 mmol) was carefully added in small portions. The mixture was stirred for 10 min, and BnBr (1.31 mL, 11.0 mmol), dissolved in DMF (5 mL), was added dropwise. The mixture was warmed to room temperature. The solvent was evaporated in vacuo, and CH₂Cl₂ and water were added. The organic layer was washed consecutively with 1 N NaOH, 1 N KHSO₄ and brine, and dried with Na₂SO₄. After filtration, the solvent was evaporated in vacuo and the crude product was purified by flash chromatography (PE/EtOAc, 9:1, 8:2). Ester **11** (1.46 g, 2.17 mmol, 99%) was obtained as a colourless oil. $[\alpha]_D^{22} = -10.0$ ($c = 0.9$,

CHCl₃). ¹H NMR (300 MHz, CDCl₃): $\delta = 1.46$ (s, 9 H), 1.77 (s, 3 H), 2.31 (s, 3 H), 3.14 (m, 1 H), 3.52–3.72 (m, 2 H), 3.75 (m, 1 H), 4.09–4.30 (m, 3 H), 4.50–4.70 (m, 4 H), 7.06 (m, 2 H), 7.24–7.31 (m, 15 H), 7.85 (m, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 18.3, 21.5, 27.8, 53.4, 68.0, 71.0, 72.8, 72.9, 74.3, 77.2, 80.1, 82.1, 127.3, 127.4, 127.5, 127.6, 127.6, 127.7, 127.9, 128.2, 128.2, 128.3, 129.1, 136.1, 137.8, 137.9, 138.3, 143.0, 171.1$ ppm. C₃₉H₄₅NO₇S (671.85): calcd. C 69.72, H 6.75, N 2.08, S 4.77; found C 69.44, H 6.56, N 2.15, S 4.81. HRMS: calcd. for C₃₉H₄₆NO₇S [M + H]⁺ 672.2969; found 672.2943.

(2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-hydroxymethyl-2-methyl-1-(p-toluenesulfonyl)piperidine (12): LiAlH₄ (17 mg, 0.45 mmol) was added at 0 °C to a solution of ester **11** (305 mg, 0.45 mmol) in THF (5 mL). The suspension was warmed to room temperature and stirred for 1 h. The mixture was diluted with Et₂O and quenched by addition of 1 N HCl. The organic layer was washed with brine and dried with Na₂SO₄. After purification by flash chromatography (PE/EtOAc 85:15), alcohol **12** (267 mg, 0.44 mmol, 98%) was obtained as a colourless oil. $[\alpha]_D^{20} = -30.6$ ($c = 1.1$, CHCl₃). ¹H NMR (500 MHz, CDCl₃): $\delta = 0.84$ (s, 3 H), 1.56 (br. s, 1 H), 2.39 (s, 3 H), 3.40 (d, $J = 13.5$ Hz, 1 H), 3.59 (m, 1 H), 3.72 (d, $J = 13.5$ Hz, 1 H), 3.79 (dd, $J = 3.4, 3.0$ Hz, 1 H), 3.97 (d, $J = 13.1$ Hz, 1 H), 4.16 (m, 1 H), 4.19 (d, $J = 3.0$ Hz, 1 H), 4.41, 4.46, 4.68 (3d, $J = 12.1$ Hz, 3 H), 4.59–4.65 (m, 3 H), 7.18–7.36 (m, 17 H), 7.69 (d, $J = 8.2$ Hz, 2 H) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 13.7, 21.5, 42.5, 64.7, 66.8, 70.3, 73.2, 73.2, 73.3, 75.3, 76.0, 127.0, 127.4, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 129.8, 138.0, 138.5, 138.5, 138.6, 143.5$ ppm. C₃₅H₃₉NO₆S (601.76): calcd. C 69.86, H 6.53, N 2.33; found C 69.33, H 6.58, N 2.35. HRMS: calcd. for C₃₅H₄₀NO₆S [M + H]⁺ 602.2548; found 602.2519.

(2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-hydroxymethyl-2-methylpiperidine (13): A solution of alcohol **12** (205 mg, 0.34 mmol) in DME (5 mL) was cooled to –60 °C. The dark green sodium naphthalide solution (1 M in DME) was added dropwise until the solution stayed green. The reaction mixture was diluted with EtOAc and quenched by addition of a small amount of water. The resulting suspension was warmed to room temperature, and Na₂SO₄ was added. After filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography (MeOH/CH₂Cl₂, 19:1 + 2% NEt₃) to yield amine **13** (150 mg, 0.34 mmol, 99%) as a colourless oil. $[\alpha]_D^{22} = -15.8$ ($c = 0.9$, CHCl₃). ¹H NMR (300 MHz, CDCl₃): $\delta = 1.23$ (s, 3 H), 2.63 (br. s, 2 H), 2.73 (dd, $J = 14.3, 4.3$ Hz, 1 H), 3.13 (dd, $J = 14.3, 2.5$ Hz, 1 H), 3.17 (d, $J = 10.8$ Hz, 1 H), 3.61 (d, $J = 10.8$ Hz, 1 H), 3.65 (m, 1 H), 3.72 (m, 1 H), 3.86 (m, 1 H), 4.46–4.74 (m, 6 H), 7.31–7.34 (m, 15 H) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 17.7, 41.0, 57.7, 66.3, 71.5, 72.6, 73.0, 75.8, 76.2, 76.3, 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 127.6, 127.7, 128.0, 128.3, 128.3, 128.4, 138.4, 138.6, 138.8$ ppm. C₂₈H₃₃NO₄ (447.57): calcd. C 75.14, H 7.43, N 3.13; found C 75.21, H 7.72, N 3.14. HRMS: calcd. for C₂₈H₃₄NO₄ [M + H]⁺ 448.2515; found 448.2542.

(2R,3R,4S,5R)-2-Hydroxymethyl-2-methylpiperidine-3,4,5-triol (14): A mixture of trifluoroacetic acid (12 µL, 0.16 mmol) and imino alcohol **13** (60 mg, 0.13 mmol) in THF (10 mL) was hydrogenated in the presence of 10% Pd/C for 72 h. The catalyst was removed by filtration through Celite. A few drops of 1 N NaOH were added to the filtrate first, and then Dowex 50WX8 (1.0 g). The mixture was shaken for 48 h and the resin was washed consecutively with methanol and water. Finally, the product was eluted with 2 N aqueous ammonia solution. After evaporation, the triol **14** (22 mg, 0.12 mmol, 92%) was obtained as a colourless oil. $[\alpha]_D^{20} = -11.6$ ($c = 1.5$, H₂O). ¹H NMR (500 MHz, CD₃OD): $\delta = 1.32$ (s, 3 H),

2.90 (dd, $J = 12.6, 5.0$ Hz, 1 H), 3.27 (d, $J = 12.0$ Hz, 1 H), 3.40 (d, $J = 11.7$ Hz, 1 H), 3.72 (d, $J = 11.7$ Hz, 1 H), 3.78 (m, 1 H), 3.81 (m, 1 H), 3.91 (m, 1 H), 4.87 (br. s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): $\delta = 16.0, 42.7, 63.9, 64.3, 67.4, 67.5, 72.1$ ppm. HRMS: calcd. for $\text{C}_7\text{H}_{16}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 178.1079; found 178.1059.

tert-Butyl (2S,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-methylpiperidine-2-carboxylate (15): Compound **11** (270 mg, 0.40 mmol) was treated with sodium naphthalide according to the synthesis of **13**. After flash chromatography (PE/EtOAc, 7:3), the amine **15** (203 mg, 0.39 mmol, 98%) was obtained as a colourless oil. $[\alpha]_{\text{D}}^{20} = +17.7$ ($c = 1.0$, CHCl_3). ^1H NMR (500 MHz, CDCl_3): $\delta = 1.22$ (s, 3 H), 1.41 (s, 3 H), 2.07 (br. s, 1 H), 2.56 (dd, $J = 12.4, 10.5$ Hz, 1 H), 3.12 (dd, $J = 12.5, 5.3$ Hz, 1 H), 3.47 (dd, $J = 9.3, 2.4$ Hz, 1 H), 3.91 (m, 1 H), 4.15 (d, $J = 2.4$ Hz, 1 H), 4.62–5.01 (m, 6 H), 7.25–7.41 (m, 15 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): $\delta = 23.2, 27.7, 45.9, 63.7, 72.3, 72.7, 75.3, 75.6, 78.6, 81.4, 82.3, 127.2, 127.3, 127.4, 127.6, 128.0, 128.1, 128.1, 128.3, 138.3, 138.5, 138.7, 173.4$ ppm. HRMS: calcd. for $\text{C}_{32}\text{H}_{40}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 518.2907; found 518.2905.

(2S,3R,4S,5R)-2-Carboxy-3,4,5-trihydroxy-2-methylpiperidinium Trifluoroacetate (16): Ester **15** (108 mg, 0.21 mmol) was dissolved in a mixture of CH_2Cl_2 (2 mL) and trifluoroacetic acid (0.3 mL). The solution was stirred at room temperature for 10 h, after which the volatile components were evaporated in vacuo. The residue was dissolved in THF (2 mL) and hydrogenated in the presence of 10% Pd/C for 14 h. After the catalyst had been removed by filtration through Celite, the solvent was evaporated in vacuo to yield salt **16** (62 mg, 0.20 mmol, 97%) as a colourless solid. $[\alpha]_{\text{D}}^{20} = -3.8$ ($c = 0.3$, MeOH). ^1H NMR (300 MHz, D_2O): $\delta = 1.47$ (s, 3 H), 3.00 (m, 1 H), 3.30 (dd, $J = 12.7, 5.7$ Hz, 1 H), 3.47 (dd, $J = 9.7, 2.5$ Hz, 1 H), 3.95 (m, 1 H), 4.19 (d, $J = 2.4$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, D_2O): $\delta = 21.3, 45.1, 64.7, 67.6, 72.2, 72.5, 116.3, 159.2, 173.8$ ppm. HRMS: calcd. for $\text{C}_7\text{H}_{14}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 192.0896; found 192.0920.

(2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-1-[2'-(diethoxyphosphoryl)acetyl]-2-hydroxymethyl-2-methylpiperidine (17): The imino alcohol **13** (160 mg, 0.36 mmol) and diethyl phosphonoacetate (71 mg, 0.36 mmol) were dissolved in CH_2Cl_2 (10 mL). The mixture was cooled to -20 °C, after which TBTU (116 mg, 0.36 mmol) and NEt_3 (155 μL , 1.11 mmol) were consecutively added. The mixture was warmed to room temperature and stirred for 10 h. After addition of 1 N KHSO_4 , the organic layer was washed with brine and dried with Na_2SO_4 . The solvent was removed in vacuo and the crude product was purified by flash chromatography (MeOH/ CH_2Cl_2 , 19:1), giving amide **17** (197 mg, 0.32 mmol, 88%) as a colourless oil. $[\alpha]_{\text{D}}^{20} = +2.8$ ($c = 1.0$, CHCl_3). ^1H NMR (500 MHz, CDCl_3): $\delta = 1.28, 1.31$ (2t, $J = 7.4$ Hz, 6 H), 1.30 (m, 1 H), 1.35 (s, 3 H), 2.93 (dd, $J = 22.9, 14.7$ Hz, 1 H), 3.19 (dd, $J = 20.7, 14.7$ Hz, 1 H), 3.71–3.85 (m, 5 H), 3.76 (d, $J = 12.1$ Hz, 1 H), 3.99 (d, $J = 12.1$ Hz, 1 H), 4.06–4.16 (m, 4 H), 4.52 (s, 2 H), 4.54 (d, $J = 12.0$ Hz, 1 H), 4.58 (d, $J = 11.4$ Hz, 1 H), 4.67 (d, $J = 12.0$ Hz, 1 H), 4.71 (d, $J = 11.4$ Hz, 1 H), 7.25–7.37 (m, 15 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): $\delta = 15.3, 16.1, 16.2, 35.9, 46.6, 62.3, 62.4, 62.5, 67.1, 71.4, 72.3, 74.4, 77.5, 78.5, 78.9, 127.3, 127.5, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.6, 137.8, 138.0, 138.0, 166.4$ ppm. $\text{C}_{34}\text{H}_{44}\text{NO}_8\text{P}$ (625.70): calcd. C 65.27, H 7.09, N 2.24; found C 64.91, H 7.16, N 2.35. HRMS: calcd. for $\text{C}_{34}\text{H}_{45}\text{NO}_8\text{P}$ $[\text{M} + \text{H}]^+$ 626.2878; found 626.2874.

(6R,7S,8R,8aR)-6,7,8-Tris(benzyloxy)-8a-methyl-5,6,7,8-tetrahydroindolizin-3-one (18): Dess–Martin periodinane (140 mg,

0.33 mmol) was added at room temperature to a solution of amide **17** (190 mg, 0.30 mmol) in CH_2Cl_2 (10 mL). After stirring for 10 h, the mixture was diluted with Et_2O . A solution of $\text{Na}_2\text{S}_2\text{O}_3$ (0.26 M) in saturated NaHCO_3 was added, and the two-layer system was stirred vigorously until both phases became clear. The organic layer was washed with saturated NaHCO_3 and dried with Na_2SO_4 . After filtration, the solvent was evaporated and the crude product was dissolved in THF (2 mL). DBU (90 μL , 0.60 mmol) was added at room temperature and the solution was stirred for 72 h. The reaction mixture was diluted with CH_2Cl_2 , washed with 1 N KHSO_4 and dried with Na_2SO_4 . After filtration, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (PE/EtOAc, 6:4) to yield lactam **18** (105 mg, 0.22 mmol, 74%) as a colourless oil. $[\alpha]_{\text{D}}^{20} = +8.7$ ($c = 1.0$, CHCl_3). ^1H NMR (500 MHz, CDCl_3): $\delta = 1.43$ (s, 3 H), 3.09 (dd, $J = 14.3, 1.3$ Hz, 1 H), 3.24 (d, $J = 3.0$ Hz, 1 H), 3.65 (m, 1 H), 3.78 (dd, $J = 3.3, 2.9$ Hz, 1 H), 4.42 (m, 1 H), 4.35 (d, $J = 11.8$ Hz, 1 H), 4.46 (d, $J = 11.8$ Hz, 1 H), 4.57 (d, $J = 11.8$ Hz, 1 H), 4.60 (d, $J = 11.8$ Hz, 1 H), 4.74 (d, $J = 11.8$ Hz, 1 H), 4.75 (d, $J = 12.1$ Hz, 1 H), 6.02 (d, $J = 5.8$ Hz, 1 H), 7.09 (d, $J = 5.8$ Hz, 1 H), 7.15–7.31 (m, 15 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): $\delta = 15.8, 34.1, 66.7, 70.6, 72.0, 73.4, 74.7, 75.4, 79.1, 125.1, 127.5, 127.6, 127.7, 127.8, 128.3, 128.4, 137.8, 137.9, 138.2, 154.2, 170.3$ ppm. $\text{C}_{30}\text{H}_{31}\text{NO}_4$ (469.58): calcd. C 76.73, H 6.65, N 2.98; found C 76.73, H 6.66, N 2.97. HRMS: calcd. for $\text{C}_{30}\text{H}_{32}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 470.2338; found 470.2345.

(6R,7S,8R,8aR)-6,7,8-Trihydroxy-8a-methylindolizin-3-one (19): A solution of indolizinone **18** (22 mg, 0.047 mmol) in THF (5 mL) was hydrogenated in the presence of 10% Pd/C for 4 d. The catalyst was removed by filtration through Celite. After evaporation, the crude product was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to yield unprotected indolizidinone **19** (9.1 mg, 0.045 mmol, 96%) as a colourless oil. $[\alpha]_{\text{D}}^{20} = +26.0$ ($c = 0.9$, EtOH). ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$):

$\delta = 1.21$ (s, 3 H), 1.71 (ddd, $J = 16.7, 10.2, 4.1$ Hz, 1 H), 1.79 (m, 1 H), 2.13 (ddd, $J = 17.0, 9.8, 4.1$ Hz, 1 H), 2.27 (m, 1 H), 2.90 (d, $J = 13.6$ Hz, 1 H), 3.42 (d, $J = 3.2$ Hz, 1 H), 3.63 (m, 1 H), 3.64 (m, 1 H), 3.67 (m, 1 H), 4.53–4.64 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 19.1, 29.5, 33.4, 38.3, 62.6, 69.2, 72.2, 72.8, 173.6$ ppm. HRMS: calcd. for $\text{C}_9\text{H}_{16}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 202.1079; found 202.1078.

Acknowledgments

We thank Dr. R. Graf and Dr. J. Gross (University of Heidelberg) for mass spectra. Financial support by the Graduiertenkolleg, the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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Received February 7, 2003