Synthesis of 5-*epi*-Isofagomine via Asymmetric Chelate–Enolate Claisen Rearrangement

Christiane Schneider and Uli Kazmaier*

Organisch-Chemisches Institut der Universität,
Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany
E-mail: ck1@ix.urz.uni-heidelberg.de

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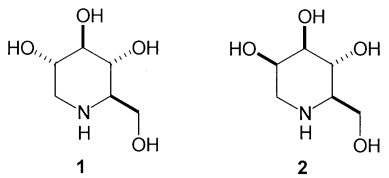
Polyhydroxylated piperidines are an interesting class of glycosidase inhibitors. Chelate enolate Claisen rearrangement of *N*-protected chiral amino acid esters gives rise to γ,δ-unsaturated amino acids, which can be converted to this type of alkaloids. The potential glycosidase inhibitor 5-*epi*-isofagomine (**5**) was synthesized by this approach in a highly stereoselective fashion.

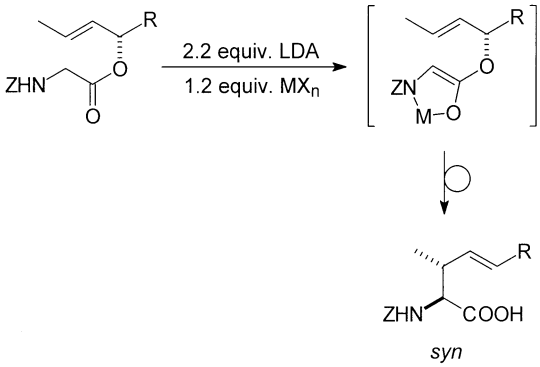
Introduction

Based on their structural relationship to sugars, polyhydroxylated piperidines (azasugars) and pipecolinic acid derivatives are interesting candidates for the inhibition of various glycosidases. Protonated azasugars act as transition state analogues of these enzymes.[1] E.g. deoxynojirimycin (**1**)[2] and deoxymannojirimycin (**2**)[3] are specific inhibitors of glucosidases,[2] mannosidases,[4] and fucosidases.[5] This biological activity is important for the therapy of diabetes,[6] cancer,[7] and viral infections.[8] These naturally occurring alkaloids are closely related to sugars, only the ring oxygen is replaced by nitrogen. Recently, Bols et al. reported the synthesis of isofagomine (**3**),[9] a new type of glycosidase inhibitor. In this structure the nitrogen replaces the anomeric carbon atom. Isofagomine (**3**) in the *N*-protonated form is especially suitable to mimic the carbenium ion **4**, a reasonable intermediate in the enzymatic glycosyl cleavage. Therefore isofagomine is the strongest inhibitor of β-glycosidases so far. Similar results were obtained with other derivatives like 1-azafagomine[10] or the isomeric *galacto*-isofagomine.[11]

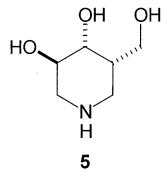


Recently, we developed a new variation of the Claisen rearrangement of amino acid esters, proceeding via chelated allylic ester enolates (Scheme 1).[12] If esters of chiral alcohols were employed, the corresponding chiral amino acids are obtained in a highly enantio- as well as diastereoselective fashion.[13]

Scheme 1



Because of our interest into the synthesis of polyhydroxylated piperidine alkaloids,[14] we investigated a synthetical approach to this class of compounds, based on this chelate enolate Claisen rearrangement. As a target an isomer if isofagomine, 5-*epi*-isofagomine **(5)** was chosen.[15]



The retrosynthetical analysis of this compound is shown in Scheme 2. The piperidine ring should be obtained from the acyclic polyhydroxylated amine, which is accessible from the corresponding unsaturated amino acid via *cis* dihydroxylation and decarboxylation. The amino acid can be ob-

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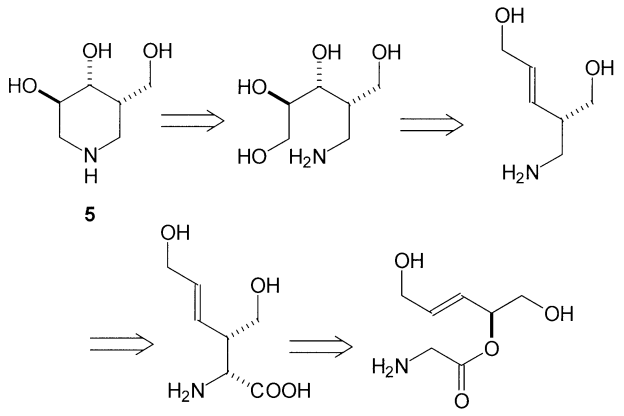
tained from the appropriate allylic ester by Claisen rearrangement.

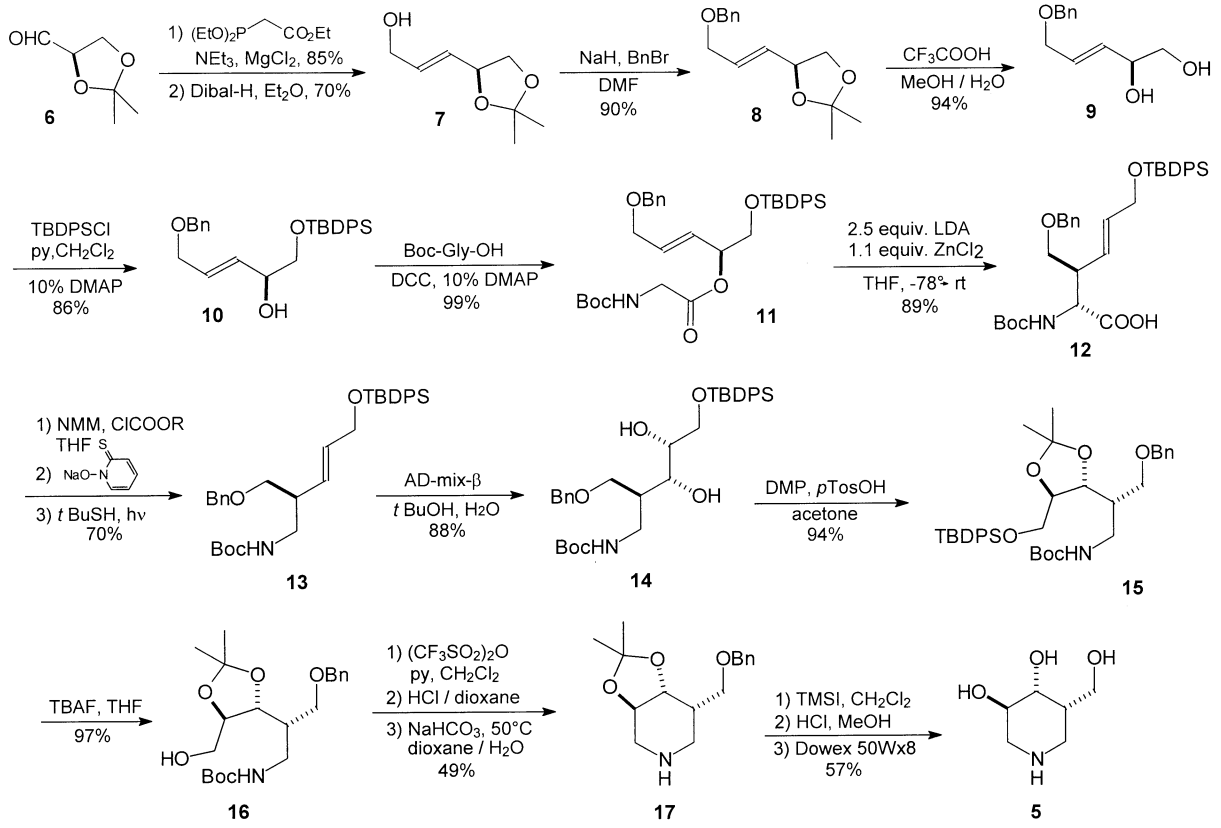
Scheme 2



Results and Discussion

Starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (**6**) the protected unsaturated alcohol **7** was synthesized via Horner-Emmons reaction (Scheme 3) and subsequent reduction of the vinylogeous ester formed with Dibal.[16] The suitable protected chiral allylic alcohol **10,** required for the Claisen rearrangement, was easily obtained by benzylation of the allylic alcohol **7**[17] and cleavage of the ketal moiety. While no cleavage was observed under mild conditions (oxalic acid in H_2O), best results were obtained using trifluoro acetic acid in aqueous methanol. The resulting diol **9** was selectively silylated at the primary OH-functionality. All three reaction steps, formation of the benzyl ether, cleavage of the ketal moiety and subsequent silylation of the sterically less hindered primary alcohol, could be carried out with overall very high yield. Also the following esterification step, using the Steglich protocol (DCC, DMAP),[18] gave nearly quantitative yield. In this case two equivalents of protected glycine were used to complete the reaction, because the reaction could not be monitored, neither by TLC nor HPLC, because of same chromatographically properties of the alcohol **10** and the ester **11**. Chelate enolate Claisen rearrangement, using LDA as a base and zinc chloride as chelating agent, gave rise to the γ,δ-unsaturated amino acid **12**. Because of their low polarity, the *N*-protected amino acid could be purified directly by flash chromatography. For the following decarboxylation step, the Barton procedure, developed for amino acids,[19] was used. Therefore **12** was converted into the corresponding *N*-hydroxythiopyridyl ester via a mixed anhydride. Although attempts to carry out the radical cleavage with AIBN and Bu_3SnH were unsuccessful, photochemical cleavage in the presence of mercaptane gave rise to **13** in good yields. Subsequent Sharpless dihydroxylation[20] using AD-mix-β® provided the corresponding diol **14**, which was converted to the isopropylidene derivative **15**. The diastereoselectivity in the hydroxylation step was excellent (> 97% ds, *matched case*). In contrast, the "*opposite*" AD-mix-α® provided a 1:1 mixture of diastereomeres (*mismatched case*). Removal of the silyl pro-

Scheme 3



tecting group gave the alcohol **16**, which was converted into the triflate. Without further purification, the triflate was used directly in the cyclization step. Therefore the *N*-protecting group was removed with HCl, and the acidic solution was added slowly to a vigorously stirred emulsion of dioxane and satd. $NaHCO_3$ solution at 50°C (high dilution). Starting from **16** the piperidine derivative **17** was obtained in 49% yield. The use of the triflate was essential, no cyclization was observed with the corresponding mesylate. To finish the synthesis, only the protecting groups had to be removed. Catalytic hydrogenation of the benzyl ether was unsuccessful, therefore the benzyl group was removed with trimethylsilyl iodide. Cleavage of the ketal and subsequent ion exchange chromatography provided 5-*epi* isofagomine (**5**).

Conclusion

In conclusion we have shown that the chelate enolate Claisen rearrangement is not only a suitable method for the construction of unsaturated amino acids, but can also be applied to other classes of natural products such as alkaloids.

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Experimental Section

Most reactions were carried out in oven-dried glassware (100°C) under argon. All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane, and diisopropylamine from calcium hydride. Dowex 50Wx8 was purchased from Aldrich. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available *n*butyllithium solution (15% in hexane) in THF at −20°C directly before use. The starting materials and the products were purified by flash chromatography on silica gel (32−63 μm). Mixtures of ethyl acetate and petrol ether (40−60°C) were generally used as eluents. − TLC: commercially precoated Polygram© SIL-G/UV 254 plates (Macherey-Nagel). Visualization was accomplished with UV light, iodine, and potassium permanganate solution. − ^1H and ^{13}C NMR: Bruker WH-200 or AC-300 spectrometer, respectively. − Enantiomeric and diastereomeric ratios were determined by analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow: 2 ml/min), as well as a Chiracel-OD-H column (Daicel) (0.5 ml/min) and a Knauer UV detector. Optical rotations were measured on a Perkin-Elmer Polarimeter PE 241.

(3E,4S)-1-Benzyloxy-4,5-isopropylidendioxy-2-pentene (**8**):[17] A solution of **7**[16] (10 g, 63.5 mmol) in 100 ml of DMF was added to a stirred suspension of NaH (60% in oil) (3.82 g, 94.4 mmol) in 100 ml of DMF at −60°C. The mixture was warmed up, until a slight gas evolution was observed (at −30°C). Benzyl bromide (13.1 g, 76.3 mmol) was added, and the mixture was allowed to warm up to room temp. overnight. 300 ml of ether as well as 200 ml of brine were added, and after separation of the layers, the aqueous phase was extracted twice with ether. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petrol ether/ethyl acetate, 9:1) giving rise to **8** (14 g, 87%) as a colorless oil. $[\alpha]_D^{20}$ = +30.0 (*c* = 1.0, $CHCl_3$), (ref.[17]: $[\alpha]_D^{20}$: = +30.1). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.43 (s, 3 H), 3.61 (dd, *J* = 8.1, 8.0 Hz, 1 H), 4.04 (m_c, 2 H), 4.10 (dd, *J* = 8.1, 6.2 Hz, 1 H), 4.50−4.57 (m, 3 H), 5.75 (dd, *J* = 15.5, 7.3 Hz, 1 H), 5.92 (dt, *J* = 15.5, 10.8 Hz, 1 H), 7.28−7.35 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.89, 26.70, 69.42, 69.81, 72.38, 76.53, 109.36, 127.60, 127.72, 128.41, 130.11, 130.71.

(2S,3E)-5-Benzyloxy-3-pentene-1,2-diol (**9**):[21] Trifluoro acetic acid (1.55 ml) was added to a solution of **8** (13.5 g, 54.4 mmol) in 75 ml of MeOH and 14 ml of H_2O. After stirring for 15 hours 1.7 ml of a conc. ammonia solution was added. After evaporation of the solvent in vacuo at 40°C, the residue was dissolved in H_2O (70 ml). The solution obtained was washed three times with a 1:1 mixture of petrol ether and ether (to remove traces of **8**), before the product was extracted with ethyl acetate (4 times with 100 ml each). The combined fractions were dried with Na_2SO_4, and the solvent was evaporated in vacuo. Yield: 10.7 g (94%) of a colorless oil, which was used without further purification. $[\alpha]_D^{20}$= +5.5 (*c* = 2.0, $CHCl_3$) (ref.[21]: $[\alpha]_D^{20}$ = +5.71). − ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (br. s, 1 H), 2.61 (br. s, 1 H), 3.48 (dd, *J* = 10.8, 7.5 Hz, 1 H), 3.64 (d, *J* = 11.1 Hz, 1 H), 4.03 (dt, *J* = 5.5, 1.0 Hz, 2 H), 4.24 (br. s, 1 H), 4.52 (s, 2 H), 5.74 (ddt, *J* = 15.5, 5.7, 1.2 Hz, 1 H), 5.91 (ddt, *J* = 15.6, 5.5, 1.1 Hz, 1 H), 7.28−7.37 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.30, 70.00, 72.47, 72.51, 127.73, 127.80, 128.44, 129.12, 131.42.

(2S,3E)-5-Benzyloxy-1-(tert-butyldiphenyl)silyloxy-3-penten-2-ol (**10**): Pyridine (7.2 ml, 89 mmol) and DMAP (550 mg, 4.5 mmol) were added to a solution of **9** (9.6 g, 46.1 mmol) in 50 ml of dichloromethane. The solution was cooled to 0°C before a solution of *tert*-butyldiphenylsilylchloride (16.4 g, 60 mmol) in 25 ml of dichloromethane was added dropwise. After stirring for about 12 hours 40 ml of 1 N HCl solution were added. After separation of the layers, the aqueous phase was washed twice with dichloromethane. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petrol ether/ethyl acetate, 9:1) giving rise to **10** (17.8 g, 86%) as a colorless oil. $[\alpha]_D^{20}$= −6.9 (*c* = 8.3, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 2.62 (d, *J* = 3.3 Hz, 1 H), 3.53 (dd, *J* = 10.3, 7.7 Hz, 1 H), 3.68 (dd, *J* = 9.9, 3.7 Hz, 1 H), 3.99 (d, *J* = 5.5 Hz, 2 H), 4.26−4.35 (m, 1 H), 4.48 (s, 2 H), 5.70 (ddt *J* = 15.6, 5.7, 1.5 Hz, 1 H), 5.90 (dtd, *J* = 15.6, 5.5, 1.5 Hz, 1 H), 7.26−7.45 (m, 11 H), 7.63 (d, *J* = 1.8 Hz, 2 H), 7.66 (d, *J* = 1.7 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.29, 26.89, 67.83, 70.10, 72.28, 127.60, 127.72, 127.82, 128.38, 129.00, 129.88, 131.05, 133.09, 133.16, 135.56, 135.59, 138.28. − $C_{28}H_{34}O_3Si$ (446.66): calcd. C 75.29, H 7.67; found C 75.19, H 7.78. − HRMS: calcd. for $C_{24}H_{25}O_3Si$ [$M^+ - C_4H_9$] 389.1425; found 389.1425.

(2S,3E)-5-Benzyloxy-1-(tert-butyldiphenyl)silyloxy-3-pentene-2-yl N-(tert-Butyloxycarbonyl)glycinate (**11**): DCC (16.19 g, 78.5 mmol) and DMAP (490 mg, 3.92 mmol) were added to a solution of **10** (17.5 g, 39.2 mmol) in 80 ml of dichloromethane at 0°C. The clear solution was cooled to −20°C, before Boc-Gly (17.5 g, 39.2 mmol) was added after 5 min. The mixture was allowed to warm to room temp. overnight. After filtration of the precipitate, the organic phase was extracted with 1 N $KHSO_4$ solution, sat. $NaHCO_3$ solution and with brine. Drying of the organic layer with Na_2SO_4 and evaporation of the solvent gave crude **11** which was purified by flash chromatography (petrol ether/ethyl acetate, 9:1). Yield: 23.5 g (99%) of a colorless oil. $[\alpha]_D^{20}$ = 12.2 (*c* = 8.4, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 9 H), 1.43 (s, 9 H), 3.73 (dd, *J* = 11.0, 4.8 Hz, 1 H), 3.77 (dd, *J* = 11.0, 6.6 Hz, 1 H), 3.80 (d, *J* = 5.2 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 3.98 (d, *J* = 5.1

Hz, 1 H), 4.47 (s, 2 H), 4.92 (br. s, 1H), 5.48−5.56 (m, 1 H), 5.72 (ddt, J = 15.8, 6.6, 1.5 Hz, 1 H), 5.88 (dt, J = 15.8, 5.1 Hz, 1 H), 7.26−7.44 (m, 11 H), 7.60−7.64 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.20, 26.72, 28.30, 45.52, 65.28, 69.64, 72.37, 75.43, 79.88, 126.68, 127.61, 127.68, 127.72, 128.36, 29.75, 129.79, 131.24, 133.13, 133.26, 135.53, 135.60, 138.08, 155.48, 169.51. − $C_{35}H_{45}NO_6Si$ (603.83): calcd. C 69.62, H 7.51, N 2.32; found C 69.57, H 7.69, N 2.17. − HRMS: calcd. for $C_{35}H_{45}NO_6Si$ [M^+] 603.3016; found 603.2979.

(2R,3S,4E)-3-Benzyloxymethyl-6-(tert-butyldiphenyl)silyloxy-2-(tert-butyloxycarbonyl)amino-4-hexenoic Acid (**12**): A solution of diisopropylamine (3.45 g, 34.1 mmol) in 15 ml abs. THF was cooled to −78°C, before BuLi (19.9 ml of a 1.55 M solution in hexane, 29.8 mmol) was added. The cooling bath was removed and the solution was warmed up to 0°C. This solution was added slowly to a solution of **11** (4.0 g, 6.6 mmol) and zinc chloride (1.33 g, 9.8 mmol) in 20 ml of abs. THF at −78°C. The resulting clear solution was warmed to room temp. overnight. After addition of 1 N $KHSO_4$ solution the phases were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petrol ether/ethyl acetate 1. 7:3, 2. 1:1, 3. 2:8) giving rise to **12** (3.56 g, 89%) as a pale yellow oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 1.55 (s, 9 H), 3.44 (m_c, 1 H), 3.68 (dd, J = 9.6, 4.6 Hz, 1 H), 3.77 (dd, J = 9.6, 4.5 Hz, 1 H), 4.31 (d, J = 3.8 Hz, 2 H), 4.37 (d, J = 6.2 Hz, 1 H), 4.59 (d, J = 11.8 Hz, 1 H), 4.66 (d, J = 11.8 Hz, 1 H), 5.86 (dt, J = 15.6, 3.8 Hz, 1 H), 6.00 (dd, J = 15.6, 7.7 Hz, 1 H), 7.35−7.59 (m, 11 H), 7.77−7.82 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.06, 27.39, 28.71, 45.25, 57.75, 65.25, 71.88, 74.42, 80.77, 128.65, 128.79, 130.30, 133.30, 134.80, 134.84, 136.64, 139.50, 157.92, 176.29. − $C_{35}H_{45}NO_6Si$ (603.83): calcd. C 69.62, H 7.51, N 2.32; found C 69.36, H 7.70, N 2.27. − HRMS: calcd. for $C_{35}H_{45}NO_6Si$ [M^+ + H] 604.3095; found 604.3091.

(2S,3E)-2-Benzyloxymethyl-5-(tert-butyldiphenyl)silyloxy-1-(tert-butyloxycarbonyl)amino-3-pentene (**13**): *N*-Methylmorpholine (0.35 g, 3.45 mmol) and isobutyl chloroformiat (0.47 g, 2.45 mmol) were added at −20°C to a solution of **12** (2.0 g, 3.45 mmol) in 30 ml of THF. After stirring for 20 min at this temperature, *N*-hydroxythiopyridone sodium salt (0.62 g, 4.14 mmol) was added. After a few minutes the reaction mixture turns yellow, and the mixture was stirred at this temperature until the complete conversion of **12** to the corresponding hydroxythiopyridylester was monitored by TLC. The reaction mixture was filtered through a plug of silica, *tert*-butylmercaptane (4.81 g, 53.3 mmol) was added to the filtrate, before the whole mixture was irradiated for 45 min at room temp. with a 300W wolfram lamp. After addition of 300 ml of ether, the organic layer was washed with 1 N $KHSO_4$ solution, 1 N NaOH and brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. Purification of the crude product by flash chromatography (petrol ether/ethyl acetate, 1:1) gave **13** (1.33 g, 77%) as a colorless oil. $[\alpha]_D^{20}$= −12.8 (c = 0.8, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 1.44 (s, 9 H), 2.46−2.66 (m, 1 H), 3.13 (ddd, J = 13.2, 6.6, 6.6 Hz, 1 H), 3.29 (ddd, J = 13.2, 6.6, 6.6 Hz, 1 H), 3.40 (dd, J = 9.2, 7.0 Hz, 1 H), 3.46 (dd, J = 9.2, 5.1 Hz, 1 H), 4.18 (d, J = 4.4 Hz, 2 H), 4.50 (s, 2 H), 5.54 (dd, J = 15.4, 7.7 Hz, 1 H), 5.67 (dt, J = 15.4, 4.4 Hz, 1 H), 7.28−7.45 (m, 11 H), 7.66 (d, J = 1.7 Hz, 2 H), 7.68 (d, J = 1.5 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.99, 26.64, 28.21, 42.23, 42.57, 64.07, 72.16, 72.99, 78.77, 127.34, 127.37, 128.16, 128.49, 129.41, 131.43, 133.54, 133.56, 135.32, 138.02, 155.71. − $C_{34}H_{45}NO_4Si$ (559.82): calcd. C 72.95, H 8.10, N 2.50; found C 73.08, H 8.31, N 2.42. − HRMS: calcd. for $C_{34}H_{46}NO_4Si$ [M^++H] 560.3196; found 560.3207.

(2R,3R,4S)-4-Benzyloxymethyl-1-(tert-butyldiphenyl)silyloxy-5-(tert-butyloxycarbonyl)amino-2,3-pentanediol (**14**): Osmium tetroxide (1.13 ml of a 0.04 M solution in toluene, 0.025 mmol) was added at 0°C to a suspension of $K_3[Fe(CN)_6]$ (3.51 g, 7.5 mmol), K_2CO_3 (1.04 g, 7.5 mmol), methanesulfonamide (0.34 g, 2.5 mmol), and $(DHQD)_2PHAL$[22] (20.5 mg, 0.025 mmol) in 15 ml H_2O and 15 ml *tert* butanol.[23] **13** (1.3 g, 2.5 mmol) was added after 5 min at once and the mixture was stirred vigorously overnight. After cooling to 0°C sodium sulfite (3.78 g, 30 mmol) was added, and stirring was continued at this temperature for 1 hour. H_2O was slowly added, until all salts were dissolved. The aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. Flash chromatography (petrol ether/ethyl acetate, 1:1) of the crude product gave **14** (1.2 g, 88%) as a colorless oil. $[\alpha]_D^{20}$= −13.5 (c = 0.5, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.40 (s, 9 H), 2.00−2.11 (m, 1 H), 2.72 (d, J = 5.8 Hz, 1 H), 3.30 (dd, J = 5.2, 4.5 Hz, 1 H), 3.35 (dd, J = 5.5, 4.5 Hz, 1 H), 3.55 (d, J = 5.5 Hz, 2 H), 3.57 (br. s, 1 H), 3.68−3.73 (m, 1 H), 3.75−3.83 (m, 3 H), 4.47 (d, J = 12.1 Hz, 1 H), 4.51 (d, J = 12.1 Hz, 1 H), 5.03 (br. s, 1 H), 7.26−7.65 (m, 11 H), 7.61−7.65 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.96, 26.65, 28.17, 39.12, 41.95, 65.58, 69.70, 71.12, 71.85, 73.40, 79.14, 127.43, 127.57, 128.25, 129.61, 132.31, 135.31, 135.35, 135.38, 137.70, 156.64. − $C_{34}H_{47}NO_6Si$ (593.83): calcd. C 68.77, H 7.98, N 2.36; found C 68.49, H 7.96, N 2.31. − HRMS: calcd. for $C_{34}H_{48}NO_6Si$ [M^++H] 594.3251; found 594.3307.

(2R,3R,4S)-4-Benzyloxymethyl-1-(tert-butyldiphenyl)silyloxy-5-(tert-butyloxycarbonyl)amino-2,3-isopropylidendioxypentane (**15**): 10 ml of 2,2-dimethoxypropane (DMP) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) were added to a solution of **14** (1.18 g, 2 mmol) in 10 ml of acetone. The solution was stirred for 24 hours, before Na_2CO_3 (210 mg, 2 mmol) was added. After filtration of the solution, the solvent was removed in vacuo. Purification of the crude product by flash chromatography (petrol ether/ethyl acetate, 8:2) gave **15** (1.18 g, 94%) as a colorless oil. $[\alpha]_D^{20}$= +15.3 (c = 0.7, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03 (s, 9 H), 1.34 (s, 3 H), 1.38 (s, 3 H), 1.41 (s, 9 H), 1.95−2.11 (m, 1 H), 3.10−3.25 (m, 1 H), 3.46 (d, J = 5.9 Hz, 3 H), 3.71 (d, J = 2.6 Hz, 1 H), 3.73 (d, J = 2.4 Hz, 1 H), 4.01−4.15 (m, 2 H), 4.34 (d, J = 11.9 Hz, 1 H), 4.40 (d, J = 11.9 Hz, 1 H), 5.12 (br. s, 1 H), 7.24−7.40 (m, 11 H), 7.63−7.67 (m, 4 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.99, 26.61, 28.22, 39.76, 41.04, 64.11, 70.34, 72.93, 108.61, 127.31, 127.38, 127.49, 127.50, 128.17, 129.50, 129.55, 132.87, 132.97, 135.44, 135.47, 137.85, 155.81. − $C_{37}H_{51}NO_6Si$ (633.90): calcd. C 70.11, H 8.11, N 2.21; found C 69.93, H 8.24, N 2.22. − HRMS: calcd. for $C_{37}H_{52}NO_6Si$ [M^+ + H] 634.3563; found 634.3592.

(2R,3R,4S)-4-Benzyloxymethyl-5-(tert-butyloxycarbonyl)amino-2,3-isopropylidendioxy-1-pentanol (**16**): A 1 M solution of tetrabutylammonium fluoride in THF (5.2 ml, 5.2 mmol) was added to a solution of **15** (1.10 g, 1.74 mmol) in 30 ml of THF. The mixture was stirred for 12 hours, before sat. NH_4Cl solution (30 ml) and ethyl acetate (50 ml) were added. After separation of the layers, the aqueous layer was extracted twice with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. Flash chromatography (petrol ether/ethyl acetate, 1. 7:3, 2. 1:1) of the crude product gave **16** (660 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$= +21.0 (c = 0.4, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37 (s, 3 H), 1.38 (s, 3 H), 4.41 (s, 9 H), 2.00 (m_c, 1 H), 2.18 (br. s, 1 H), 3.15−3.33 (m, 1 H), 3.70−3.84 (m, 5 H), 3.95

(dd, J = 8.0, 6.1 Hz, 1 H), 4.00 (dd, J = 8.0, 3.8 Hz, 1 H), 4.46 (s, 2 H), 5.28 (br. s, 1 H), 7.27−7.36 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.95, 27.08, 27.08, 40.25, 42.02, 62.61, 70.01, 73.37, 76.58, 79.09, 79.61,108.59, 127.63, 127.70, 127.80, 128.44, 137.52, 156.11. − $C_{21}H_{33}NO_6$ (395.49): calcd. C 63.78, H 8.41, N 3.54; found C 63.75, H 8.51, N 3.41. − HRMS: calcd. for $C_{21}H_{34}NO_6$ [M^++H] 396.2386; found 396.2412.

(3R,4R,5S)-5-Benzyloxymethyl-3,4-isopropylidendioxypiperidine (**17**): Abs. pyridine (0.83 ml, 10 mmol) and trifluoromethansulfonic acid anhydride (0.83 ml, 4.93 mmol) were subsequently added to a solution of **16** (600 mg, 1.52 mmol) in 15 ml of dichloromethane at −15°C. Stirring was continued at this temperature for 1 hour, before 50 ml each of H_2O and ether were added. After separation of the layers, the organic phase was washed with 1 N $KHSO_4$ solution, sat. $NaHCO_3$ solution and with brine. Drying over Na_2SO_4 and evaporation of the solvent gave a yellow oil, which was dissolved in 10 ml of dichloromethane. The solution was cooled to 0°C, before 10 ml of a 4 M solution of HCl in dioxane was added. The solution was stirred for 2 hours, before the solvent was removed at room temp. under high vacuo. The yellow, semi-solid product obtained was dissolved in 50 ml of dioxane. This solution was added slowly, via a syringe pump, over a period of 3 hours to a vigorously stirred emulsion of 50 ml of dioxane and 100 ml of sat. $NaHCO_3$ solution at 50°C. Under these conditions stirring was continued for further 12 hours, before the solvent was removed in vacuo. The residue was dissolved in 50 ml each of H_2O and ethyl acetate. After separation of the layers, the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (dichloromethane/methanol, 95:5) giving rise to **17** (203 mg, 49%) as a pale yellow oil. $[\alpha]_D^{20}$= −82.2 (c = 0.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.36 (s, 3 H), 1.41 (s, 3 H), 1.87 (m_c, 1 H), 2.49 (m_c, 1 H), 2.55−2.70 (m, 2 H), 3.24−3.40 (m, 2 H), 3.45−3.57 (m, 2 H), 3.35−3.77 (m, 2 H), 4.47 (d, J = 11.9 Hz, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 7.26−7.36 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.63, 26.73, 39.58, 46.25, 48.92, 66.29, 72.77, 73.34, 80.37, 108.33, 127.56, 127.62, 128.34, 128.41, 138.32. − HRMS: calcd. for $C_{16}H_{24}NO_3$ [M^++H] 278.1756; found 278.1750. MS (70eV) m/z (%): 278 (99.2), 262 (13.8), 248 (14.7), 220 (100.0), 91 (28.9).

5-epi-Isofagomine (**5**): Trimethylsilyl iodide (20 µl, 0.14 mmol) was added to a solution of **17** (15 mg, 0.054 mmol) in 1 ml of dichloromethane under argon. After stirring for 1 hour at room temp. 5 ml of methanol were added and the solvent was removed in vacuo. The residue was dissolved in 5 ml of methanol and after addition of 2 ml of a 1 N HCl solution the mixture was stirred overnight at room temp. After evaporation of the solvent in vacuo, the residue obtained was dissolved in 1 ml of methanol. After addition of Dowex 50Wx8-200 (50 mg) the mixture was stirred for 10 min. The whole mixture was transferred to a short column (8 cm) filled with the same ion exchange resin. Washing the column with methanol and H_2O, and subsequent elution of the product with 2 N ammonia solution gave pure **5** (4.5 mg, 57%) after evaporation of the solvent as a pale yellow oil. $[\alpha]_D^{20}$= −10.3 (c = 0.5, MeOH). − ^{1}H NMR ([D_4]methanol, 200 MHz): δ = 2.10 (m_c, 1 H), 2.65−2.90 (m, 3 H), 3.07 (dd, J = 13.4 , 2.4 Hz, 1 H), 3.55−3.69 (m, 3 H), 3.8 (m_c, 1 H). − ^{13}C NMR ([D_4]methanol, 75 MHz): δ = 39.76, 43.75, 47.61, 62.69, 68.88, 69.95. − HRMS: calcd. for $C_6H_{14}NO_3$ [M^+ + H] 148.0974; found 148.0996. MS (70eV) *m/z* (%):148 (100.0), 147 (15.8), 130 (30.0), 107 (36.1), 93 (26.93).

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[23] Comercial available AB-mix-β® (purchased from Aldrich) can also be used, and gives the same result.

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