Synthesis of the Sugar Building Block of Bicyclo-RNA

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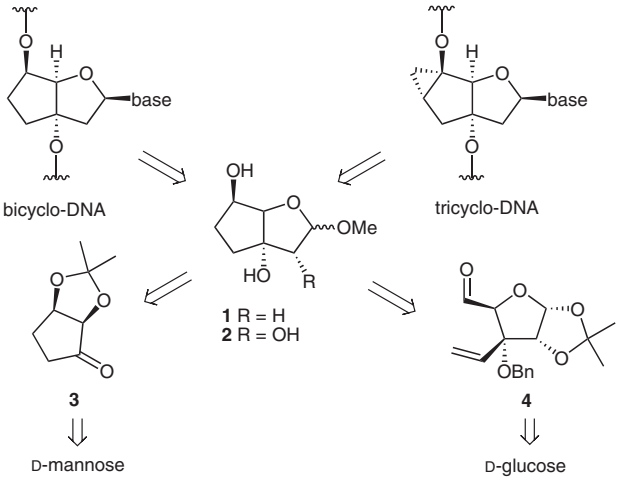
Abstract: We present the novel synthesis of two sugar units that are central intermediates for the formation of members of the bicyclo-DNA and -RNA family. The synthesis starts from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The key step involves the elaboration of a carbocyclic ring in a furanoside by rhodium(I)-catalyzed hydroacylation. Via this pathway, one of the sugar units is available in 8 steps and in an overall yield of 27%, while its deoxy derivative is obtained in 11 steps, which is 5 steps fewer than in our previous synthesis of this compound.

Key words: glycosides, fused-ring systems, DNA, rhodium, catalysis

The recent finding that genetically encoded microRNAs (miRNAs) or small interfering RNAs (siRNAs) function as regulators for protein translation has raised their profile in pharmaceutical research and has boosted the search for chemically modified oligonucleotide analogues as inhibitors and potential therapeutic agents.[1] In the context of oligonucleotide therapeutics, during the 1990s, our group developed the molecular platform of bicyclo-DNA (bc-DNA) (Scheme 1).[2] One member of this family, tricyclo-DNA (tc-DNA) shows high affinity and selectivity in binding to complementary RNA, is highly resistant towards biodegradation, and is functionally active as an antisense agent.[3]



Scheme 1 Retrosynthetic relations between the bicyclo-DNA molecular platform, the common sugar precursor **1**, and common hexoses

An important prerequisite for the extensive biological testing of oligonucleotide analogues is convenient, high-yielding access to the corresponding nucleosides and building blocks for solid-phase oligonucleotide synthesis. Our current synthesis of the nucleosides of bc- and tc-DNA is based on the central sugar intermediate **1** (Scheme 1), which is available in six steps from bicyclic compound **3** and in an overall yield of 33%.[2a] Compound **3** in turn is available from D-mannose in 10 steps and in an overall yield of 23% on a one-mole scale.[4] Thus, a total of 16 steps are required to obtain compound **1** from D-mannose in an overall yield of 8%.

We recently became interested in the synthesis and biological properties of members of the bicyclo-RNA (bc-RNA) series. To study this series, convenient, high-yielding access to the corresponding hydroxylated sugar intermediate **2** is necessary. In previous work, Ravn and Nielsen synthesized an unsaturated derivative of compound **2** from olefin **4** via a ring-closing-metathesis strategy.[5] We felt that a more direct approach to form the cyclopentane ring via intramolecular, rhodium(I)-catalyzed hydroacylation of intermediate **4** might be shorter and superior to existing methods. This approach would not only permit easy access to hydroxylated sugar **2** to be used for the synthesis of bc-RNA or tricyclo-RNA (tc-RNA), but could also lead to the shorter and improved synthesis of deoxy derivative **1**. Here, we report on the successful realization of this synthetic strategy.

Our synthesis started with the already known benzyl-protected aldehyde **4** (Scheme 2), which is readily available from commercial 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose in four steps according to published procedures[5,6] and in an overall yield of 65%. With compound **4** in hand, we investigated the rhodium(I)-catalyzed hydroacylation reaction to give tricyclic compound **5**. Initial experiments using Wilkinson's catalyst [10 mol% $(Ph_3P)_3RhCl$] according to a known procedure[7] unfortunately gave, in our hands, desired compound **5** in only 5–24% yield. We, therefore, started to optimize the catalyst system by changing the rhodium(I) source and varying the phosphine ligands.[8]

Fairlie and Bosnich reported that cationic rhodium catalysts are typically more active and provide fewer side products compared with neutral rhodium derivatives.[8a] Such catalysts are readily prepared in situ from a rhodium chloride precursor by substitution with silver(I) tetrafluoroborate ($AgBF_4$) or silver(I) perchlorate. We, therefore, investigated complexes prepared in situ from

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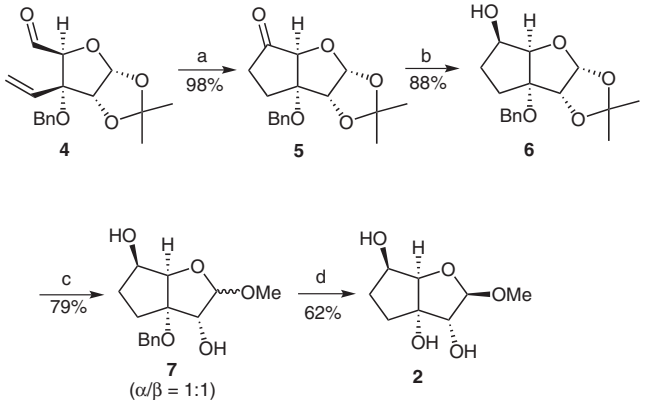


Scheme 2 *Reagents and conditions*: (a) $[Rh(nbd)_2]BF_4$ (10 mol%), 1,2-bis(diphenylphosphino)benzene (12 mol%), DCE, 75 °C, 20 h; (b) $NaBH_4$ (2 equiv), MeOH, 0 °C, 1 h; (c) TsOH, MeOH, r.t., 24 h; (d) H_2, $Pd(OH)_2$/C, MeOH, r.t., 16 h.

$[Rh(cod)Cl]_2$ (cod = cycloocta-1,5-diene), $AgBF_4$, and nine different bis-phosphine ligands. The most active complex in converting aldehyde **4** into cyclopentanone **5** turned out to be that containing 1,2-bis(diphenylphosphino)benzene as a ligand. However, the cyclization reaction was very slow and the maximum yield of product **5** was only 45%. A dramatic improvement came by changing the rhodium(I) source to $[Rh(nbd)_2]BF_4$ (nbd = norbornadiene). After activation with hydrogen and using the bis-phosphine ligand described above, ketone **5** was obtained in reproducible yields of 78–98% with 10 mol% catalyst loading. We attribute the higher activity to the better leaving properties of norbornadiene compared with those of cycloocta-1,5-diene upon catalyst activation.

Encouraged by these results, we continued the synthesis of target compound **2** via the reduction of ketone **5** with sodium borohydride which afforded alcohol **6** in a highly selective manner and in 88% yield. Only 4% yield of the C-5 epimeric compound could be isolated. The relative configuration of the hydroxy group in product **6** could be unambiguously assigned by ^{1}H NMR-NOE spectroscopic experiments (Figure 1).

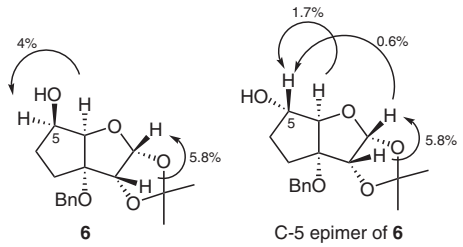
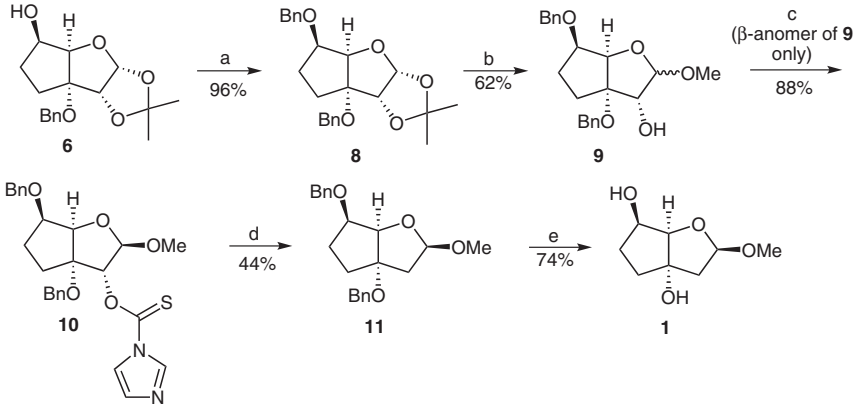


Figure 1 ^{1}H NMR-NOE spectroscopic results relevant for the assignment of the configuration at C-5 in compound **6** and for its C-5 epimer

The synthesis of compound **2** was then completed by the conversion of tricyclic compound **6** into methyl glycoside **7**,[9] which was obtained in a 1:1 anomeric ratio and in 79% yield, followed by hydrogenolytic cleavage of the benzyl group yielding target compound **2** in 62% yield. For the purpose of synthesizing bc-RNA nucleosides, there is no need for the separation of the anomers of compound **2** as the mixture can be used directly.

To explore whether the above would also provide a convenient entry into the bc-DNA sugar series, we converted hydroacylation/reduction product **6** into bis-benzylated intermediate **8** (96% yield), which was then transformed into an approximately 1:1 anomeric mixture of methyl glycoside **9** (62% yield) (Scheme 3). The β-anomer of this product could be separated off in pure form by flash chromatography. For ease of spectroscopic analysis, we performed the rest of the steps with the pure β-anomer of **9**.

With the aim of removing the remaining hydroxy group using Barton and McCombie chemistry, we transformed methyl glycoside **9** into the corresponding thiocarbamate **10** (88% yield),[10] which after radical reduction with tributylstannane gave deoxy sugar **11** in 44% yield. Considerable efforts to improve this reaction by changing the nature of the thiocarbamate group and the reducing agent unfortunately did not lead to a higher yield of product **11**. The reason for this is most likely due to steric constraints around the reacting center. The removal of the benzyl groups by catalytic hydrogenation finally led to bc-DNA sugar building block **1**[2a] in 74% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) NaH (2 equiv), BnBr (2.5 equiv), DMF, r.t., 20 h; (b) TsOH, MeOH, r.t., 24 h; (c) 1,1′-thiocarbonyldiimidazole (2 equiv), THF, reflux, 4 h; (d) AIBN (0.2 equiv), Bu_3SnH (4 equiv), toluene, reflux, 2 h; (e) H_2, $Pd(OH)_2$/C, MeOH, r.t., 16 h.

In conclusion, we have presented a robust and efficient synthesis of the central sugar unit **2**, which can be used for the formation of bc- and tc-RNA. Starting from commercial 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose, the product is formed in eight steps and in an overall yield of 27%. In addition, along the same synthetic avenue, building block **1** for the synthesis of bc- or tc-DNA becomes available in 11 steps. Under the assumption that the conversion of dibenzyl derivative **9** into deoxy compound **1** (Scheme 3) in the α-anomeric series is of similar efficiency, an overall yield of 10% would be obtained. This corresponds to an improvement over the current synthesis, which takes 16 steps (from D-mannose) and gives the product in an overall yield of 8%.

Thin-layer chromatography (TLC) was performed on silica gel plates (SIL G-25 UV_{254}, Machery-Nagel). Visualization was effected by dipping the TLC plates into a staining reagent [phosphomolybdic acid (12.5 g), cerium(IV) sulfate (5 g), concd H_2SO_4 (40 mL), H_2O (460 mL)]. Flash chromatography was performed on silica gel 60A (particle size 0.040–0.063 mm). ^1H NMR spectra were recorded on a Bruker AC-300, Bruker DRX-400, or Bruker DRX-500 spectrometer; chemical shifts are reported in ppm relative to the undeuterated residual solvent peak (calibrated to 7.26 ppm for $CDCl_3$ and 2.49 ppm for DMSO-d_6). ^{13}C NMR spectra were recorded at 75 MHz on a Bruker Avance 300 MHz spectrometer; chemical shifts are reported in ppm relative to the solvent peak (calibrated to 77.16 ppm for $CDCl_3$ and to 39.7 ppm for DMSO-d_6). Difference ^1H NMR-NOE experiments were recorded at 400 MHz. High-resolution ESI mass spectra were recorded on an Applied Biosystems Sciex QSTAR Pulsar instrument. All reactions were performed in oven-dried glassware under an atmosphere of Ar. Solvents for reactions were dried over alumina (THF and CH_2Cl_2) or purchased from Fluka (DMF and MeOH). Solvents for extractions and flash chromatography were distilled before use.

7a-Benzyloxy-2,2-dimethylhexahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxol-5-one (5)

Complex $[Rh(nbd)_2]BF_4$ (0.49 g, 1.30 mmol, 10 mol%) and 1,2-bis(diphenylphosphino)benzene (0.44 g, 1.5 mmol, 12 mol%) were suspended in DCE (20 mL), and the mixture was stirred at r.t. under an atmosphere of Ar for ca. 10 min. Then, H_2 was bubbled through the solution for 10 min, followed by flushing again with Ar for 20 min to remove H_2. Compound **4** (4.00 g, 13 mmol) in DCE (30 mL) was then added dropwise to the solution, and the mixture was stirred for 20 h at 75 °C. Product **5** was isolated by flash chromatography (CH_2Cl_2–2% acetone) as a yellow oil. Yield: 3.92 g (98%); R_f = 0.32 (CH_2Cl_2–acetone, 98:2).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.69–1.81 (m, 1 H, H-7β), 2.50–2.57 (m, 3 H, 2 H-6, H-7α), 4.17 (s, 1 H, H-4a), 4.61–4.65 (m, 2 H, CH_2Ph, H-7b), 4.75 (d, *J* = 10.9 Hz, 1 H, CH_2Ph), 5.95 (d, *J* = 3.6 Hz, 1 H, H-3a), 7.29–7.42 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 27.2, 27.4, 35.9, 67.6, 81.9, 83.6, 97.4, 107.9, 114.3, 127.6, 127.7, 128.8, 137.9, 209.9.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{20}O_5Na$: 327.1208; found: 327.1218.

7a-Benzyloxy-2,2-dimethylhexahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxol-5-ol (6)

Compound **5** (3.92 g, 12 mmol) was dissolved in MeOH (80 mL) and treated at 0 °C with $NaBH_4$ (0.97 g, 25 mmol); the resulting mixture was stirred for 1 h at 0 °C. After dilution with H_2O (100 mL) followed by neutralization with 4 M AcOH (27 mL), the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexane–EtOAc, 1:3) to give product **6** as a white solid, together with its C-5 epimer (0.15 g, 4%) as a clear oil. Yield: 3.44 g (88%); R_f = 0.44 (hexane–EtOAc, 1:3).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.69–1.80 (m, 1 H, H-6β), 1.95–2.20 (m, 3 H, 2 H-7, H-6α), 4.15–4.30 (m, 1 H, H-5), 4.46–4.50 (m, 2 H, CH_2Ph, H-4a), 4.55 (d, *J* = 3.6 Hz, 1 H, H-7b), 4.65 (d, *J* = 10.7 Hz, 1 H, CH_2Ph), 5.88 (d, *J* = 3.6 Hz, 1 H, H-3a), 7.28–7.42 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 27.6, 30.2, 31.4, 67.3, 73.4, 84.6, 87.1, 90.8, 107.1, 114.2, 127.8, 128.5, 138.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}O_5Na$: 329.1364; found: 329.1365.

C-5 Epimer of 6

R_f = 0.55 (hexane–EtOAc, 1:3).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.90–2.10 (m, 2 H, H-6β, H-7β), 2.15–2.42 (m, 2 H, H-6α, H-7α), 4.21 (s, 1 H, H-5), 4.40 (s, 1 H, H-4a), 4.53–4.63 (m, 2 H, CH_2Ph, H-7b), 4.70 (d, *J* = 10.9 Hz, 1 H, CH_2Ph), 5.80 (d, *J* = 3.0 Hz, 1 H, H-3a), 7.28–7.42 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.6, 27.7, 31.3, 33.6, 68.0, 76.4, 82.7, 90.7, 93.5, 106.7, 113.9, 127.6, 128.8, 138.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}O_5Na$: 329.1364; found: 329.1365.

3a-Benzyloxy-2-methoxyhexahydrocyclopenta[*b*]furan-3,6-diol (7)

Compound **6** (1.06 g, 3.26 mmol) was stirred with 3% TsOH in MeOH (15 mL) at r.t. for 24 h. The mixture was neutralized with sat. aq Na_2CO_3 (3 mL), concentrated, diluted with H_2O (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexane–EtOAc, 1:3) to give product **7** as a 1:1 mixture of anomers in the form of a clear oil. Yield: 0.72 g (79%).

If needed, the anomers can be separated by flash chromatography under these conditions. Samples of the pure anomers were used for analytical characterization.

β-Anomer

R_f = 0.32 (hexane–EtOAc, 1:3).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.90–2.29 (m, 4 H, 2 H-4, 2 H-5), 2.32 (d, *J* = 6.5 Hz, 1 H, OH-6), 3.02 (d, *J* = 3.5 Hz, 1 H, OH-3), 3.44 (s, 3 H, OMe), 3.96 (dd, *J* = 0.9, 3.4 Hz, 1 H, H-3), 4.10–4.20 (m, 1 H, H-6), 4.36–4.46 (m, 2 H, CH_2Ph, H-6a), 4.50–4.75 (m, 1 H, CH_2Ph), 5.00 (d, *J* = 1.1 Hz, 1 H, H-2), 7.28–7.42 (m, 5 H, Ph).

^1H NMR-NOE (400 MHz, $CDCl_3$): 3.96 (H-3) → 5.03 (H-2, 2.06%); 4.18 (H-6) → 2.32 (OH-6, 1.12%), 3.05 (OH-3, 0.57%), 4.44 (H-6a, 4.98%), 5.00 (H-2, 0.26%); 4.43 (H-6a) → 2.32 (OH-6, 0.87%), 3.05 (OH-3, 1.21%), 4.17 (H-6, 3.03%), 5.00 (H-2, 0.28%); 5.00 (H-2) → 3.96 (H-3, 2.13%).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.1, 32.3, 56.5, 65.1, 67.4, 72.5, 79.8, 87.7, 91.3, 112.1, 127.9, 128.4, 129.0, 137.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{20}O_5Na$: 303.1208; found: 303.1209.

α-Anomer

R_f = 0.23 (hexane–EtOAc, 1:3).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–2.15 (m, 4 H, 2 H-4, 2 H-5), 2.25 (d, *J* = 8.4 Hz, 1 H, OH-6), 3.04 (d, *J* = 11.1 Hz, 1 H, OH-3),

3.45 (s, 3 H, OMe), 3.86 (dd, *J* = 4.3, 10.9 Hz, 1 H, H-3), 4.05–4.15 (m, 1 H, H-6), 4.38 (d, *J* = 5.6 Hz, 1 H, H-6a), 4.59 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.75 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.96 (d, *J* = 4.3 Hz, 1 H, H-2), 7.28–7.42 (m, 5 H, Ph).

^{1}H NMR-NOE (400 MHz, $CDCl_3$): 3.81 (H-3) → 2.25 (OH-6, 0.65%), 3.04 (OH-3, 0.79%), 4.38 (H-6a, 0.40%), 4.96 (H-2, 6.33%); 4.05 (H-6) → 2.18 (OH-6, 1.07%), 3.44 (OH-3, 0.74%), 4.34 (H-6a, 5.68%), 4.92 (H-2, 0.63%); 4.37 (H-6a) → 3.04 (OH-3, 0.52%), 4.05 (H-6, 5.11%), 4.91 (H-2, 0.91%); 4.96 (H-2) → 3.86 (H-3, 5.25%).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.5, 31.5, 55.3, 66.9, 72.0, 79.1, 84.0, 86.9, 103.7, 126.8, 127.4, 128.4, 138.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_5Na$: 303.1208; found: 303.1209.

2-Methoxyhexahydrocyclopenta[*b*]furan-3,3a,6-triol (2)

Compound **7** (β-anomer) (0.36 g, 1.28 mmol) was dissolved in anhyd MeOH (5 mL), and $Pd(OH)_2$/C (300 mg) was added to the solution. The mixture was degassed with Ar for 10 min, followed by flushing with H_2 for 10 min. Then, the mixture was stirred for 16 h at r.t. After filtration through Celite, the solvent was removed and the residue was purified by flash chromatography (hexane–EtOAc, 1:5) to give compound **2** as a colorless oil. Yield: 0.15 g (62%); R_f = 0.22 (hexane–EtOAc, 1:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.85 (m, 2 H, H-4β, H-5β), 1.90–2.15 (m, 2 H, H-4α, H-5α), 2.46 (d, *J* = 6.0 Hz, 1 H, OH-6), 3.00 (s, 1 H, OH-3a), 3.26 (s, 1 H, OH-3), 3.46 (s, 3 H, OMe), 3.78 (s, 1 H, H-3), 4.15–4.19 (m, 1 H, H-6), 4.21 (d, *J* = 6.0 Hz, 1 H, H-6a), 4.94 (d, *J* = 3.0 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.2, 34.3, 56.6, 72.4, 80.4, 84.8, 89.1, 111.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{14}O_5Na$: 213.0739; found: 213.0735.

5,7a-Bis(benzyloxy)-2,2-dimethylhexahydrocyclopenta[4,5]furo[2,3-*d*][1,3]dioxole (8)

Sodium hydride (0.38 g, 16 mmol) was suspended in anhyd DMF (20 mL) and the mixture was cooled to 0 °C. To the mixture was added a solution of alcohol **6** (2.47 g, 8 mmol) in anhyd DMF (5 mL) dropwise over a period of 30 min. The mixture was stirred at 50 °C for 1 h, then cooled to 0 °C. Then, BnBr (2.37 mL, 0.02 mol) was added dropwise and the mixture was stirred at r.t. for 20 h. After, DMF was removed in vacuo, the residue was taken up in CH_2Cl_2 (50 mL), and the solution was extracted with sat. $NaHCO_3$ (2 × 50 mL). The organic phase was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexane–EtOAc, 1:2) to yield compound **8** as a slightly yellow oil. Yield: 3.06 g (96%); R_f = 0.71 (hexane–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.70–2.15 (m, 4 H, 2 H-6, 2 H-7), 4.04–4.10 (m, 1 H, H-5), 4.40–4.70 (m, 6 H, 2 CH_2Ph, H-7b, H-4a), 5.93 (d, *J* = 3.7 Hz, 1 H, H-3a), 7.28–7.45 (m, 10 H, 2 Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 27.5, 27.8, 29.7, 67.2, 72.1, 80.1, 83.9, 84.4, 90.8, 107.0, 113.6, 127.72, 127.77, 127.8, 128.0, 128.5, 138.46, 138.48.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{28}O_5Na$: 419.1834; found: 419.1828.

3a,6-Bis(benzyloxy)-2-methoxyhexahydrocyclopenta[*b*]furan-3-ol (9)

Compound **8** (3.06 g, 7 mmol) was stirred with 3% TsOH in MeOH (20 mL) at r.t. for 24 h. The mixture was neutralized with sat. aq Na_2CO_3 (3 mL), concentrated in vacuo, diluted with H_2O (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexane–EtOAc, 1:2) to give the anomers of product **9** as colorless oils. Yield: 0.94 g (33%) (β-anomer), 0.83 g (29%) (α-anomer).

β-Anomer

R_f = 0.68 (hexane–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (d, *J* = 4.3 Hz, 4 H, 2 H-4, 2 H-5), 2.97 (d, *J* = 3.7 Hz, 1 H, OH-3), 3.44 (s, 3 H, OMe), 3.85–3.95 (m, 1 H, H-6), 3.99 (d, *J* = 3.7 Hz, 1 H, H-3), 4.39 (d, *J* = 10.9 Hz, 1 H, CH_2Ph), 4.47–4.60 (m, 3 H, CH_2Ph, H-6a), 4.73 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 5.02 (s, 1 H, H-2), 7.28–7.45 (m, 10 H, 2 Ph).

^{1}H NMR-NOE (400 MHz, $CDCl_3$): 3.02 (OH-3) → 3.44 (OMe, 0.29%), 3.99 (H-3, 4.09%), 4.52 (H-6a, 3.17%), 5.00 (H-2, 2.18%); 3.88 (H-6) → 4.52 (H-6a, 8.84%); 3.99 (H-3) → 5.00 (H-2, 4.46%); 5.00 (H-2) → 3.44 (OMe, 6.07%), 3.99 (H-3, 3.70%).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 29.1, 55.4, 67.1, 71.6, 79.3, 79.4, 85.3, 91.3, 110.6, 127.7, 127.8, 127.9, 128.3, 128.5, 128.8, 137.3, 138.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{26}O_5Na$: 393.1678; found: 393.1673.

α-Anomer

R_f = 0.58 (hexane–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–2.15 (m, 4 H, 2 H-4, 2 H-5), 2.98 (d, *J* = 11.1 Hz, 1 H, OH-3), 3.47 (s, 3 H, OMe), 3.60–3.90 (m, 2 H, H-3, H-6), 4.43 (d, *J* = 4.3 Hz, 1 H, H-6a), 4.50–4.75 (m, 4 H, 2 CH_2Ph), 5.00 (d, *J* = 4.3 Hz, 1 H, H-2), 7.30–7.45 (m, 10 H, 2 Ph).

^{1}H NMR-NOE (400 MHz, $CDCl_3$): 3.02 (OH-3) → 3.50 (OMe, 0.61%), 3.78 (H-6, 0.63%), 3.88 (H-3, 4.60%), 4.40 (H-6a, 1.01%), 5.00 (H-2, 1.40%); 3.78 (H-6) → 3.01 (OH-3, 0.34%), 3.50 (OMe, 3.14%), 4.40 (H-6a, 9.38%), 5.00 (H-2, 0.15%); 4.40 (H-6a) → 3.01 (OH-3, 0.73%), 3.50 (OMe, 2.63%), 3.78 (H-6, 7.23%), 5.00 (H-2, 0.28%); 5.00 (H-2) → 3.01 (OH-3, 1.36%), 3.50 (OMe, 6.33%), 3.88 (H-3, 8.08%), 4.41 (H-6a, 0.83%).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 29.7, 55.4, 67.0, 72.0, 78.5, 79.3, 82.7, 87.1, 103.5, 126.9, 127.6, 127.9, 128.1, 128.5, 128.6, 138.2, 139.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{26}O_5Na$: 393.1678; found: 393.1674.

***O*-[3a,6-Bis(benzyloxy)-2-methoxyhexahydrocyclopenta[*b*]furan-3-yl] Imidazole-1-carbothioate (10)**

To a solution of the β-anomer of compound **9** (0.94 g, 2.5 mmol) in THF (20 mL) was added 1,1′-thionocarbonyldiimidazole (0.91 g, 5.0 mmol) and the mixture was stirred at reflux for 4 h. The solvent was evaporated and the residue was purified by flash chromatography (hexane–EtOAc, 1:2) to give compound **10** as a yellowish oil. Yield: 1.08 g (88%); R_f = 0.60 (hexane–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04–2.10 (m, 3 H, 2 H-4, H-5α), 2.22–2.25 (m, 1 H, H-5β), 3.50 (s, 3 H, OMe), 3.95–4.20 (m, 2 H, H-3, H-6), 4.48–4.73 (m, 4 H, 2 CH_2Ph), 5.13 (s, 1 H, H-6a), 5.77 (s, 1 H, H-2), 7.00 (d, *J* = 0.9 Hz, 1 H, H-$2_{imidazole}$), 7.10–7.45 (m, 10 H, 2 Ph), 7.57 (d, *J* = 3.2 Hz, 1 H, H-$4_{imidazole}$), 8.28 (d, *J* = 3.2 Hz, 1 H, H-$5_{imidazole}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 28.5, 30.4, 56.2, 68.0, 70.1, 72.2, 79.7, 87.1, 87.6, 90.0, 108.3, 118.3, 127.7, 128.0, 128.1, 128.3, 128.8, 128.9, 131.2, 131.4, 137.2, 137.5, 138.7, 183.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_5S$: 481.1797; found: 481.1782.

3a,6-Bis(benzyloxy)-2-methoxyhexahydrocyclopenta[*b*]furan (11)

A solution of compound **10** (1.08 g, 2.2 mmol) in toluene (40 mL) containing AIBN (65.6 mg, 0.4 mmol) was added dropwise within 1 h to a refluxing mixture of Bu_3SnH (2.36 mL, 8.8 mmol) in toluene (80 mL). The mixture was stirred under reflux for 2 h. Evaporation of the solvent and flash chromatography (hexane–EtOAc, 1:1) yielded product **11** as a yellowish oil. Yield: 0.35 g (44%); R_f = 0.81 (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90–2.30 (m, 5 H, H-3β, 2 H-4, 2 H-5), 2.54–2.63 (m, 1 H, H-3α), 3.40 (s, 3 H, OMe), 3.83–3.86 (m, 1 H, H-6), 4.40 (d, *J* = 8.4 Hz, 1 H, CH_2Ph), 4.41–4.51 (m, 2 H, H-6a, CH_2Ph), 4.56 (d, *J* = 8.9 Hz, 1 H, CH_2Ph), 4.74 (d, *J* = 8.9 Hz, 1 H, CH_2Ph), 5.19 (dd, *J* = 1.6, 5.8 Hz, 1 H, H-2), 7.30–7.45 (m, 10 H, 2 Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.9, 33.6, 46.1, 55.3, 67.1, 71.8, 72.2, 79.4, 86.8, 92.4, 106.5, 127.8, 128.0, 128.1, 128.3, 128.9, 138.8, 139.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}O_4Na$: 377.1723; found: 377.1714.

2-Methoxyhexahydrocyclopenta[*b*]furan-3a,6-diol (1)

Compound **11** (0.35 g, 0.9 mmol) was dissolved in anhyd MeOH (3 mL), and $Pd(OH)_2/C$ (200 mg) was added to the solution. The mixture was degassed with Ar for 10 min, flushed with H_2 for 10 min, and then stirred for 16 h at r.t. The mixture was then filtered, the solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc, 1:3) to give compound **1** as a white solid. Yield: 0.12 g (74%).

The analytical data were identical with those reported in the literature.[2a]

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