Synthesis of Spirocyclic Glucose–Proline Hybrids (GlcProHs)

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Abstract: A short synthetic route to polyhydroxylated spirocyclic glucose-based L-proline analogues is described from easily prepared 2,3,4,6 tetra-*O*-benzyl-D-glucono-lactone. The synthesis involves C-glycosylation of an exocyclic glucose-based epoxide with allyltributylstannane that affords functionalized C-ketosides containing an α-hydroxy ester moiety. Oxidation of the alcohol function, followed by stereoselective reductive amination provides an amine that undergoes iodine-induced aminocyclization to provide spirocyclic glucose–proline hybrids bearing an iodomethylene side-chain. The iodo function of the side-chain can be converted into other functional groups such as ester and hydroxyl groups, thereby allowing additional modifications to the pyrrolidine ring.

Key words: amino acids, carbohydrates, glycopeptides, glycosyl amino acids, proline

Proline plays an important role in the formation of secondary structures in peptides and proteins because it induces a reversal in backbone conformation resulting in the formation of reverse turns and disruption of helices and sheets in proteins. Besides the occurrence of proline in β-turns, proline-rich sequences also exist as extended helices[1] (polyproline-I and polyproline-II) and antimicrobial peptides.[2] Hydroxylated proline residues occur in nature in the form of collagenous peptides, virotoxin cyclic heptapeptides[3] and other peptides[4,5] and the role of hydroxylated proline residues on the conformational stability of the collagen triple helix have been extensively investigated.[6] Over the years a plethora of proline analogues such as C^{β}-, C^{γ}- and C^{δ}-substituted prolines,[7–10] azaprolines,[11] pseudoprolines,[12] silaproline,[13] proline amino acid chimera[14] and fused bicyclic proline[15–17] analogues have been developed to study the structural and biological properties of proline surrogates in peptides (Figure 1).[18]

To extend the molecular repertoire of bicyclic proline analogues, we became interested in the design and synthesis of spirocyclic sugar–proline hybrids[19] (SProHs, Figure 2). Spirocyclic sugar–proline analogues combine the molecular features of carbohydrates (furan- or pyran-based polyol) with the unique features of proline. The resulting hybrid is a polyfunctional building block, which may find use as glycomimetic, prolinemimetic, peptidomimetic[19c] and scaffold for combinatorial synthesis. In particular, the proline mimetic properties of spirocyclic SProHs have attracted our interest, because polyhydroxylated amino acids may induce novel secondary structures in small

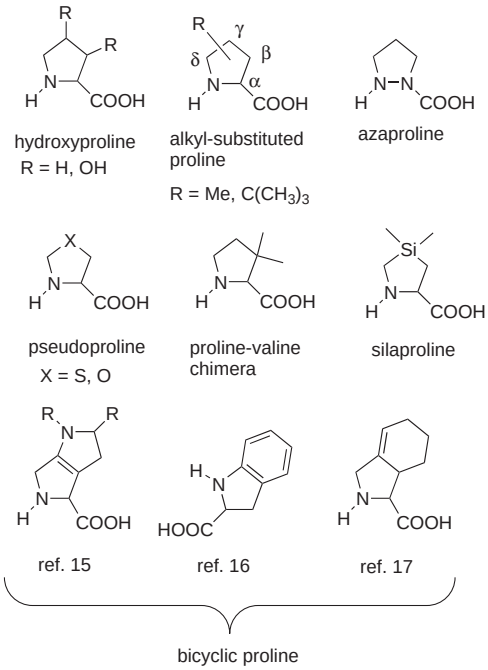

Figure 1 Previously synthesized proline analogues that have been proposed to mimic the properties of proline when incorporated into peptides.

peptides. For instance, incorporation of unprotected sugar amino acids into small peptides such as gramicidin S[20] and opioid peptides[21] prohibited the formation of the targeted secondary structural motif. Instead, unusual turn structures stabilized by intramolecular hydrogen bonds between sugar hydroxyl groups and the peptidic amide backbone were observed.[22] Similar effects may also be observed with spirocyclic SProHs. In addition, derivatization or decoration of the polyol scaffold may be used as a tool to tailor the chemical, physical, biological and conformational properties of the proline analogue in peptides. To explore the proline mimetic properties of spirocyclic SProHs we report here the synthesis of a spirocyclic glucose-based proline hybrids (GlcProHs). To the best of our knowledge glucose-based spirocyclic proline analogues have previously not been reported.[23]

The synthesis started with the readily available D-gluco-based lactone **1**[25] (Scheme 1) which reacts with the enolate of α-bromo acetic acid methylester generated from lithium bis(trimethylsilyl)amide [$LiN(SiMe_3)_2$] in tetrahydrofuran (THF) at –78 °C, to produce the exocyclic epoxide **2** in 80% yield as a single stereoisomer.[28] Trimethylsilyltrifluoromethanesulfonate (TMSOTf)-promoted C-glycosylation of epoxide **2** with allyltributyl-

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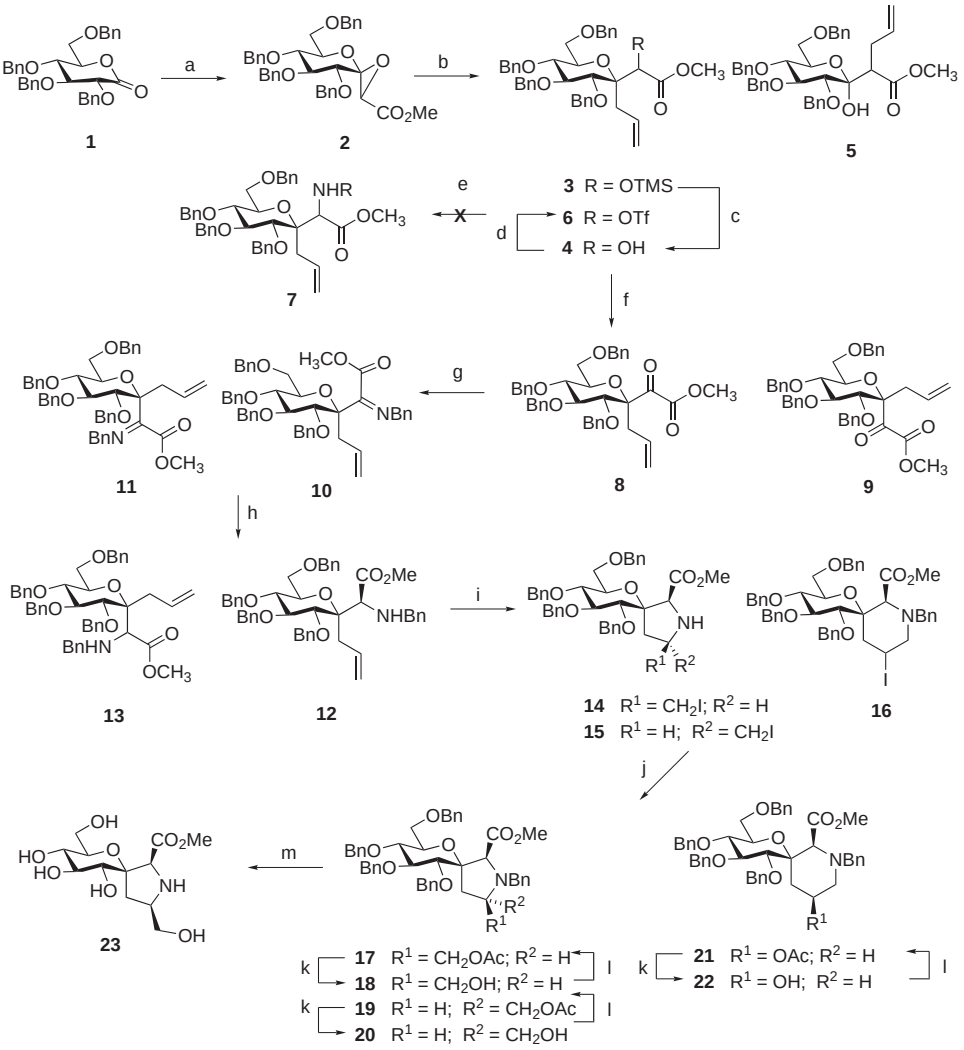


Scheme 1 Synthesis of glucose–proline hybrids **17** and **20**. *Reagents and conditions*: a) $BrCH_2CO_2Me$, LHMDS, THF, –78 °C, 2 h, 80%; b) $Bu_3SnCH_2CHCH_2$, TMSOTf, CH_2Cl_2, 0 °C, 0.5 h, 70%; c) TFA (5 equiv), THF–H_2O (5:1), r.t., overnight, quant.; d) Tf_2O, pyridine, 0 °C, 2 h, 92%; e) NH_2R' (R′ = Bn, PMB, *tert*-butyl-carbamate), CH_2ClCH_2Cl, 50 °C, 2 d; f) DMSO, TFAA, CH_2Cl_2, TEA, –78 °C, 3 h, 80%; g) NH_2Bn, $TiCl_4$, Et_2O, 0 °C to r.t., 2 × 4 h, 96%; h) $NaCNBH_3$, AcOH, MeOH, 0 °C, 3h, quant.; i) I_2, CH_2Cl_2–Et_2O 1:1, 0 °C to r.t., overnight; j) AgOAc, toluene, r.t., overnight; k) K_2CO_3, MeOH, r.t., 1 h, 95% (combined yield); l) pyridine, Ac_2O, r.t., 1 h, quant.; m) $Pd(OH)_2$, H_2, HCl, MeOH, r.t., 6 h, quant.

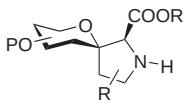


Figure 2 Design of sugar–proline hybrids (SProHs). The bicyclic and polyfunctional nature of SProHs may induce novel secondary structures when incorporated into peptides. In addition, decoration of the polyhydroxylated scaffold may be used to tailor the physical, chemical and biological properties of proline.

stannane in dichloromethane at 0 °C afforded a mixture containing silylether **3** and alcohol **4** (ratio: **3**:**4** = 7.5:1) in a combined yield of 70%. Compounds **3** and **4** were obtained as a single diastereoisomer with uncharacterized stereochemistry at C-2. In addition, we were also able to obtain 20% of the acetal **5** as a diastereomeric mixture. The silylether **3** was hydrolyzed quantitatively into alcohol **4** by exposure to trifluoroacetic acid-containing wet THF. Compound **4** served as starting material for the installation of the amino function at C-2. Initially, we attempted to introduce the amino function by nucleophilic displacement of the triflate **6** prepared by reaction with trifluoromethanesulfonic anhydride in pyridine. However, exposure of the triflate to various nucleophiles including benzylamine, *p*-methoxybenzylamine and *tert*-butyl carbamate at low and elevated temperatures resulted only in trace amounts of the desired amine **7**.[29] To install the amino function, we turned to reductive amination. Initially, the alcohol **4** was oxidized to ketone **8** at –78 °C using a mixture containing trifluoroacetic anhydride, triethylamine and dimethylsulfoxide in dichloromethane to produce ketone **8** in 80% isolated yield. During this reaction, we also observed ketone **9** as a by-product in 10% yield. The configuration at the anomeric position in compounds **8** and **9** was deduced on the basis of observed/unobserved NOE[30] contacts (Figure 3). For instance, subjection H-5 to a one-dimensional GOESY[24] experiment showed inter-

proton effects to one of the allylic protons (7.9% NOE[30]) measured relative to the singlet H-5 signal. This is consistent with the structure **8** bearing an allyl group at the axial position. In contrast, the C-3 epimer **9** showed interproton effects between the two allylic protons and H-4 (3.3% and 1.1% NOE, respectively, Figure 3).

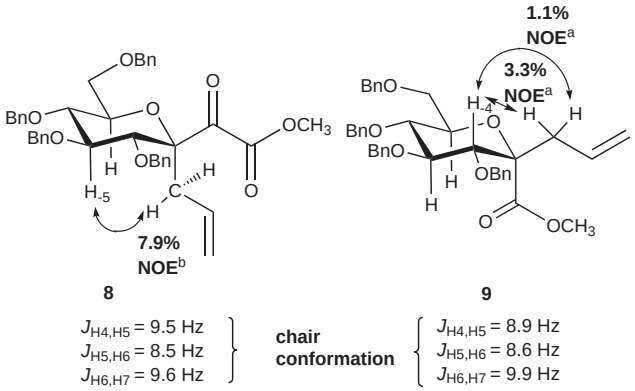
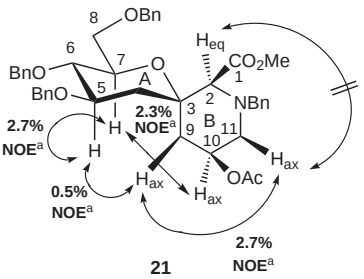


Figure 3 Interproton effects (NOE) and homonuclear proton coupling constants observed for C-glycosidic ketones **8** and **9**. Solvents: [a] C_6D_6; [b] $CDCl_3$.



1. A ring $^6C_3$ chair conformation:

H-4 (d, $J_{4,5}$ = 9.1 Hz), H-5 (dd, $J_{5,6}$ = 9.5 Hz); H-6 (dd, $J_{6,7}$ = 9.5 Hz)

2. B ring chair conformation:

H-9_{ax} (dd, $J_{9ax,10}$ = 11.7 Hz, J_{gem} = 13.5 Hz), H-11_{ax} (dd, J_{gem} = $J_{10,11ax}$ = 10.7 Hz) long-range couplings: $J^4_{H\text{-}9eq,H\text{-}11eq}$ = 0.9Hz; $J^4_{H\text{-}9eq,H\text{-}2eq}$ = 1.0 Hz

3. C-2 (S) configuration:

NOE: H-7/H-10_{ax}; H-7/H-5; H-5/H-9_{ax}; NOE (unobserved): H-11ax/H-2_{eq}

Figure 4 Interproton effects and conformational properties of piperidine-based amino ester **21** used in the assignment of the configuration at C-2. In particular, the observed interproton NOE between H-7 and H-10_{ax} is indicative of the C-2 *S* configuration. [a] Recorded in C_6D_6.

Subsequently, the ketones **8** and **9** were converted to the α-amino esters **12** and **13** in a two-step procedure. At first, compounds **8** and **9** were converted to the Schiff bases **10** and **11** using titanium tetrachloride promoted imination with benzylamine in diethyl ether to afford imines **10** and **11** in 96% and 90% yield, respectively, after chromatographic purification. Both imines were reduced to the corresponding amino esters **12** and **13** in quantitative yield using sodium cyanoborohydride in acetic acid-containing methanol. In both cases, the reduction of the imine produced a single stereoisomer. The absolute stereochemistry at C-2 of amino ester **12** was assigned at a later stage while the stereochemistry at C-2 in compound **13** has yet to be determined.

With amino ester in hand we installed the pyrrolidine ring by iodocyclization in dichloromethane and ether to produce an inseparable isomeric mixture containing iodo compounds **14**, **15** and **16**. To separate the compounds from each other we converted the mixture into the alcohols **18**, **20** and **22** by a two-step process. At first, **14**, **15** and **16** were exposed to silver acetate in toluene to produce an inseparable mixture of esters **17**, **19** and **21** that by treatment with potassium carbonate in methanol afforded the alcohols **18**, **20** and **22** in 44%, 45% and 6% yield, respectively, after column chromatography.

To assign the stereochemistry at C-2 the alcohols **18**, **20** and **22** were converted into the acetates **17**,[26] **19**,[26] and **21**[26] using standard conditions (acetic anhydride in pyridine). We selected the rigid spirocyclic pipecolic acid analogue **21** to assign the stereochemistry at C-2 (Figure 4). Spirocyclic compound **21** contains two rings referred to as ring A and B. The large coupling constants for $J_{4,5}$, $J_{5,6}$ and $J_{6,7}$ > 9.0 Hz in conjunction with interproton NOE effects between H-5 and H-7 establish the $^4C_1$ chair conformation of the A-ring. The chair conformation of ring B is consistent with the observed vicinal diaxial and long-range coupling constants. For instance, the axial position of protons H-9_{ax}, H-10_{ax} and H-11_{ax} can be deduced by their large vicinal diaxial coupling constants $J_{9ax,H10ax}$, $J_{10ax,H11ax}$ > 10.5 Hz, while the observed long-range coupling constants between $J_{9eq,11eq}$ = 0.9 Hz and $J_{9eq,2eq}$ = 1.0 Hz confirm the equatorial position of H-9_{eq}, H-11_{eq} and H-2_{eq} in ring B. Finally, the observed interproton effects (NOE[30]) between H-7/H-10_{ax}; H-7/H-5; H-5/H-9_{ax} and the unobserved effect between H-11_{ax}/H-2_{eq} using a one-dimensional GOESY[24] experiment determines the C-2(*S*) configuration (Figure 4).

Once we had established the configuration at C-2 in compound **21**, we turned our interest to the stereochemistry at C-10 of the spirocyclic proline analogues **17** and **19**. Since the iodocyclization was performed on a single stereoisomer **12**, we assume that the stereochemistry at C-2 of the proline analogues **17** and **19** remains *S* based on the previous assignment with piperidine analogue **21**.[31] To discriminate between compounds **17** and **19** we used NOE experiments (Figure 5). For instance, the observed interproton effects between H-10/H-2 and H-10/H-7 for compound **17** are consistent with the C-10(*R*) stereochemistry. By comparison, proline analogue **19** did not show any interproton effect between H-2/H-10 that is consistent with a C-10(*S*) configuration. Finally, deprotection of the *O*- and *N*-benzyl ether protecting groups in compound **18** was achieved by catalytic hydrogenation using Pearlman's catalyst in acidified MeOH to afford polyhydroxylated proline analogue **23** in quantitative yield.[27]

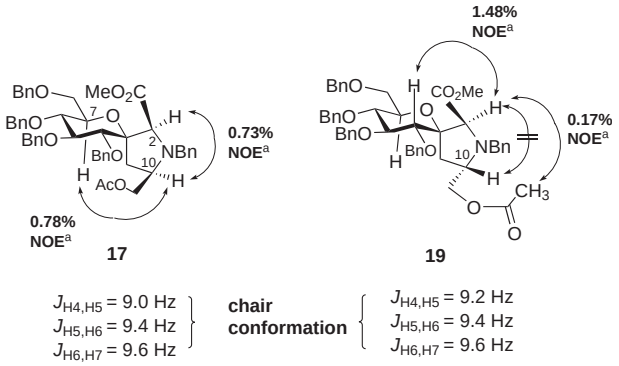


Figure 5 Interproton effects (NOE) observed for GlcProHs **17** and **19**. The observed NOE between H-2 and H-10 and H-10 and H-7 are a diagnostic tool to discriminate between C-10 epimers **17** and **19**. [a] Recorded in C_6D_6.

In summary, we have developed a novel and short synthetic pathway into spirocyclic polyhydroxylated glucose-based L-proline analogues. It can be envisaged that decoration of the carbohydrate scaffold provides a tool to adjust the physical, biological and pharmacological properties of the proline analogues. We are currently investigating the prolinemimetic and glycomimetic properties of the synthesized GlcProHs and glucose–pipecolic acid hybrid.

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(26) Analytical data for compounds **17**, **19** and **21**.
Compound **17**: ^{1}H NMR (500 MHz, C_6D_6, r.t., TMS): δ = 1.76 (s, 3 H), 2.20 (dd, H-9a, *J* = 13.7 Hz, *J* = 6.2 Hz), 2.38 (dd, H-9b, *J* = 13.7 Hz, *J* = 10.3 Hz), 3.00 (s, 3 H), 3.34 (m, H-10), 3.56–3.70 (m, 5 H, H-5, H-6, H-7, H-8a,b), 3.75 (s, H-2), 3.83–3.91 (m, H-4, 1 H, *J* = 9.0 Hz, *J* = 14.5 Hz), 4.12 (d, 1 H, *J* = 13.5 Hz), 4.28 (dd, H-11a, *J* = 10.6 Hz, *J* = 4.6 Hz), 4.44–4.53 (m, 2 H, H-11b), 4.54–4.58 (d, 2 H, *J* = 11.0 Hz), 4.60 (d, 1 H, *J* = 11.2 Hz), 4.80 (d, 2 H, *J* = 11.2 Hz), 4.83 (d, 1 H, *J* = 11.2 Hz), 5.17 (d, 1 H, *J* = 12.4 Hz), 6.98–7.21 (m, 25 H). ^{13}C NMR (300 MHz, $CDCl_3$, r.t.): δ = 20.95, 29.99, 51.54, 60.41, 60.84, 67.20, 69.39, 72.48, 72.77, 73.52, 75.05, 75.52, 76.04, 76.69, 78.66, 86.14, 87.48, 126.01–128.79 (arom. C), 138.03, 138.04, 138.35, 138.91, 139.32, 170.99, 171.96. HRMS: *m/z* calcd for $C_{49}H_{54}NO_9$ $[M + H]^+$: 800.3793; found: 800.3794.
Compound **19**: ^{1}H NMR (500 MHz, C_6D_6, r.t., TMS): δ = 1.68 (s, 3 H), 2.14 (dd, H-9a, *J* = 14.2 Hz, *J* = 1.1 Hz), 2.82 (dd, H-9b, *J* = 14.2 Hz, *J* = 9.6 Hz), 3.07 (s, 3 H), 3.57 (dd, H-6, *J* = 9.4 Hz, *J* = 9.3 Hz), 3.63 (dd, H-5, *J* = 9.4 Hz, *J* = 9.2 Hz), 3.65–3.72 (m, H-4, H-8a), 3.75 (dd, H-8b, *J* = 11.1 Hz, *J* = 1.6 Hz), 3.77–3.81 (m, H-7, H-10), 3.84 (d, 1 H, *J* = 14.4Hz), 3.92 (s, H-2), 4.11 (d, 1 H, *J* = 14.2 Hz), 4.28 (dd, H-11a, *J* = 10.7 Hz, *J* = 7.8 Hz), 4.38 (dd, H-11b, *J* = 10.7

Hz, J = 5.4 Hz), 4.47 (d, 1 H, J = 12.5 Hz), 4.49–4.56 (m, 3 H), 4.58 (d, 1 H, J = 12.4 Hz), 4.76 (d, 1 H, J = 11.2 Hz), 4.77 (d, 1 H, J = 11.1 Hz), 5.20 (d, 1 H, J = 12.4 Hz), 7.00–7.28 (m, 25 H). ^{13}C NMR (300 MHz, $CDCl_3$, r.t.): δ = 20.99, 27.69, 51.14, 53.04, 59.97, 67.23, 69.04, 72.86, 73.04, 73.21, 73.71, 75.12, 75.63 (2 C), 78.74, 85.88, 86.94, 126.03-128.49 (arom. C), 137.00 (2 C), 138.50, 138.90, 139.47, 170.91, 170.93. HRMS: *m/z* calcd for $C_{49}H_{54}NO_9$ $[M + H]^+$: 800.3793; found: 800.3793.

Compound **21**: ^{1}H NMR (500 MHz, C_6D_6, r.t., TMS): δ = 1.66 (s, 3 H), 2.67 (dd, 1 H, J = 13.6 Hz, J = 11.6 Hz), 2.81 (dd, J = 13.6 Hz, J = 4.1 Hz), 3.04 (s, 3 H), 3.10 (dd, H-11a, J = 10.2 Hz, J = 5.6 Hz), 3.41 (d, H-4, J = 9.1 Hz), 3.63 (s, H-2), 3.64–3.74 [m, H-11b, 2 H (NBn), H-6], 3.79 (dd, H-8a, J = 11.2 Hz, J = 4.4 Hz), 3.84–3.91 (m, H-5, H-8b), 4.07 (m, H-7,), 4.38 (d, 1 H, J = 12.5 Hz), 4.44 (d, 1 H, J = 12.0 Hz), 4.59 (d, 1 H, J = 12.0 Hz), 4.63 (d, 1 H, J = 11.4 Hz), 4.69 (d, 1 H, J = 12.0 Hz), 4.76 (d, 1 H, J = 11.1 Hz), 4.77 (d, 1 H, J = 11.4 Hz), 5.14 (d, 1 H, J = 12.5 Hz), 5.49 (m, H-10), 6.99–7.16 (m, 25 H). ^{13}C NMR (300 MHz, C_6D_6, r.t.): δ = 21.56, 26.39, 50.15, 50.44, 59.47, 69.73, 72.78, 73.44, 74.35 (2 C), 75.38 (2 C), 75.82, 78.74, 79.36, 80.95, 85.26, 126.50–128.90 (arom. C), 138.78 (3 C), 139.24, 139.38, 170.71 (2 C). HRMS: *m/z* calcd for $C_{49}H_{54}NO_9$ $[M + H]^+$: 800.3793; found: 800.3791.

(27) Analytical data for compound **23**.
^{1}H NMR (300 MHz, CD_3OD, r.t., TMS): δ = 2.13 (m, 1 H), 2.41 (m, 1 H), 3.23–3.21 (m, H-5, H-6), 3.49 (m, H-7), 3.60–3.71 (m, H-4, H-8a), 3.85 (s, 3 H), 3.87–4.00 (m, H-10, H-8b, H-11a,b), 4.22 (s, H-2). ^{13}C NMR (300 MHz, CD_3OD, r.t.): δ = 27.27, 54.30, 61.46, 61.85, 62.98, 68.74, 70.77, 71.57, 76.64, 77.03, 88.31, 168.49. HRMS: *m/z* calcd for $C_{12}H_{22}NO_8$ $[M + H]^+$: 308.1340; found: 308.1343.

(28) Subjection of the singlet H-2 proton in **2** to a one-dimensional GOESY[24] experiment showed interproton effects to H-5 (0.65% NOE) and H-7 (0.4% NOE) measured relative to the singlet H-2 signal. This is consistent with the epoxide structure **2**.

(29) Unreacted starting material was recovered in over 90% yield together with trace amounts of the corresponding amines and amides that were identified by HPLC-MS.

(30) A 40 ms gaussian pulse with a 560 ms mixing time was used.

(31) **Synthetic Procedures for the Synthesis of Compounds 2, 4, 8, 10, 12, 17, 19, 21.**

Synthesis of 2.

Methyl bromoacetate (4.1 mmol) was dissolved in dry THF (20 mL) and cooled to –78 °C before lithium bis(trimethylsilyl)amide (4 mL of a 1 M solution in THF) was slowly added. The reaction mixture was kept at –78 °C for an additional 30 min. Subsequently, a THF solution (5 mL) containing the lactone **1** (1 mmol) was added over a period of 10 min. After 1 h, the temperature was raised to r.t. and stirred for 15 min before sat. aq NH_4Cl solution (20 mL) was added. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 and partitioned with H_2O. The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexane–EtOAc, 5:1) to provide **2** as a solid (488 mg, 80%).

Synthesis of 4.

To a mixture of epoxide **2** (480 mg, 0.79 mmol) and allyltributylstannane (0.995 mL, 3.15 mmol) in anhyd CH_2Cl_2 (15 mL) was added dropwise TMSOTf (0.427 mL, 2.36 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C before sat. $NaHCO_3$ solution (10 mL) was added to quench the reaction. The organic layer was dried (Na_2SO_4), concentrated and purified by flash column chromatography using hexane–EtOAc 8:1 → 2:1 to get **3** (449 mg) and **4** (53 mg) as a syrup. The trimethylsilyl ether **3** was converted to **4** (368 mg, quant.) by exposure to TFA (0.196 mL, 5 equiv) in aq THF (THF–H_2O, 5:1) overnight.

Synthesis of 8.

To a solution of dry DMSO (133 μL, 1.88 mmol)) in anhyd CH_2Cl_2 (12 mL) at –78 °C was added trifluoroacetic anhydride (200 μL, 1.41 mmol). After 10 min, a solution of compound **4** (307 mg, 0.47 mmol) dissolved in CH_2Cl_2 (8 mL) was added slowly and stirred for 40 min at –78 °C. Then, Et_3N (394 μL, 2.82 mmol) was added dropwise and the reaction was kept at –78 °C for 2 h. The cooling bath was removed and the reaction was quenched with H_2O (10 mL). The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic solution was dried with anhyd Na_2SO_4, concentrated and purified by flash column chromatography (hexane–EtOAc, 6:1) to give **8** (244 mg, 80%).

Synthesis of 10.

To an ice-cooled solution of **8** (296 mg, 0.45 mmol) and benzylamine (148 μL, 1.36 mmol) in anhyd Et_2O (15 mL) was added dropwise $TiCl_4$ (0.544 mL of a 1 M solution in CH_2Cl_2, 0.54 mmol) at 0 °C. After complete addition, the ice bath was removed and the reaction mixture was stirred for 4 h. Then, sat. $NaHCO_3$ solution was added. The organic layer was separated and the water layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was dried (Na_2SO_4), concentrated and purified by flash column chromatography (hexane–EtOAc, 6:1) to provide a mixture of **8** (30%) and **10** (70%). Complete conversion of **8** to **10** was achieved by repetition of the previous imination procedure to provide **10** (323 mg, 96%).

Synthesis of 12.

To an ice-cooled solution of **10** (240 mg, 0.32 mmol) in MeOH (9 mL) was added $NaCNBH_3$ (128 mg, 1.95 mmol), followed by 98% AcOH (39 μL, 0.65 mmol). The reaction mixture was stirred for 3 h at 0 °C and then quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), concentrated and purified by flash column chromatography (hexane–EtOAc, 5:1) to afford **12** (239 mg, quant.).

Synthesis of 17, 19 and 21.

To a solution of **12** (340 mg, 0.46 mmol) in a 50% mixture of CH_2Cl_2 in Et_2O (12 mL, 1:1) was added iodine (175 mg, 0.69 mmol) at 0 °C. After 5 min, the ice bath was removed and the reaction was stirred for 12 h. The organic layer was washed with sat. $Na_2S_2O_3$ solution, H_2O (2 mL) and dried (Na_2SO_4). The crude mixture (396 mg) was dissolved in toluene (15 mL), AgOAc (1.146 g, 6.88 mmol) was added and stirred for 12 h. Subsequently, the suspension was filtered and the solution was concentrated under reduced pressure to provide an inseparable mixture of **17**, **19** and **21** (323 mg). The mixture was dissolved in MeOH (8 mL), K_2CO_3 (73 mg, 0.53 mmol) was added and stirred for 1 h before quenching with sat. NH_4Cl solution (1 mL) and H_2O (9 mL). The solvent was removed under reduced pressure and the dry residue was dissolved in CH_2Cl_2 (15 mL) and partitioned with H_2O (10 mL). The organic layer was concentrated, dried and purified by flash column chromatography (hexane–EtOAc, from 4:1 to 2:1) to yield **18** (135 mg, 44%), **20** (138 mg, 45%) and **22** (20 mg, 6.5%). Acetylation with a 1:1 mixture of pyridine in Ac_2O afforded compounds **17**, **19** and **21** in quantitative yield.