Scalable Synthesis of a Mycosamine Donor. Overcoming Difficult Reactivity in Allose Systems

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Abstract: Mycosamine is a dideoxyaminosugar found in medicinally relevant macrolides, including amphotericin B and nystatin. Herein we report a reliable, high yielding, scalable synthesis of a mycosamine donor. A major goal of our approach was to minimize purifications via judicious selection of protecting groups; the inherent properties of the allose framework created some deprotection obstacles that were ultimately solved.

Key words: asymmetric synthesis, natural products, glycosylations, protecting groups, medicinal chemistry

Amphotericin B[1] is the most prominent member of the family of mycosamine macrolides and an important clinical agent for the treatment of systemic and chronic fungal infections. Despite being known for over a half century, its mechanism of action is still not clearly understood.[2] Amphotericin B (Figure 1) contains several intriguing domains: a conjugated heptaene (which gives amphotericin B its distinctive yellow color), a polyacetate segment, and two polypropionate derived subunits.

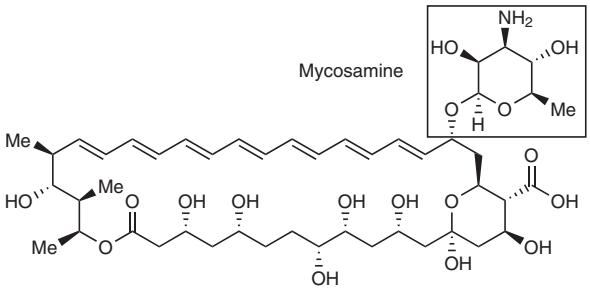
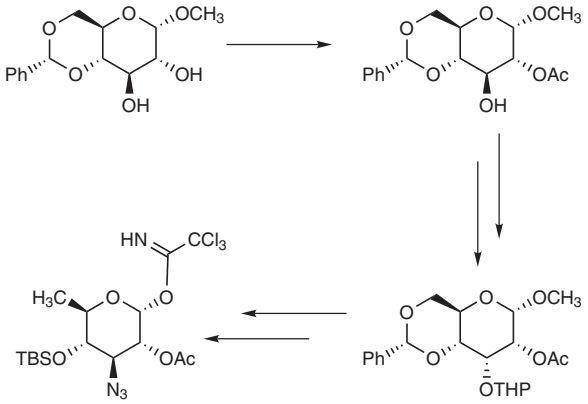


Figure 1 Amphotericin B.

An additional domain is the mycosamine, an unusual dideoxyaminomannose that is linked to the aglycon as the β-anomer. Although syntheses of the related mycosamine macrolide aglycons of rimocidin[3] and candidin[4] have been reported, successful coupling with a mycosamine donor has only been achieved by Nicolaou and co-workers in their synthesis of amphotericin B.[5] Two other reports of mycosamine donors exist in the literature.[6] The donor prepared by Packard and Rychnovsky was obtained in 6% yield and used nystatin,[7] another mycosamine macrolide, as starting material.[6a] The protecting group scheme employed by Alais and David[6b] is incompatible with the functionalities of amphotericin B.

Within the context of our ongoing research program to explore the behavior of amphotericin B and its conjugates[8] we required significant amounts of a mycosamine donor. We initially considered following the existing route that has been employed in the context of the total synthesis of amphotericin B (sketched in Scheme 1). However the reported use of stoichiometric amounts of $HgCl_2$[9] was not acceptable for the scale we required. This 15-step route also necessitated 13 to 14 chromatographic purifications and produced only 900 μmol of the donor. Given the large number of chromatographic unit operations and its untested scalability it was not clear whether the existing route would serve our needs. In our analysis, we attributed the lack of clean reactions to the potential lability of the THP and acetate groups and therefore elected to employ sturdier alternatives.



Scheme 1 Synthesis of a mycosamine donor by Nicolaou et al.

The reported step for the glycosylation of amphoteronolide relied on anchimeric assistance from a C(2)-acetate group to ensure selective β-glycosylation (Scheme 2).[5] However this reaction also produced a *virtually equal* amount of the corresponding orthoester [19% yield as compared to a 20% yield of the desired glycoside (50% of the aglycon was also recovered)]. As it has been demonstrated that the amount of orthoester formation can be reduced by changing from acetate to a more sterically demanding ester (e.g. pivaloate or benzoate),[10] we decided to include a benzoate ester in our synthetic design. This would have the additional benefit of providing the increased stability we sought in the C(2)-ester.

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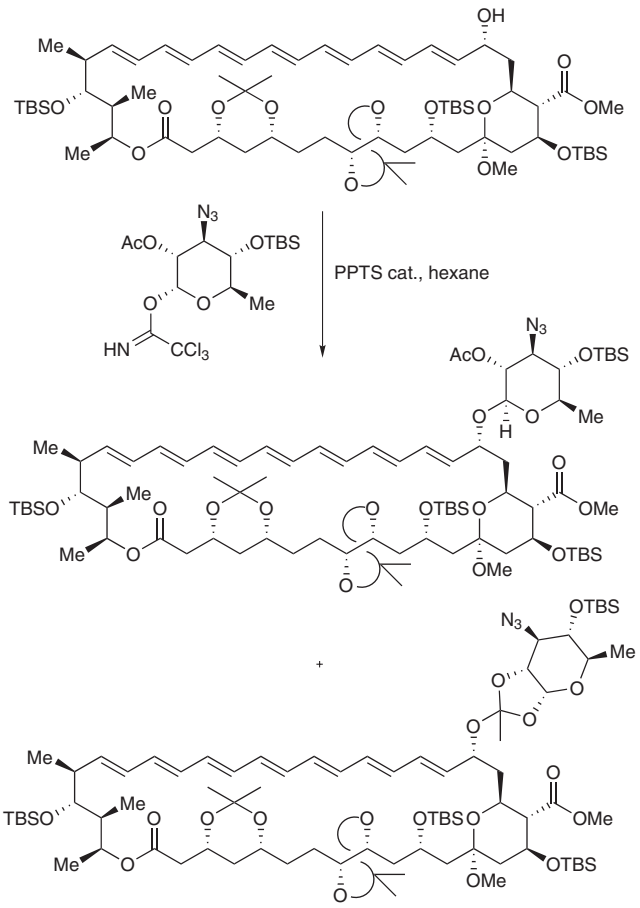
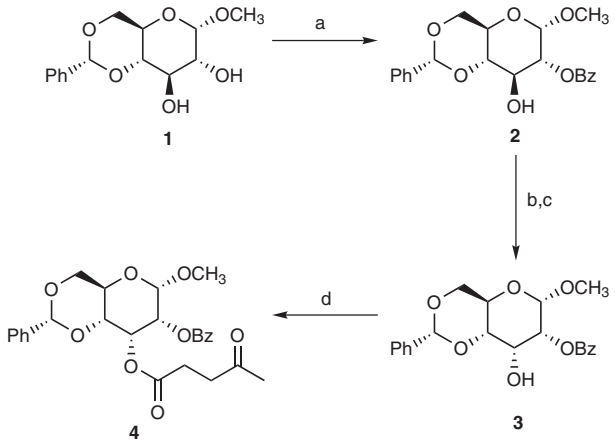


Scheme 2 Reported glycosylation of protected amphoteronolide.

Our approach to a mycosamine donor began from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) (Scheme 3). The stoichiometric use of stannylidene acetals for the selective acylation of the C(2) of glucose systems is widely used.[11] However, as removal of tin by-products is known to be problematic and/or tedious, especially on large scale, we elected to employ the one-step method of Matsumura et al., which utilizes only a catalytic amount of dimethyltin dichloride.[12] On a >900 mmol scale we obtained 81% of the desired product **2**.

Inversion of configuration at the C(3) was achieved through a two-step sequence involving PDC oxidation and $NaBH_4$ reduction. Notably, the only purification required after either of these reactions was filtration over Florisil® after the PDC oxidation. With allose derivative **3** in hand, we had to select an appropriate protecting group for the C(3)-hydroxyl group. As discussed, a THP group was not deemed suitable. As the protecting group would have to survive hydrogenolysis, iodination, silylation and radical reduction and be orthogonal to a TBS ether, benzoate ester and methyl acetal, our options were limited. We chose to utilize a second ester that could be readily removed in the presence of the benzoate. Phenoxyacetate and methoxyacetate are both known to hydrolyze at rates much higher than benzoate.[13] Much to our surprise, initial experiments revealed that in this system the rate of benzoate cleavage was competitive. We attributed these results to inherent reactivity afforded by the allose scaffold and this led us to seek a protecting group that could be removed under conditions completely orthogonal to the benzoate.

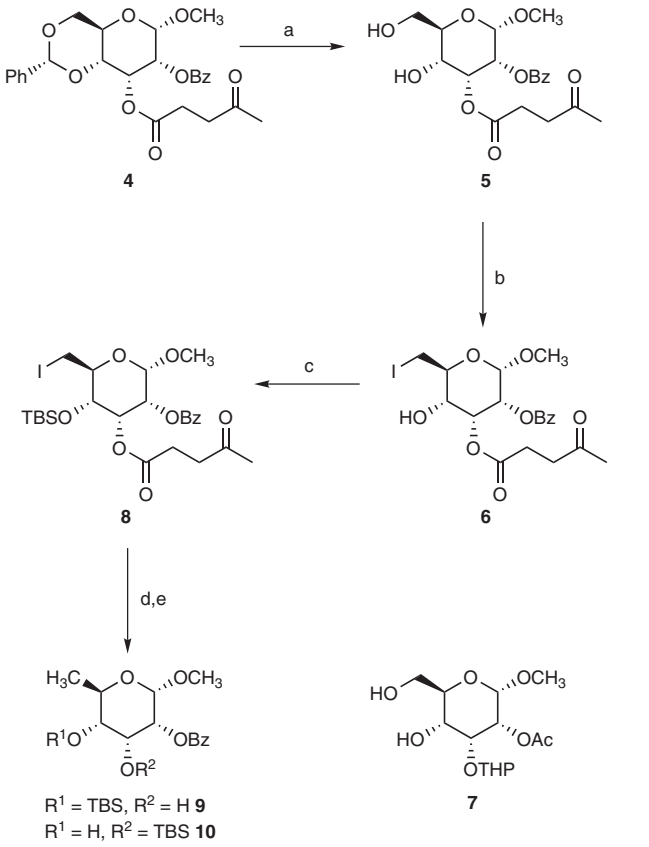


Scheme 3 *Reagents and conditions*: (a) BzCl (1.2 equiv), K_2CO_3 (2.0 equiv), Me_2SnCl_2 cat., THF, r.t., 72 h, 81%; (b) PDC (5.0 equiv), 3 Å MS, CH_2Cl_2, 24 h; (c) $NaBH_4$ (1.0 equiv), MeOH–THF (8.5:1), –15 °C, 45 min, 89% over 2 steps; (d) levulinic acid (2.0 equiv), DCC (2.0 equiv), DMAP (0.7 equiv), CH_2Cl_2, r.t., 21 h, 88%.

Levulinate esters are known to be readily cleaved in the presence of hydrazine, generally requiring only a small excess of reagent and short reaction time (<15 min) to achieve deprotection.[14] The levulinate group has also been shown to be less prone to migration than acetate or benzoate.[14e,f] Under standard esterification conditions (DCC, DMAP), protection of **3** was achieved in 88% yield.

Hydrogenolysis of **4** using palladium on carbon proved a clean reaction, needing no purification step, save filtration to remove the catalyst (Scheme 4). Regioselective iodination at C(6) of diol **5** was readily achieved using Appel-like conditions,[15] affording hydroxy iodide **6** in 86% yield over 2 steps. Although the use of benzene as solvent at 45 °C for 4 hours has been reported necessary to achieve full conversion,[5] we found that the use of THF[16] led to complete conversion of **7** in 30 to 60 minutes at room temperature. It is unclear the extent to which this disparity is a solvent effect or altered reactivity resulting from the different protecting groups in **5** and **7**.

While the highly reactive, expensive TBSOTf has been employed to silylate the C(4)-hydroxyl group in high yield in a similar system,[5] we were concerned that this reagent would lead to formation of the silyl enol ether of the levulinate ketone; consequently, we opted for the mild and cheap reagent, TBSCl. The use of this reagent could however create the possibility of halogen exchange at C(6). In order to avoid this potential pitfall, the reaction was performed at high concentration (0.44 M with respect to **6**) in CH_2Cl_2 – conditions which caused precipitation of the imidazole hydrochloride byproduct. The silyl ether **8** was isolated in 95% yield and no iodide–chloride exchange could be detected by NMR or mass spectrometry. Reduction of iodide **8** proceeded in 95% yield.



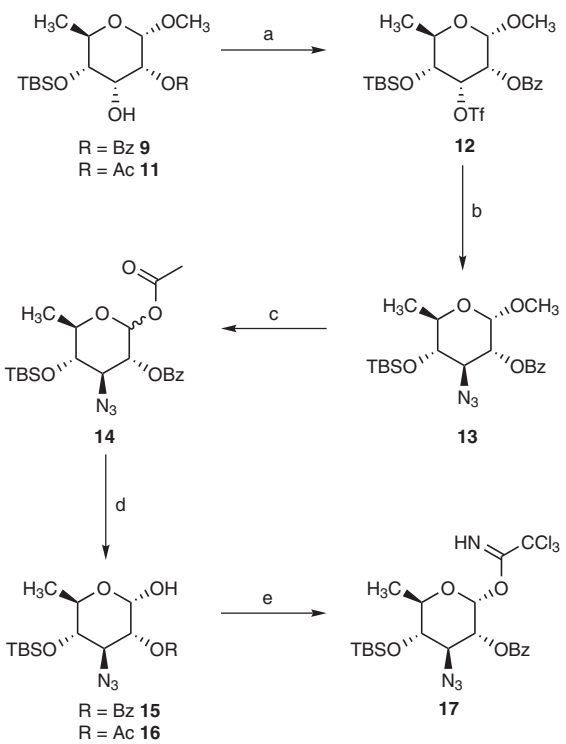
Scheme 4 *Reagents and conditions*: (a) H_2, 10% Pd/C cat., EtOAc, r.t., 16 h; (b) PPh_3 (2.0 equiv), I_2 (2.0 equiv), imidazole (7.5 equiv), THF, r.t., 1 h, 86% over 2 steps; (c) TBSCl (2.0 equiv), imidazole (4.5 equiv), CH_2Cl_2, r.t., 50 h, 95%; (d) Bu_3SnH (2.0 equiv), AIBN cat., toluene, Δ, 2 h, 95%; (e) $NH_2NH_2{\cdot}H_2O$ (20 equiv), pyridine–AcOH (3:2), r.t., 24 h, 95%.

At this stage we needed to carry out the selective cleavage of the levulinate ester – typically a facile endeavor (vide supra). However, in this instance this group proved to be extraordinarily recalcitrant to cleavage. The use of hydrazine acetate in methanol or anhydrous hydrazine in THF led to isolation of an *E/Z* mixture of hydrazones and only traces of desired product. Heating the hydrazones in either the presence or absence of base did not lead to cleavage. Attempts to effect removal using hydroxylamine hydrochloride in pyridine–ethanol were equally unsuccessful. $NaBH_4$ has been shown to readily cleave levulinates via ketone reduction followed by rapid spontaneous lactonization.[14g] In the case of levulinate **9** ketone reduction occurred readily but lactone formation was not observed. We also scanned a variety of bases, including KHMDS, *t*-BuOK, LDA, and NaH, in an attempt to induce lactonization. This afforded either no reaction or TBS and/or benzoate migration occurred. The same battery of bases was investigated in an attempt to induce cleavage via a Dieckmann-like reaction but only complex mixtures of products were observed.

The 2,3,4-*cis,cis* arrangement of hydroxyl groups in allose should be well poised for migrations of protecting groups. During our attempts to hydrolyze the levulinate ester we were mindful that strongly acidic or basic conditions could lead to deleterious results (vide supra). Being weary of such issues we nevertheless elected to revisit the use of hydrazine in a mixture of pyridine and acetic acid as solvent. Using 20 equivalents of hydrazine for 24 hours, we found that the levulinate could be removed from **8** to afford the desired 6-deoxyallose derivative **9** in an optimized yield of 95%, along with only minimal amounts (<2%) of the silyl migrated compound **10**. This extraordinary stability is testament to the sterically congested environment created around the levulinate carboxyl function by the adjacent *cis*-benzoate and TBS groups.

Although the triflation of **9** proceeded cleanly, the reaction time increased noticeably compared to the corresponding acetate **11** (16 h vs. 2 h,[5] Scheme 5). The crude triflate **12** rapidly reacted with sodium azide to afford the desired azido sugar **13** in a crude yield of 93% over two steps. Isolated **13** from the reaction mixture was of such purity that it could be used directly in the next step without additional purification. The sensitive functionalities of the subsequent compounds prompted us to store material at this stage and proceed in smaller batches from this point. The efficiency of this synthesis to this point has allowed us to prepare >98 mmol of **13** from a single batch of **1**.

Conversion of the methyl acetal of **13** to the corresponding anomeric ester **14** was carried out using catalytic amounts of H_2SO_4 in Ac_2O. We found that the formation



Scheme 5 *Reagents and conditions*: (a) Tf_2O (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, –40 °C – r.t., 16 h; (b) NaN_3 (1.1 equiv), 15-crown-5 (1.1. equiv), DMF, r.t., 30 min, 93% over 2 steps (crude); (c) Ac_2O, H_2SO_4 cat., 0 °C to r.t., 55 min, 60% over 3 steps; (d) $NH_2NH_2{\cdot}AcOH$ (1.2 equiv), DMF, r.t., 3 h, 94% (crude); (e) NaH (1.1. equiv), Cl_3CCN (10 equiv), CH_2Cl_2, 89% over 2 steps, based on

of anomeric acetate **14** was quite rapid, commonly being complete as the reaction reached room temperature. Allowing the reaction to proceed for two hours at room temperature, as previously reported,[5] resulted in nearly complete conversion of the TBS ether to the corresponding acetate. Moreover, to the best of our knowledge, this work and Nicolaou's report[5] constitute the only examples in the literature of a secondary TBS ether surviving these reaction conditions.[17] Careful TLC monitoring of this reaction allowed us to isolate the desired anomeric acetate **14** in 60% yield over three steps. While the isolation of only α-acetate[5] has been reported, we isolated a mixture of anomeric acetates. Typically the α-anomer is the thermodynamically favored product, as governed by the exo-anomeric effect.[18] However, with a benzoate at C(2) it is reasonable to expect that the β-acetate would be kinetically favored. As prolonged reaction time resulted in destruction of the C(4)-TBS ether, the reaction was quenched before the thermodynamic equilibrium was reached.[19]

We elected to access the lactol **15** in a single step from the anomeric acetate **14** using hydrazine acetate.[20] Whereas the C(2)-acetate lactol **16** required at least two iterations of silica gel chromatography to obtain primarily the α-anomer,[5] C(2)-benzoate hemiacetal **15** upon workup was found to be solely the α-anomer (as detected by ^{1}H NMR spectroscopy) and of sufficient purity to be used directly in the subsequent reaction.

Formation of the trichloroacetimidate donor **17** was achieved in 89% yield over two steps (based on 25% recovered lactol **15**) using NaH and trichloroacetonitrile in methylene chloride. It was originally reported that the β-anomer of lactol **16** does not react under these conditions.[5] We have found that the β-anomer does indeed react but the β-trichloroacetimidate is not stable to silica gel chromatography.

In conclusion, we have developed an alternate, readily scalable synthesis of a mycosamine donor, which proceeds in an overall yield of 25% and requires only 8 purifications, thus making it amenable to preparing the multigram quantities we require for our ongoing investigations of this important natural product.

Unless otherwise noted, all reagents were purchased from commercial sources. All non-aqueous reactions were carried out using oven-dried or flame-dried glassware under a positive pressure of dry nitrogen or argon, unless otherwise noted. THF, toluene, and CH_2Cl_2 were dried by passage over activated alumina under argon (H_2O content <30 ppm, Karl Fischer titration)[21] or for volumes greater than 500 mL, HPLC grade solvents (<200 ppm H_2O) were used. Except as indicated otherwise, reactions were magnetically stirred and monitored by TLC using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light and staining using ceric ammonium molybdate. Flash chromatographic purification of products was performed on Merck Silica Gel 60 (32–63 mm) using a forced flow of eluent.[22] Dry column vacuum chromatography was performed on Merck Silica Gel 60 (18–32 mm). Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure compounds unless explicitly indicated as crude.

Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell. NMR spectra were recorded on a Varian Mercury 300 spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. Coupling constants (*J* values) are reported in Hz. IR spectra were recorded on a Perkin-Elmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm^{-1}). Mass spectra were recorded by the MS service at ETH Zurich using an IonSpec Ultima Fourier transform mass spectrometer (MALDI-MS) or a Finnigan TSQ 7000 mass spectrometer (ESI-MS). Low resolution peaks are given in percent (*m*/*z*).

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-Hydroxy-6-methoxy-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine (2)

Me_2SnCl_2 (9.91 g, 45.1 mmol, 0.05 equiv) was added to a stirred mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**;[23] 254.59 g, 902 mmol, 1.0 equiv) and flame-dried K_2CO_3 (249.3 g, 1800 mmol, 2.0 equiv) in THF (4 L) at r.t. After 5 min, benzoyl chloride (125.6 mL, 1080 mmol, 1.2 equiv) was added and stirring was continued for 20 h at which time another portion of Me_2SnCl_2 (9.91 g, 45.1 mmol, 0.05 equiv) was added and stirring was continued for an additional 72 h. Approximately half of the reaction mixture was poured into a 6-L separatory funnel containing CH_2Cl_2 (3 L) and H_2O (1 L). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 1 L). The second half of the reaction mixture was worked up in the same manner and the combined organic layers were dried (Na_2SO_4), filtered and concentrated onto Celite. The material was purified in two equal portions via dry-column vacuum chromatography (15-cm diameter funnel, 10 cm silica, 400-mL fractions, gradient of 10% → 100% EtOAc–hexanes) to afford **2**;[24] yield: 282.04 g (81%); white solid; mp 153–164 °C (Lit.[24a] mp 169–170 °C); R_f 0.17 (25% EtOAc–hexanes); $[\alpha]_D^{32}$ +106.4 (*c* = 0.712, $CHCl_3$) {Lit.[24a] $[\alpha]_D^{25}$ +107.0 (*c* = 1.3, $CHC1_3$)}.

IR (film): 3478 (s), 2936 (m), 2862 (m), 1716 (s), 1602 (w), 1452 (m), 1378 (m), 1334 (w), 1316 (w), 1275 (s), 1147 (w), 1095 (s), 1040 (m), 992 (m), 918 (w), 752 (m), 712 (m), 699 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.12 (m, 2 H), 7.36–7.61 (m, 8 H), 5.58 (s, 1 H), 5.02–5.09 (m, 2 H), 4.31–4.39 (m, 2 H), 3.92 (m, 1 H), 3.80 (dd, *J* = 10.2, 10.2 Hz, 1 H), 3.63 (dd, *J* = 9.3, 9.3 Hz, 1 H), 3.40 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 136.8, 133.2, 129.8, 129.3, 129.2, 128.3, 128.2, 126.2, 102.0, 97.7, 81.4, 76.6, 74.0, 68.9, 68.8, 62.0, 55.5.

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{21}H_{22}O_7$ + Na: 409.1258; found: 409.1251.

(2*R*,4a*R*,6*S*,7*R*,8*R*,8a*R*)-8-Hydroxy-6-methoxy-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine (3)

Pyridinium dichromate (128.7 g, 339.5 mmol, 5.0 equiv) was added to a mixture of **2** (26.24 g, 67.9 mmol, 1.0 equiv) and dried, powdered 3Å molecular sieves (133 g) in CH_2Cl_2 (540 mL). The resulting heterogeneous mixture was stirred at r.t. for 24 h and filtered over Celite. The filter cake was washed with a 1:1 mixture of EtOAc and CH_2Cl_2 (4 × 100 mL). The resulting liquid was poured onto a column of Florisil (approx. 250 mL) and allowed to filter through the column. The column was washed with a 1:1 mixture of EtOAc and CH_2Cl_2 (700 mL) and all of the collected solvent was evaporated to afford (2*R*,4a*R*,6*S*,7*S*,8a*R*)-6-methoxy-8-oxo-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine.[25]

(2*R*,4a*R*,6*S*,7*S*,8a*R*)-6-Methoxy-8-oxo-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine

Crude yield: 23.26 g (89%) (attempts to scale this reaction to 175 g resulted in lower yield but the reaction could be reproducibly run at approximately 30-g scale); white solid; mp 197–198 °C (dec.) (Lit.[25a] mp 210–213 °C; Lit.[25b] mp 211–213 °C); R_f 0.69 (1% MeOH–CH_2Cl_2); $[\alpha]_D^{32}$ +96.6 (c = 0.635, $CHCl_3$) {Lit.[25a] $[\alpha]_D^{23}$ +69.6 (c = 1.02, $CHCl_3$)}.

IR (film): 2946 (m), 2931 (m), 2872 (m), 1754 (vs), 1736 (vs), 1602 (w), 1582 (w), 1445 (m), 1283 (m), 1263 (m), 1214 (w), 1190 (w), 1136 (w), 1111 (s), 1092 (s), 1072 (m), 1048 (m), 979 (m), 773 (m), 748 (m), 714 (m), 694 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.15 (m, 2 H), 7.36–7.63 (m, 8 H), 5.63 (dd, J = 1.2, 4.5 Hz, 1 H), 5.60 (s, 1 H), 5.34 (d, J = 4.4 Hz, 1 H), 4.40–4.48 (m, 2 H), 4.19 (ddd, J = 4.6, 9.9, 9.9 Hz, 1 H), 3.98 (dd, J = 10.2, 10.2 Hz, 1 H), 3.49 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 165.1, 136.3, 133.6, 130.3, 130.1, 129.3, 128.7, 128.4, 128.2, 126.3, 101.9, 101.4, 82.1, 74.8, 69.3, 65.4, 55.7.

HRMS (MALDI): m/z [M + Na^+] calcd for $C_{21}H_{20}O_7$ + Na: 407.1101; found: 407.1100.

$NaBH_4$ (9.92 g, 262 mmol, 1.0 equiv) was added to a stirred solution of (2*R*,4a*R*,6*S*,7*S*,8a*R*)-6-methoxy-8-oxo-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine prepared above (100.76 g, 262 mmol, 1.0 equiv) in THF (1.65 L) and MeOH (187 mL) at –15 °C (internal temperature). The resulting mixture was stirred at this temperature for 45 min and then poured into a separatory funnel containing ice (300 g) and sat. aq NH_4Cl solution (300 mL) – **Caution!** Gas evolution! – The mixture was gently shaken with frequent venting every few min for 15 min, at which point the aqueous layer was saturated with solid NaCl and diluted with EtOAc (1 L). The layers were separated and the aqueous layer was washed with EtOAc (4 × 300 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to afford **3**[26] which was used in the next step without further purification.

3

Crude yield: 102.0 g ('101%'); white solid; mp 97–98 °C [Lit.[26a] mp 114–116 °C (EtOH), Lit.[26b] mp 110–115 °C]; R_f 0.63 (1% MeOH–CH_2Cl_2); $[\alpha]_D^{32}$ +77.3 (c = 1.355, $CHCl_3$) {Lit.[26a] $[\alpha]_D^{23}$ +71 (c = 1, $CHCl_3$); Lit.[26b] $[\alpha]_D^{23}$ +74 (c = 1.5, $CHCl_3$)}.

IR (film): 3512 (m), 3210 (w), 2936 (m), 2863 (m), 1719 (s), 1601 (w), 1583 (w), 1451 (m), 1378 (m), 1315 (w), 1270 (s), 1218 (w), 1180 (w), 1106 (s), 1070 (m), 1047 (m), 1027 (m), 1011 (m), 988 (m), 918 (w), 872 (w), 757 (m), 712 (m), 700 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.16 (m, 2 H), 7.27–7.63 (m, 8 H), 5.63 (s, 1 H), 5.04–5.11 (m, 2 H), 4.51 (m, 1 H), 4.43 (dd, J = 5.1, 10.2 Hz, 1 H), 4.26 (ddd, J = 5.1, 10.0, 10.0 Hz, 1 H), 3.84 (dd, J = 10.2, 10.2 Hz, 1 H), 3.68 (dd, J = 2.6, 9.7 Hz, 1 H), 3.49 (s, 3 H), 3.23 (d, J = 7.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 137.0, 133.5, 130.0, 129.2, 129.1, 128.4, 128.2, 126.3, 102.0, 98.7, 78.6, 69.7, 69.1, 68.2, 57.9, 56.1.

HRMS (MALDI): m/z [M + Na^+] calcd for $C_{21}H_{22}O_7$ + Na: 409.1258; found: 409.1250.

(2*R*,4a*R*,6*S*,7*R*,8*R*,8a*R*)-6-Methoxy-8-(3-oxobutylcarbonyloxy)-2-phenyl-7-phenylcarbonyloxyperhydropyrano[3,2-*d*][1,3]dioxine (4)

Compound **3** (129 g, 333.8 mmol, 1.0 equiv) was azeotropically dried with toluene (300 mL) and dissolved in CH_2Cl_2 (1.7 L). Levulinic acid (68.6 mL, 77.52 g, 667.7 mmol, 2.0 equiv) was added followed by dicyclohexylcarbodiimide (137.7 g, 667.7 mmol, 2.0 equiv) in one portion to afford a suspension. The reaction was stirred for 10 min during which time the internal temperature rose to 35 °C. DMAP (28.55 g, 233.6 mmol, 0.7 equiv) was added in 3–4 gram portions every 5 min over 40 min. The reaction flask was fitted with a mechanical stirrer and the mixture was stirred for 17 h. The brown mixture was poured into sat. aq NH_4Cl solution (1.5 L) and the resulting emulsion was filtered over Celite and the phases were separated. The filter cake was washed with EtOAc (5 × 250 mL). Each portion was in turn used to extract the aqueous phase. The combined organic phases were washed with sat. aq $NaHCO_3$ solution (1 L) and brine (500 mL), dried (Na_2SO_4), filtered and concentrated onto Celite. Purification by three consecutive dry-column vacuum chromatographies (15-cm diameter funnel, 10 cm silica, 400-mL fractions, gradient 10% → 55% EtOAc–hexanes) afforded **4**; yield: 143.0 g (88% or 78% over 3 steps); pale yellow oil; R_f 0.16 (30% EtOAc–hexanes); $[\alpha]_D^{32}$ +78.1 (c = 2.67, $CHCl_3$).

IR (film): 2937 (m), 2863 (m), 1743 (s), 1731 (s), 1601 (w), 1584 (w), 1452 (m), 1408 (w), 1365 (m), 1216 (m), 1272 (s), 1201 (w), 1179 (m), 1158 (m), 1108 (s), 1070 (m), 1050 (s), 1009 (m), 989 (m), 763 (m), 714 (m), 700 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.99–8.02 (m, 2 H), 7.30–7.53 (m, 8 H), 5.80 (dd, J = 2.7, 2.7 Hz, 1 H), 5.50 (s, 1 H), 5.10 (dd, J = 3.7, 3.7 Hz, 1 H), 4.99 (m, 1 H), 4.18–4.34 (m, 2 H), 3.66–3.73 (m, 2 H), 3.37 (s, 3 H), 2.60–2.76 (m, 4 H), 2.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 133.4, 129.9, 129.3, 128.5, 96.2, 75.2, 73.3, 67.7, 65.3, 55.1, 25.9, 18.1, –4.2, –4.3.

HRMS (MALDI): m/z [M + Na^+] calcd for $C_{26}H_{28}O_9$ + Na: 507.1626; found: 507.1617.

(2*S*,3*R*,4*R*,5*R*,6*R*)-5-Hydroxy-6-hydroxymethyl-2-methoxy-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran (5)

Compound **4** (114 g, 235 mmol, 1.0 equiv) was dissolved in EtOAc (1.7 L) and the resulting solution was split into 8 equal portions. Each portion was placed in a 1-L round-bottomed flask and Pd/C (1.1 g, 10%, w/w Pd) was added. The flask was fitted with a septum and placed in a well-ventilated hood. An argon atmosphere was introduced by placing the flask under a strong argon flow for 1 h with vigorous stirring. A H_2 atmosphere was then introduced by flushing the flask twice with ca. 1 L of H_2. The flask was then fitted with two 1.5-L balloons of H_2 and stirred for 12 h. The H_2 atmosphere was removed with a strong flux of argon for 1 h and remaining H_2 was quenched by the addition of 2-methylbut-2-ene (20 mL). The contents of all 8 flasks were then filtered through a Celite pad on top of anhyd Na_2SO_4. The filter cake was washed with EtOAc (1.5 L) and the solvent was removed in vacuo to afford **5**, which was used in the next step without further purification; crude yield: 92.1 g (99%); colorless oil; R_f 0.17 (100% EtOAc); $[\alpha]_D^{28}$ +76.5 (c = 0.971, $CHCl_3$).

IR (film): 3451 (br, s), 3064 (w), 2931 (m), 2839 (w), 1722 (s), 1601 (w), 1585 (w), 1452 (w), 1405 (w), 1358 (m), 1328 (m), 1273 (s), 1198 (m), 1160 (m), 1098 (s), 1050 (s), 992 (m), 873 (w), 767 (w), 714 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–8.00 (m, 2 H), 7.54 (m, 1 H) 7.40–7.49 (m, 2 H), 5.71 (d, J = 2.8 Hz, 1 H), 5.05 (m, 1 H), 5.00 (m, 1 H), 3.79–3.85 (m, 4 H), 3.32 (s, 3 H), 2.60–2.74 (4 × ABXZ, 4 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 172.6, 165.6, 133.3, 129.9, 129.2, 128.4, 96.7, 70.1, 68.8, 67.7, 66.2, 62.1, 55.8, 38.2, 29.7, 28.3.

HRMS (MALDI): m/z [M + Na^+] calcd for $C_{19}H_{24}O_9$ + Na: 419.1312; found: 419.1305.

(2*S*,3*R*,4*R*,5*S*,6*S*)-5-Hydroxy-6-iodomethyl-2-methoxy-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran (6)

Compound **5** (48.0 g, 121.1 mmol, 1.0 equiv) was azeotropically dried with benzene (2 × 200 mL) and divided into 5 equal portions (9.60 g, 24.2 mmol, 1.0 equiv). Each portion was dissolved in THF (242 mL) and Ph_3P (12.70 g, 48.4 mmol, 2.0 equiv), I_2 (12.29 g, 48.4 mmol, 2.0 equiv) and imidazole (12.37 g, 182 mmol, 7.5 equiv) were added. The mixture was stirred in a r.t. water bath (to control an initial exotherm) for 1 h. The contents of the five reaction flasks were then collectively added to a separatory funnel containing EtOAc (3 L), sat. aq $NaHCO_3$ solution (750 mL) and sat. aq $Na_2S_2O_3$ solution (750 mL). After mixing, the layers were separated and the aqueous layer was washed with EtOAc (1 × 1 L). The combined organic layers were washed with phosphate buffer (0.8 M, pH 6.5, 2 L), H_2O (1 × 1 L) and brine (1 × 1 L), dried (Na_2SO_4), filtered and concentrated onto Celite in vacuo. Purification by dry column vacuum chromatography (15-cm diameter funnel, 10 cm silica gel, 400-mL fractions, gradient of 30% → 75% EtOAc–hexanes) afforded **6** (45.18 g) and an impure material which was repurified by flash chromatography (30% → 40% EtOAc–hexanes) to afford an additional amount of **6** (7.82 g); combined yield: 53.00 g (86% over 2 steps); colorless oil; R_f 0.69 (100% EtOAc), 0.28 (50% EtOAc–hexanes); $[\alpha]_D^{23}$ +46.9 (*c* = 0.886, $CHCl_3$).

IR (film): 3482 (br, m), 2929 (m), 2842 (w), 1739 (s), 1720 (s), 1601 (w), 1451 (w), 1405 (m), 1363 (m), 1327 (m), 1271 (s), 1200 (m), 1158 (m), 1096 (s), 1070 (m), 1041 (m), 1028 (m), 984 (w), 937 (w), 866 (w), 762 (w), 713 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.99 (m, 2 H), 7.54–7.60 (m, 1 H), 7.41–7.46 (m, 2 H), 5.69 (dd, *J* = 3.3, 3.3 Hz, 1 H), 5.02 (m, 1 H), 5.08 (m, 1 H), 3.61–3.79 (m, 3 H), 3.49 (s, 3 H), 3.33 (dd, *J* = 7.7, 10.7 Hz, 1 H), 2.96 (br d, *J* = 9.3 Hz, 1 H), 2.83–2.87 (2 × ABXZ, 2 H), 2.64–2.69 (2 × ABXZ, 2 H), 2.19 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6, 172.2, 165.1, 133.0, 129.6, 128.9, 128.1, 96.6, 69.6, 69.3, 68.6, 67.1, 55.8, 37.9, 29.5, 28.0, 6.8.

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{19}H_{23}IO_8$ + Na: 529.0330; found: 529.0321.

(2*S*,3*R*,4*R*,5*S*,6*S*)-5-*tert*-Butyldimethylsilyloxy-6-iodomethyl-2-methoxy-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran (8)

Imidazole (34.0 g, 499.5 mmol, 4.5 equiv) was added to a stirred solution of *tert*-butyldimethylsilyl chloride (33.46 g, 222 mmol, 2.0 equiv) and **6** (56.27 g, 111.1 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C, resulting in the formation of copious amounts of white precipitate. The ice bath was removed and stirring was continued for 50 h. The mixture was diluted with Et_2O (750 mL) and washed with sat. aq NH_4Cl solution (500 mL). The layers were separated and the aqueous layer was washed with Et_2O (1 × 100 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (500 mL). The layers were separated and the aq $NaHCO_3$ layer was washed with Et_2O (1 × 100 mL). The combined organic layers were washed with sat. aq $CuSO_4$ solution (1 L). The layers were separated and the aqueous $CuSO_4$ layer was washed with Et_2O (1 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated onto Celite. Purification by dry column vacuum chromatography (15-cm diameter funnel, 8 cm silica gel, 400-mL fractions, gradient of 10% → 50% EtOAc–hexanes) afforded **8**; 65.68 g (95%); colorless oil; R_f 0.62 (50% EtOAc–hexanes); $[\alpha]_D^{25}$ +69.2 (*c* = 0.827, $CHCl_3$).

IR (film): 2949 (m), 2929 (m), 2886 (m), 2856 (m), 1740 (s), 1722 (s), 1602 (w), 1583 (w), 1466 (w), 1448 (w), 1408 (w), 1359 (m), 1323 (m), 1269 (s), 1197 (m), 1269 (s), 1197 (m), 1157 (s)m 1099 (s), 1072 (m), 1045 (m), 1032 (m), 987 (w), 938 (w), 839 (s), 781 (s), 714 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–8.00 (m, 2 H), 7.56 (m, 1 H), 7.42–7.48 (m, 2 H), 5.58 (dd, *J* = 3.2 Hz, 1 H), 5.08 (m, 1 H), 4.99 (m, 1 H), 3.84 (ddd, *J* = 2.7, 7.0, 9.4 Hz, 1 H), 3.64 (dd, *J* = 3.2, 9.2 Hz, 1 H), 3.55 (dd, *J* = 2.6, 10.5 Hz, 1 H), 3.26 (dd, *J* = 7.0, 10.5 Hz, 1 H), 2.62–2.83 (m, 4 H), 2.16 (s, 3 H), 0.86 (s, 9 H), 0.15 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 172.0, 165.6, 133.3, 130.0, 129.3, 128.4, 97.1, 70.3, 69.7, 68.9, 66.8, 56.2, 37.8, 29.8, 28.2, 25.6, 17.8, 7.40, –4.4, –4.6.

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{25}H_{37}IO_8Si$ + Na: 643.1195; found: 643.1184.

(2*S*,3*R*,4*R*,5*R*,6*R*)-4-Hydroxy-2-methoxy-6-methyl-3-phenylcarbonyloxy-5-*tert*-butyldimethylsilyloxytetrahydro-2*H*-pyran (9)

2,2′-Azobis(isobutyronitrile) (AIBN, 347 mg, 2.11 mmol, 0.05 equiv) was added to a refluxing solution of **8** (65.58 g, 105.7 mmol, 1.0 equiv) and Bu_3SnH (56.8 mL, 211 mmol, 2.0 equiv) in degassed toluene (1 L). The mixture was heated at reflux for 2.5 h, cooled to r.t. and concentrated in vacuo. The resulting oil was dissolved in EtOAc (1 L), cooled to 0 °C and KF·xH_2O (44.3 g) in H_2O (500 mL) was added. The resulting milky mixture was stirred at 0 °C for 1 h and filtered over Celite. The two layers were separated and the aqueous layer was washed with EtOAc (1 × 400 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (10% → 15% EtOAc–hexanes) afforded (2*S*,3*R*,4*R*,5*R*,6*R*)-5-*tert*-butyldimethylsilyloxy-2-methoxy-6-methyl-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran.

(2*S*,3*R*,4*R*,5*R*,6*R*)-5-*tert*-Butyldimethylsilyloxy-2-methoxy-6-methyl-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran

Yield: 49.58 g (95%); white solid; mp 78–82 °C; R_f 0.72 (50% EtOAc–hexanes), 0.25 (25% EtOAc–hexanes); $[\alpha]_D^{27}$ +98.4 (*c* = 0.865, $CHCl_3$).

IR (film): 2931 (m), 1740 (s), 1722 (s), 1601 (w), 1583 (w), 1448 (w), 1408 (w), 1359 (w), 1314 (w), 1265 (s), 1157 (m), 1099 (s), 1072 (m), 1050 (m), 1027 (m), 996 (w), 861 (w), 839 (m), 776 (s), 714 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97–8.00 (m, 2 H), 7.56 (m, 1 H), 7.41–7.46 (m, 2 H), 5.57 (dd, *J* = 3.1, 3.1 Hz, 1 H), 5.04 (dd, *J* = 3.9, 3.9 Hz, 1 H), 4.92 (m, 1 H), 4.05 (m, 1 H), 3.48 (dd, *J* = 3.1, 9.4 Hz, 1 H), 3.38 (s, 3 H), 2.61–2.83 (m, 4 H), 2.16 (s, 3 H), 1.25 (d, *J* = 6.4 Hz, 3 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.5, 171.6, 165.1, 132.8, 129.6, 129.1, 128.0, 96.4, 71.4, 69.6, 68.9, 63.4, 55.4, 37.7, 29.6, 28.2, 25.5, 17.7, 17.4, –4.6, –5.1.

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{25}H_{38}O_8Si$ + Na: 517.2228; found: 517.2219.

Hydrazine monohydrate (108.9 mL, 2.24 mol, 20 equiv) was added to a stirred solution of (2*S*,3*R*,4*R*,5*R*,6*R*)-5-*tert*-butyldimethylsilyloxy-2-methoxy-6-methyl-4-(3-oxobutylcarbonyloxy)-3-phenylcarbonyloxytetrahydro-2*H*-pyran (55.50 g, 112.2 mmol, 1.0 equiv) in pyridine (673 mL) and AcOH (445 mL) in a r.t. water bath. The mixture was stirred at r.t. for 24 h, at which time the reaction was quenched by the addition of acetone (200 mL). The resulting mixture was stirred for 10 min and then added over 1 h to a mechanically stirred mixture of Na_2CO_3 (600 g), $NaHCO_3$ (400 g) and H_2O (1.5 L) at 0 °C in an open flask – **Caution!** gas evolution! – The resulting mixture was washed with EtOAc (1 × 2 L, 1 × 1 L) and the combined organic layers were washed with sat. aq $CuSO_4$ solution (2 L). The aqueous $CuSO_4$ layer was washed with EtOAc (1 L). The combined organic layers were washed with brine (1 L), dried (Na_2SO_4), filtered and concentrated in vacuo. Residual pyridine was azeotro-

pically removed using toluene (1 × 1 L) and the residue was purified by flash chromatography (20% EtOAc–hexanes) to afford **9**.

9

Yield: 42.09 g (95%); colorless oil; R_f 0.67 (50% EtOAc–hexanes), 0.62 (30% EtOAc–hexanes); $[\alpha]_D^{24}$ +89.6 (*c* = 1.23, $CHCl_3$).

IR (film): 3532 (m), 2955 (m), 2931 (m), 2857 (m), 1721 (s), 1602 (w), 1583 (w), 1472 (w), 1463 (w), 1452 (w), 1380 (w), 1317 (w), 1297 (w), 1283 (w), 1272 (s), 1107 (s), 1072 (m), 1051 (m), 1029 (m), 1016 (m), 954 (w), 915 (w), 861 (w), 837 (w), 777 (m), 714 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.814 (m, 2 H), 7.55–7.60 (m, 2 H), 5.01 (m, 1 H), 4.94 (m, 1 H), 4.19 (m, 1 H), 3.98 (m, 1 H), 3.43 (s, 3 H), 3.41 (m, 1 H), 3.32 (d, *J* = 7.1 Hz, 1 H), 1.30 (d, *J* = 6.3 Hz, 3 H), 0.92 (s, 9 H), 0.13 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 133.2, 129.9, 129.4, 128.3, 97.8, 74.1, 70.6, 70.0, 63.1, 55.8, 25.8, 17.7, –4.1, –4.5.

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{20}H_{32}O_6Si$ + Na: 419.1860; found: 419.1864.

(2*S*,3*R*,4*R*,5*R*,6*R*)-5-*tert*-Butyldimethylsilyloxy-2-methoxy-6-methyl-3-phenylcarbonyloxy-4-trifluoromethylsulfonyloxytetrahydro-2*H*-pyran (12)

Trifluoromethanesulfonic anhydride (26.7 mL, 158 mmol, 1.5 equiv) was added over 7 min to stirred solution of pyridine (15.4 mL, 190 mmol, 1.8 equiv) and **9** (41.89 g, 105.6 mmol, 1.0 equiv) at –40 °C. The cooling bath was removed and the initial thick, pale yellow slurry became homogeneous as the solution warmed to r.t. The mixture was stirred at r.t. for 18 h, diluted with Et_2O (2 L), sequentially washed with H_2O (500 mL), aq 2 M HCl (500 mL), sat. aq $NaHCO_3$ (500 mL), and brine (500 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **12** as a yellow oil which was used in the next step without further purification; R_f 0.57 (30% EtOAc–hexanes).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.11 (m, 2 H), 7.58–7.62 (m, 1 H), 7.44–7.49 (m, 2 H), 5.28 (dd, *J* = 2.5, 2.5 Hz, 1 H), 5.18 (dd, *J* = 3.0, 4.1 Hz, 1 H), 4.88 (d, *J* = 4.1 Hz, 1 H), 4.10 (m, 1 H), 3.60 (dd, *J* = 2.4, 9.4 Hz, 1 H), 3.42 (s, 3 H), 1.28 (d, *J* = 6.4 Hz, 3 H), 0.94 (s, 9 H), 0.16 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 133.6, 130.0, 128.6, 128.4, 96.5, 84.9, 71.4, 68.0, 63.4, 56.0, 25.9, 18.1, 17.5, –3.8, –4.6.

^{19}F NMR (282.5 MHz, $CHCl_3$): δ = –74.7

(2*S*,3*R*,4*S*,5*S*,6*R*)-4-Azido-5-*tert*-butyldimethylsilyloxy-2-methoxy-6-methyl-3-phenylcarbonyloxytetrahydro-2*H*-pyran (13)

NaN_3 (7.55 g, 116 mmol, 1.1 equiv) was added to a solution of **12** prepared above (azeotropically dried with toluene) and 15-crown-5 (23.07 mL, 116 mmol, 1.1 equiv) in DMF (422 mL) and stirred at r.t. for 1 h. The mixture was poured into H_2O (1 L) and a 1:1 mixture of Et_2O and hexane (2 L). The layers were separated and the organic layer was washed with water (2 × 1 L). The combined aqueous phases were washed with a 1:1 mixture of Et_2O and hexane (500 mL). The combined organic layers were washed with a 1:1 mixture of H_2O and sat. aq $NaHCO_3$ solution, brine (500 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford **13**; crude yield: 41.47 g (93% over 2 steps); yellow oil; R_f 0.72 (30% EtOAc–hexanes), 0.48 (15% EtOAc–hexanes); $[\alpha]_D^{23}$ +165.7 (*c* = 0.863, $CHCl_3$).

IR (film): 2954 (m), 2932 (m), 2904 (m), 2858 (m), 2109 (s), 1727 (s), 1602 (w), 1583 (w), 1472 (w), 1462 (w), 1452 (w), 1379 (w), 1362 (w), 1332 (w), 1316 (w), 1262 (s), 1108 (s), 1060 (s), 998 (w), 976 (w), 925 (w), 906 (w), 862 (m), 837 (s), 778 (m), 743 (w), 711 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.12 (m, 2 H), 7.59 (m, 1 H), 7.44–7.50 (m, 2 H), 5.00 (d, *J* = 3.6 Hz, 1 H), 4.87 (dd, *J* = 3.7, 10.6 Hz, 1 H), 3.90 (dd, *J* = 9.2, 10.6 Hz, 1 H), 3.73 (m, 1 H), 3.37 (s, 3 H), 3.17 (dd, *J* = 9.2, 9.2 Hz, 1 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 0.93 (s, 9 H), 0.20 (s, 3 H), 0.13 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 133.3, 129.8, 129.1, 128.4, 96.1, 75.2, 73.3, 67.7, 65.3, 55.2, 26.0, 18.2, 18.2, –4.0, –4.2.

HRMS (MALDI): *m*/*z* [M + H^+ – N_2] calcd for $C_{20}H_{32}NO_5Si$: 394.2044; found: 394.2035.

MS (ESI): *m*/*z* (%) = 444 (40) [M + Na^+], 413 (100) [M + H^+].

(3*R*,4*S*,5*S*,6*R*)-4-Azido-5-*tert*-butyldimethylsilyloxy-6-methyl-2-methylcarbonyloxy-3-phenylcarbonyloxytetrahydro-2*H*-pyran (14)

H_2SO_4 in Ac_2O (4.29 mL, 10 drops of H_2SO_4/1 mL Ac_2O) was added to a stirred solution of **13** [9.04 g (crude), 21.44 mmol, 1.0 equiv] in Ac_2O (42.9 mL) at 0 °C. After stirring at 0 °C for 20 min, the cooling bath was removed and stirring was continued for 35 min with careful TLC monitoring. The mixture was diluted with CH_2Cl_2 (25 mL) and added over 2 min to a mechanically stirred mixture of $NaHCO_3$ (100 g) and H_2O (1 L) at 0 °C – **Caution!** Gas evolution! – The cooling bath was removed and stirring was continued for 1 h. The mixture was diluted with Et_2O (1 L) and the layers were separated. The aqueous layer was washed with Et_2O (2 × 500 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (7% EtOAc–hexanes) to afford **14**; yield: 6.20 g (60% over 3 steps); colorless oil; ca. 7.7:1 mixture of β:α anomers; R_f 0.36 (15% EtOAc–hexanes); $[\alpha]_D^{26}$ +126.3 (*c* = 1.293, $CHCl_3$).

IR (film): 2957 (m), 2931 (m), 2886 (m), 2858 (m), 2107 (vs), 1758 (s), 1732 (s), 1602 (w), 1585 (w), 1472 (w), 1462 (w), 1452 (w), 1371 (w), 1262 (s), 1222 (s), 1146 (s), 1110 (s), 1094 (s), 1062 (m), 1033 (m), 1008 (m), 933 (w), 903 (w), 860 (m), 838 (m), 778 (m), 711 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.00–8.06 (m, 2 H), 7.60 (m, 1 H), 7.43–7.49 (m, 2 H), 6.38 (d, *J* = 3.7 Hz, 1 H), 5.82* (d, *J* = 8.3 Hz, 1 H), 5.23* (dd, *J* = 8.3, 10.2 Hz, 1 H), 5.08 (dd, *J* = 3.7, 10.6 Hz, 1 H), 3.89 (dd, *J* = 9.3, 10.7 Hz, 1 H) 3.83 (m, 1 H), 3.61* (dd, *J* = 9.2, 10.2 Hz, 1 H), 3.59* (dd, *J* = 6.2, 9.0 Hz, 1 H), 3.28* (dd, *J* = 9.1, 9.1 Hz, 1 H), 3.24 (dd, *J* = 9.3, 9.3 Hz, 1 H), 2.13 (s, 3 H), 2.01* (s, 3 H), 1.33* (d, *J* = 6.2 Hz, 3 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 0.94 (s, 9 H), 0.92* (s, 9 H), 0.22 (s, 3 H), 0.21* (s, 3 H), 0.14 (s, 3 H), 0.13* (s, 3 H) (Assignments with * refer to the α-anomer).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 165.2, 133.5, 129.8, 129.7, 128.9, 128.5, 92.0*, 88.8, 74.6, 74.5, 71.5, 70.5, 68.5*, 65.1, 25.8, 20.9, 20.8, 18.1 –4.2, –4.3 (Assignments with * refer to the α-anomer).

HRMS (MALDI): *m*/*z* [M + Na^+] calcd for $C_{21}H_{31}N_3O_6Si$ + Na: 472.1874; found: 472.1867.

MS (ESI): *m*/*z* (%) = 472 (47) [M + Na^+], 390 (100) [M + H^+ – AcOH], 347 (60) [M + H^+ – AcOH – HN_3].

(2*S*,3*R*,4*S*,5*S*,6*R*)-4-Azido5-*tert*-butyldimethylsilyloxy-2-hydroxy-6-methyl-3-phenylcarbonyloxytetrahydro-2*H*-pyran (15)

Hydrazine acetate (307 mg, 3.33 mmol, 1.3 equiv) was added to a solution of **14** (1.15 g, 2.56 mmol, 1.0 equiv) in DMF (12.8 mL) at r.t. The mixture was stirred for 3 h and poured into a separatory funnel containing H_2O (100 mL) and 1:1 mixture of Et_2O and hexane (100 mL). The layers were separated and the aqueous layer was washed with a 1:1 mixture of Et_2O and hexane (2 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated in

vacuo to afford **15** as a single anomer (α) by ^{1}H NMR spectroscopy, which was used in the next step without further purification; crude yield: 0.98 g (94%); white crystalline solid; mp 112–116 °C; R_f 0.25 (15% EtOAc–hexanes); $[\alpha]_D^{28}$ +142.8 (c = 0.930, $CHCl_3$).

IR (film): 3439 (br, m), 2956 (m), 2931 (m), 2891 (m), 2859 (m), 2110 (vs), 1727 (s), 1602 (w), 1585 (w), 1473 (w), 1452 (w), 1386 (w), 1362 (w), 1337 (w), 1277 (s), 1148 (m), 1107 (s), 1061 (m), 1028 (m), 997 (w), 936 (w), 915 (w), 861 (s), 838 (s), 778 (s), 751 (w), 710 (s), 686 (w), 665 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.09 (m, 2 H), 7.56 (m, 1 H), 7.39–7.46 (m, 2 H), 5.49 (d, J = 3.6 Hz, 1 H), 4.85 (dd, J = 3.6, 10.6 Hz, 1 H), 4.10 (br s, 1 H), 3.96 (m, 1 H), 3.16 (dd, J = 9.2, 9.2 Hz, 1 H), 1.23 (d, J = 6.3 Hz, 3 H), 0.93 (s, 9 H), 0.20 (s, 3 H), 0.12 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 133.4, 129.8, 129.0, 128.4, 89.3, 75.1, 73.6, 67.8, 64.8, 25.8, 18.0, –4.2, –4.4.

HRMS (MALDI): m/z [M + H^+ – H_2O] calcd for $C_{19}H_{28}N_3O_4Si$: 390.1844; found: 390.1839; [M + H^+ – N_2] calcd for $C_{19}H_{30}NO_5Si$: 380.1888; found: 380.1867.

MS (ESI): m/z (%) = 430 (100) [M + Na^+].

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-Azido-5-*tert*-butyldimethylsilyloxy-6-methyl-3-phenylcarbonyloxy-2-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran (17)

NaH [60% (w/w) in oil, 106 mg, 2.65 mmol, 1.1 equiv] was added to a stirred solution of **15** (0.98 g, 2.40 mmol, 1.0 equiv) and trichloroacetonitrile (2.41 mL, 24.0 mmol, 10.0 equiv) in CH_2Cl_2 (4.8 mL) at 0 °C – **Caution!** Gas evolution! – The resulting mixture was stirred at 0 °C for 1.5 h, diluted with Et_2O (100 mL), poured into H_2O (25 mL) and the resulting layers were separated. The aqueous layer was washed with Et_2O (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (5–10% EtOAc–hexanes) to afford **17**; yield: 0.92 g (65% over 2 steps, 89% over 2 steps based on recovered lactol **15**); colorless oil; R_f 0.47 (15% EtOAc–hexanes); $[\alpha]_D^{30}$ +106.1 (c = 0.551, $CHCl_3$); and 0.24 g (25%) of lactol **15**.

IR (film): 3343 (w), 2958 (m), 2931 (m), 2887 (m), 2858 (m), 2110 (s), 1732 (s), 1674 (s), 1602 (w), 1587 (w), 1474 (w), 1464 (w), 1450 (w), 1258 (s), 1146 (m), 1106 (s), 1097 (s), 1062 (s), 1033 (m), 1018 (m), 964 (m), 905 (m), 861 (m), 837 (s), 792 (m), 778 (m), 709 (s), 645 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H), 8.03-8.07 (m, 2 H), 7.57 (m, 1 H), 7.40–7.46 (m, 2 H), 6.56 (d, J = 3.6 Hz, 1 H), 5.16 (dd, J = 3.6, 10.5 Hz, 1 H), 3.97 (dd, J = 9.4, 10.4 Hz, 1 H), 3.95 (m, 1 H), 3.30 (dd, J = 9.3, 9.3 Hz, 1 H), 1.32 (d, J = 6.3 Hz, 3 H), 0.95 (s, 9 H), 0.23 (s, 3 H), 0.15 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 160.5, 133.5, 129.7, 128.7, 128.4, 92.8, 74.6, 71.9, 71.0, 65.2, 26.0, 18.3, –4.0, –4.1.

HRMS (MALDI): m/z [M + H^+ – $C_2H_2Cl_3NO$] calcd for $C_{19}H_{28}N_3O_4Si$: 390.1844; found: 390.1850; [M + H^+ – $C_2H_2Cl_3NO$ – HN_3] calcd for $C_{19}H_{27}O_4Si$: 347.1673; found: 347.1672.

MS (ESI): m/z (%) = 579 (6), 578 (10), 577 (34), 576 (32), 575 (100), 574 (28), 573 (99) [all M + Na^+].

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