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A Julia olefination approach to the synthesis of functionalized enol ethers and their transformation into carbohydrate-derived spiroketals

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Abstract

A synthesis of spiroketals from carbohydrate lactones is reported. A modified Julia olefination is used to synthesize trisubstituted and highly functionalized *exo*-glycals, which were subsequently transformed into spiroketals under acidic conditions.

Substituted spiroketals are common substructures in natural products from various sources including insects, microbes, plants, fungi, and marine organisms (Fig. 1).[1] In particular, 1,6-dioxaspiro[4.5]decanes and 1,7-dioxaspiro[5.5]undecanes have attracted considerable interest from synthetic organic chemists over the past several decades.[2] The elaboration of functionalized spiroketals from carbohydrate precursors has proven to be a productive approach. General strategies include the addition of acetylide anions to carbohydrate lactones,[3] C-alkylation of carbohydrate-derived dithioacetals,[4] ring closing metathesis of *C*-alkenyl substituted allyl glycosides,[5] and others.[6] *Endo*- and *exo*-glycals have proven to be useful intermediates for the synthesis of spiroketals. They have been cyclized under mild acidic or electrophilic conditions or have been further transformed into 1-deoxy-1-haloketose allyl glycosides, which were cyclized under radical conditions.[7] However, the main drawback in the use of *exo*-glycals[8] as precursors of spiroketals has been that the suitably functionalized trisubstituted *exo*-glycals could not be prepared easily from the available carbohydrate derivatives, such as lactones. Only a few stepwise methods, including Ramberg–Backlund olefination,[9] addition–elimination reactions,[10] palladium-catalyzed coupling reactions,[11] or Wittig reactions[12] provide an access to carbohydrate *exo*-glycals.

As part of an ongoing project on *exo*-[13] and *endo*-[14] glycal derivatives, we report a two-step procedure for the synthesis of spiroketals from the easily available

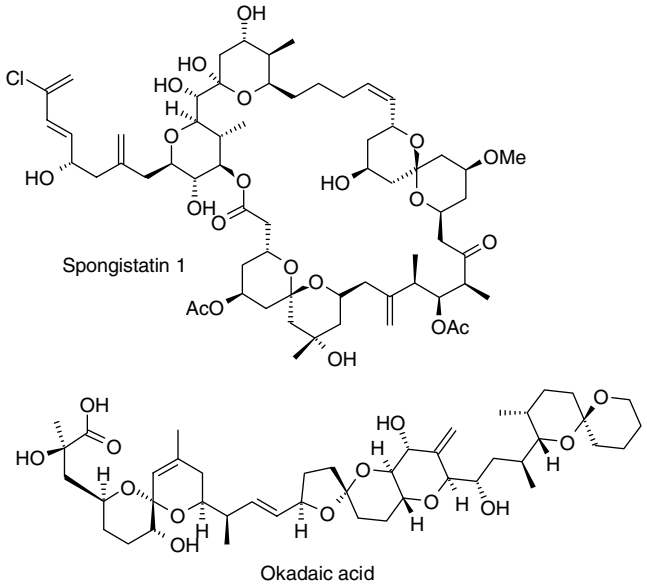

Fig. 1. Spiroketal units in natural products.

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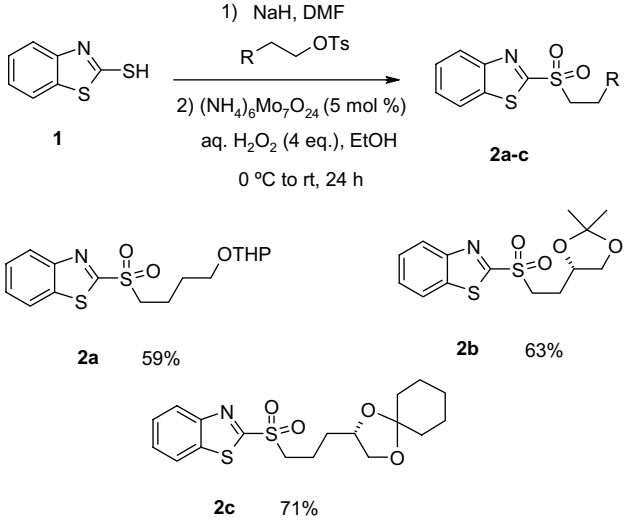
carbohydrate-derived lactones. Our recently published methodology using modified Julia olefination conditions for the synthesis of enol ethers from carbohydrate lactones is extended here to functionalized trisubstituted *exo*-glycals. These are subsequently converted into [4.5] and [5.5] spiroketals by intramolecular spiroketalisation under conventional acidic conditions described by Ley.[15] We chose the readily available 2-deoxy-3,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone[16] as starting material to address the influence of the C-2 substituent on the sugar on the enol ether synthesis.[17] As most natural spiroketals are unsubstituted on the carbon adjacent to the spirocenter, it is of interest to show whether the C-2 substituent exerts an essential steric, electron-withdrawing, or Thorpe–Ingold effect. Functionalized benzothiazol-2-yl sulfones were prepared from 2-mercaptobenzothiazole by base-mediated S-alkylation followed by ammonium molybdate catalyzed oxidation with hydrogen peroxide in good yields (Scheme 1).[18]

Initial studies toward spiroketal **5** focused on optimizing the coupling conditions and on the compatibility of the protecting groups. The preparation of *exo*-glycal **4**[19] under the Barbier conditions used previously (LiHMDS, THF, −78 °C, 1.2 equiv of sulfone, then treatment of the isolated hemiacetal with DBU)[13] gave the desired product in 52% yield (Table 1, entry 1). A short study allowed us to increase the yield to 67% by modifying the lactone-to-sulfone ratio. The yield improved either upon adding a large excess of the sulfone (entry 2) or upon working with a slight excess of lactone (entry 3). Indeed, α-lithiated sulfones have been shown to undergo self-condensation side-reactions,[20] which can account for the observed results (see Scheme 2).

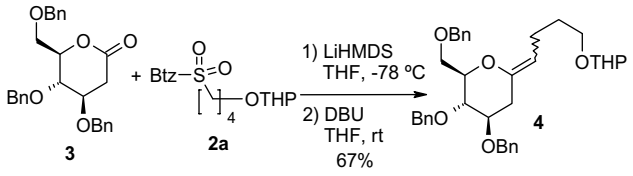
Acidic treatment of the enol ether **4** in protic media (*p*-toluenesulfonic acid in methanol) gave the corresponding spirocyclic product **5**[21] as a single diastereoisomer by NMR in excellent yield (Scheme 3). Indeed, as described



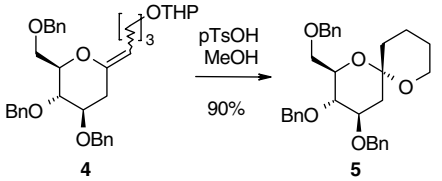
Scheme 1. Synthesis of the benzothiazolyl sulfones.

Table 1
Optimization of the *exo*-glycal synthesis

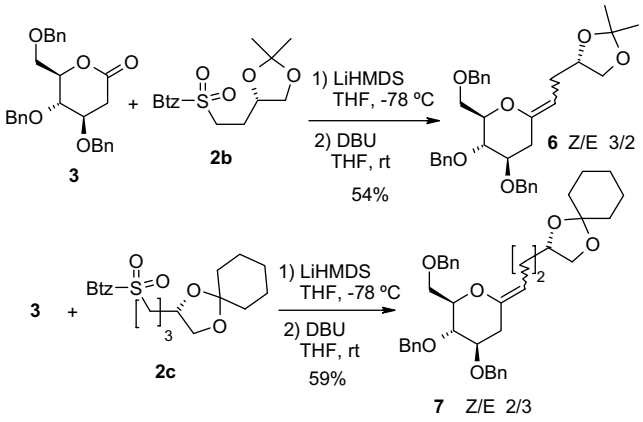
Entry	Lactone/sulfone ratio	Yield (%)	*Z*/*E* ratio
1	1/1.2	52	2/3
2	1/1.5	59	3/2
3	1.2/1	67	2/3
4	1.5/1	39	1/1



Scheme 2. Synthesis of the *exo*-glycal **4**.



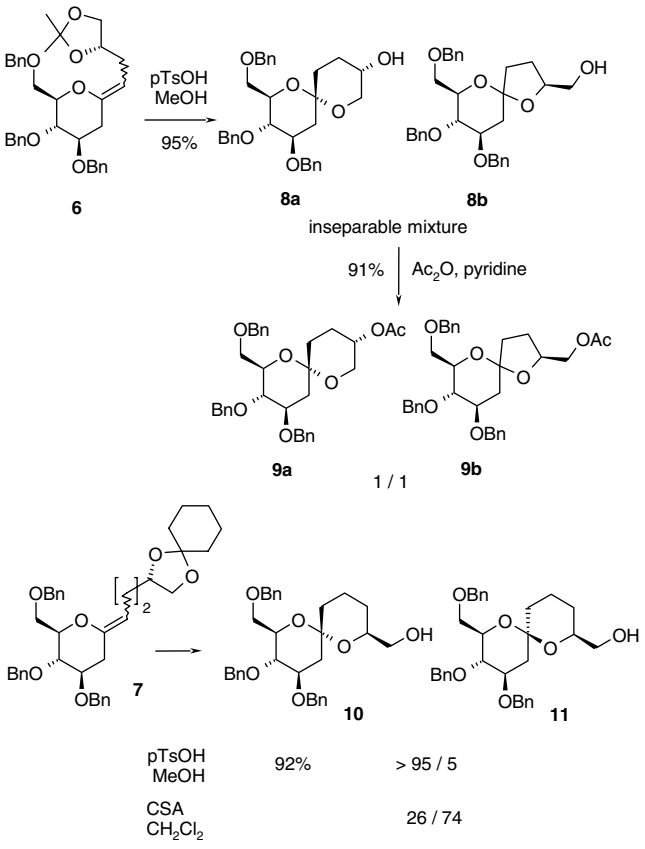
Scheme 3. Spirocyclization under acidic conditions.



Scheme 4. Synthesis of functionalized *exo*-glycals **6** and **7**.

by Deslonchamps et al.,[22] the thermodynamic product **5**, which benefits from two anomeric effects, was obtained with strong acids in protic solvents such as methanol (see Scheme 4).

This result shows that there is no dominant influence of the functionality on the sulfone nor of the C-2 substituent of the sugar on the olefination step, and establishes the feasibility of a spiroketal synthesis using this methodology. To further evaluate the scope of this sequence, more highly functionalized *exo*-glycals were prepared. Condensation of benzothiazol-2-yl sulfones **2b** and **2c** with the sugar lactone under the conditions described above gave *exo*-glycals **6**[23] and **7**[24] in 54% and 59% yields, respectively (see Scheme 5).



Scheme 5. Spirocyclization reaction under acidic conditions.

Spirocyclization of the enol ether **6** with *p*-toluenesulfonic acid in methanol led to a mixture of [5.5] and [4.5] spiroketals **8a** and **8b** in 95% yield. Acetylation and separation of the mixture by flash chromatography allowed the structures to be assigned based on the chemical shift of the protons α to the acetoxy group.[25] Treatment of **7** under the same conditions gave the corresponding spirocyclic product **10**[26] as a single diastereoisomer in high yield.

The spirocyclization reaction was also attempted under kinetic conditions[3] in $CDCl_3$ in the presence of CSA. The reaction was followed by NMR and yielded a 2.8:1 ratio of diastereomeric spiroketals after 15 min, which progressively isomerized in favor of the thermodynamic isomer **10**. Extrapolating back to $t = 0$ would suggest an initial kinetic selectivity of the order of 3.3:1 in favor of the non-thermodynamic spiroketal **11**. The configuration of spiroketal **10** was confirmed by NOE experiments. NOE enhancements are observed between H-5 and H-5′, as would be expected from structure I in its most stable conformation. In addition, no correlation was observed between H-3′ and H-3 or H-1, which would indicate the presence of diastereoisomer II (see Fig. 2).

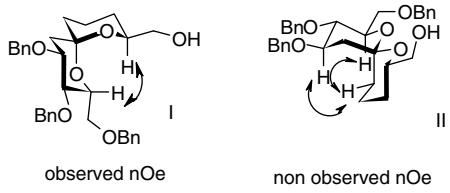


Fig. 2. Configuration and conformation of spiroketal **10**.

In conclusion, we have developed a route to functionalized *exo*-glycals, which were transformed into [4.5] and [5.5] spiroketals under acidic conditions. Further studies targeting spiroketals of biological interest are in progress.

Acknowledgments

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21. *Typical procedure for the spirocyclization*: A solution of (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-6-(4-(tetrahydro-2*H*-pyran-2-yloxy)butylidene)tetrahydro-2*H*-pyran (200 mg, 0.35 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 10 mL of methanol at room temperature was stirred overnight, concentrated in vacuo and purified by flash chromatography to afford the desired product (153 mg, 0.31 mmol) in 90% yield. *Selected data*: (2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1,7-dioxaspiro[5.5]undecan (**5**) Eluent: petroleum ether/ethyl acetate (10:1). Yield: 90% (colorless oil). $[\alpha]_D^{25}$ +45 (*c* 1, $CHCl_3$). NMR (^{1}H, CD_3OD, 300 MHz), δ (ppm): 7.36–7.17 (m, 15H, *H*ar); 4.82 (d, 1H, $J = 10.8$ Hz, CH_2Ph); 4.62 (d, 1H, $J = 11.4$ Hz, CH_2Ph); 4.57–4.50 (m, 4H, CH_2Ph); 3.92 (ddd, 1H, $J = 11.4$, 9.0, 5.1 Hz, H_3); 3.69 (m, 2H, H_6); 3.61 (m, 2H, $H_{5'}$); 3.52 (m, 1H, H_5); 3.44 (dd, 1H, $J = 9.3$, 9.3 Hz, H_4); 2.20 (dd, 1H, $J = 12.9$, 5.1 Hz, H_{2eq}); 1.87 (m, 1H, $H_{3'a}$); 1.70–1.39 (m, 6H, $H_{2'}$, $H_{3'b}$, $H_{4'}$ and H_{2ax}). NMR (^{13}C, $(CD_3)_2CO$, 75 MHz), δ (ppm): 140.1, 139.9 and 139.7 (*C*ar); 129.4, 129.3, 129.0, 128.9, 128.8, 128.7 and 128.6 (15*C*Har); 98.2 (C_1); 79.8 (C_4); 79.0 (C_3); 75.8 (*C*H_2Ph); 74.3 (*C*H_2Ph); 72.5 (C_5); 72.4 (*C*H_2Ph); 70.4 (C_6); 61.6 ($C_{5'}$); 42.0 (C_2); 35.7 ($C_{2'}$); 26.1 ($C_{4'}$); 19.7 ($C_{3'}$). MS (ESI): *m*/*z* 380.9 $(MH-BnOH)^+$, 489.0 $(M+H)^+$, 511.2 $(M+Na)^+$. HRMS: $C_{31}H_{36}O_5Na$ calcd, 511.2460; found, 511.2446.
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23. (2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)tetrahydro-2*H*-pyran (**6**) Eluent: petroleum ether/ethyl acetate (7:1). Yield: 54% (colorless oil). MS (ESI): *m*/*z* 436.9 $(MH-(BnOH))^+$, 567.3 $(M+Na)^+$. HRMS: $C_{34}H_{40}O_6Na$ calcd, 567.2723; found, 567.2709. (*Z* isomer) $[\alpha]_D^{25}$ +18 (*c* 1, $CHCl_3$). NMR (^{1}H, CD_3OD, 300 MHz), δ (ppm): 7.38–7.17 (m, 15H, Har); 4.79 (d, 1H, $J = 11.1$ Hz, CH_2Ph); 4.66 (d, 1H, $J = 11.8$ Hz, CH_2Ph); 4.63 (t, 1H, $J = 7.3$ Hz, H_7); 4.60–4.48 (m, 4H, CH_2Ph); 4.09 (m, 1H, H_9); 3.95 (dd, 1H, $J = 7.9$, 6.0 Hz, H_{10a}); 3.73 (m, 2H, $H_{6a,b}$); 3.70–3.48 (m, 4H, H_3, H_4, H_5 and H_{10b}); 2.72 (dd, 1H, $J = 13.3$, 4.5 Hz, H_{2eq}); 2.36 (dd, 2H, $J = 6.6$, 6.6 Hz, $H_{8a,b}$); 2.23 (dd, 1H, $J = 12.6$, 9.6 Hz, H_{2ax}), 1.34 and 1.29 (2s, 6H, 2CH_3). NMR (^{13}C, CD_3OD, 75 MHz), δ (ppm): 151.5 (C_1); 139.9, 139.7 and 139.6 (Car); 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7 (15*C*Har); 110.0 (*C*$(CH_3)_2$); 105.3 (C_7); 80.4 (C_4); 80.1 (C_3); 78.8 (C_9); 77.1 (C_5); 75.3 (C_6); 74.4, 72.3 and 70.5 (*C*H_2Ph); 70.0 (C_{10}); 35.0 (C_2); 29.8 (C_8); 27.3 (*C*H_3); 26.0 (*C*H_3). (*E* isomer) $[\alpha]_D^{25}$ +17 (*c* 1, $CHCl_3$). NMR (^{1}H, CD_3OD, 300 MHz), δ (ppm): 7.38–7.17 (m, 15H, Har); 5.03 (t, 1H, $J = 7.9$ Hz, H_7); 4.79 (d, 1H, $J = 11.1$ Hz, CH_2Ph); 4.70 (d, 1H, $J = 11.5$ Hz, CH_2Ph); 4.61 (d, 1H, $J = 11.7$ Hz, CH_2Ph); 4.57 (d, 1H, $J = 11.5$ Hz, CH_2Ph); 4.54 (d, 1H, $J = 11.1$ Hz, CH_2Ph); 4.49 (d, 1H, $J = 12.1$ Hz, CH_2Ph); 4.10–3.94 (m, 2H, H_9 and H_{10a}); 3.69 (m, 2H, $H_{6a,b}$); 3.65–3.57 (m, 2H, H_3 and H_4); 3.55–3.48 (m, 2H, H_5 and H_{10b}); 2.94 (dd, 1H, $J = 13.9$, 4.3 Hz, H_{2eq}); 2.30–2.00 (m, 3H, $H_{8a,b}$ and H_{2ax}), 1.37 and 1.31 (2s, 6H, 2CH_3). NMR (^{13}C, CD_3OD, 75 MHz), δ (ppm): 152.1 (C_1); 139.9, 139.7 and 139.4 (Car); 129.5, 129.4, 129.2, 129.1, 129.0, 128.8, 128.7 (15*C*Har); 110.2 (*C*$(CH_3)_2$); 106.5 (C_7); 80.5 (C_4); 80.3 (C_3); 78.8 (C_9); 77.3 (C_5); 75.4 (C_6); 74.4, 72.6 and 70.3 (*C*H_2Ph); 69.8 (C_{10}); 31.5 (C_2); 30.3 (C_8); 27.3 (*C*H_3); 25.9 (*C*H_3).
24. (*S*)-2-(3-((4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-ylidene)propyl)-1,4-dioxaspiro[4.5]decan (**7**) Eluent: petroleum ether/ethyl acetate (7/1). Yield: 59% (yellow oil). HRMS: $C_{38}H_{46}O_6Na$ calcd, 621.3192; found, 621.3165. The *E* isomer cannot be obtained in pure form (*Z* isomer) $[\alpha]_D^{25}$ +28 (*c* 1, $CHCl_3$). NMR (^{1}H, CD_3OD, 300 MHz), δ (ppm): 7.36–7.18 (m, 15H, Har); 4.79 (d, 1H, $J = 11.1$ Hz, CH_2Ph); 4.69–4.50 (m, 6H, CH_2Ph and H_7); 4.00 (m, 2H, H_{10} and H_{11a}); 3.73 (m, 2H, $H_{6a,b}$); 3.64–3.42 (m, 4H, H_3, H_4, H_5 and H_{11b}); 2.70 (dd, 1H, $J = 13.5$, 4.5 Hz, H_{2eq}); 2.22–2.07 (dd, 3H, $J = 6.6$, 6.6 Hz, $H_{8a,b}$ and H_{2ax}), 1.62–1.36 (m, 12H, 5CH_2 and H_9). NMR (^{13}C, CD_3OD, 75 MHz), δ (ppm): 149.9 (C_1); 139.9, 139.7 and 139.5 (Car); 129.4, 129.3, 129.1, 128.9, 128.7, 128.6 (15*C*Har); 110.4 and 110.2 (*C*$(CH_2R)_2$ and C_7); 80.7 (C_4); 80.2 (C_3); 78.9 (C_{10}); 76.8 (C_5); 75.3 (C_6); 74.4, 72.2, 70.5 and 70.1 (*C*H_2Ph and C_{11}); 37.7; 36.3; 35.1, 35.0, 26.3, 25.0, 24.9, 22.1 (C_2, C_8,C_9 and *C*H_2).
25. (3*S*,8*R*,9*S*,10*R*)-9,10-Bis(benzyloxy)-8-(benzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-3-yl acetate (**9a**) $[\alpha]_D^{25}$ +37 (*c* 1, $CHCl_3$). NMR (^{1}H,

CD_3OD, 300 MHz), δ (ppm): 7.38–7.17 (m, 15H, H_{ar}); 4.85 (d, 1H, $J = 11.1$ Hz, CH_2Ph); 4.75 (dddd, 1H, $J = 15.8$, 10.6, 5.8, 5.8 Hz, $H_{4'}$); 4.69–4.50 (m, 5H, CH_2Ph); 3.90 (ddd, 1H, $J = 11.3$, 8.9, 5.3 Hz, H_3); 3.72 (m, 2H, $H_{6a,b}$); 3.68–3.53 (m, 2H, $H_{5'a}$ and H_5); 3.48 (dd, 1H, $J = 8.7$, 8.7 Hz, H_4); 3.40 (dd, 1H, $J = 10.4$, 10.4 Hz, $H_{5'ax}$); 2.24 (dd, 1H, $J = 13.0$, 5.1 Hz, H_{2eq}); 2.01 (s, 3H, CH_3); 1.95–1.80 (m, 3H, $H_{3'a,b}$ and $H_{2'b}$); 1.70 (m, 1H, $H_{2'a}$); 1.52 (dd, 1H, $J = 12.8$, 12.8 Hz, H_{2ax}). NMR (^{13}C, $CDCl_3$, 75 MHz), δ (ppm): 170.2 (CO), 138.6, 138.5 and 138.4 (*C*ar); 128.3, 128.2, 127.8, 127.6, 127.5, 127.4 (15*C*Har); 96.3 (C_1); 78.2 (C_4); 77.9 (C_3); 74.8 (*C*H_2Ph); 73.3 (*C*H_2Ph); 71.7 (*C*H_2Ph); 71.5 (C_5); 69.2 (C_6); 67.8 ($C_{4'}$); 61.1 ($C_{5'}$), 39.7 (C_2); 33.5 ($C_{2'}$); 24.5 ($C_{3'}$), 21.0 (CH_3). HRMS: $C_{33}H_{38}O_7Na$ calcd, 569.2515; found, 569.2520. ((2*S*,7*R*,8*S*,9*R*)-8,9-Bis(benzyloxy)-7-(benzyloxymethyl)-1,6-dioxaspiro[4.5]decan-2-yl)methyl acetate (**9b**) $[\alpha]_D^{25}$ +28 (*c* 1, $CHCl_3$). NMR (^{1}H, CD_3OD, 300 MHz), δ (ppm): 7.38–7.17 (m, 15H, Har); 4.82 (d, 1H, $J = 11.3$ Hz, CH_2Ph); 4.69–4.43 (m, 5H, CH_2Ph); 4.25 (dddd, 1H, $J = 11.1$, 9.4, 5.5, 5.5 Hz, $H_{4'}$); 4.10 (dd, 1H, $J = 11.7$, 4.0 Hz, $H_{5'a}$); 4.04 (dd, 1H,$J = 11.7$, 6.0 Hz, $H_{5'b}$); 3.92 (ddd, 1H, $J = 11.5$, 8.9, 5.1 Hz, H_3); 3.74 (m, 1H, H_5); 3.70–3.58 (m, 2H, $H_{6a,b}$); 3.45 (dd, 1H, $J = 9.0$, 9.0 Hz, H_4); 2.24 (dd, 1H, $J = 12.6$, 5.1 Hz, H_{2eq}); 2.16 (m, 1H, $H_{3'a}$); 2.04 (s, 3H, CH_3); 1.99 (m, 1H, $H_{2'a}$); 1.92–1.80 (m, 1H, $H_{2'b}$); 1.75 (dd, 1H, $J = 12.4$, 12.4 Hz, H_{2ax}); 1.68 (m, 1H, $H_{3'b}$). NMR (^{13}C, CD_3OD, 75 MHz), δ (ppm): 172.7 (CO), 140.0, 139.9 and 139.5 (*C*ar); 129.4, 129.3, 129.2, 128.1, 129.0, 128.9, 128.6 (15*C*Har); 108.4 (C_1); 79.9 (C_4); 79.6 (C_3); 77.7 ($C_{4'}$); 75.8 (*C*H_2Ph); 74.3 (*C*H_2Ph); 73.1 (C_5); 72.6 (*C*H_2Ph); 70.4 (C_6); 67.3 ($C_{5'}$), 39.6 (C_2); 37.6 ($C_{2'}$); 26.7 ($C_{3'}$), 20.8 (CH_3). HRMS: $C_{33}H_{38}O_7Na$ calcd, 569.2515; found, 569.2520.

26. *Selected data*: ((2*S*,6*S*,8*R*,9*S*,10*R*)-9,10-Bis(benzyloxy)-8-(benzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (**10**) Eluent: petroleum ether/ethyl acetate (7/2). Yield: 92% (colorless oil). $[\alpha]_D^{25}$ +42 (*c* 0.5, $CHCl_3$). NMR (^{1}H, C_6D_6, 500 MHz), δ (ppm): 7.48–7.18 (m, 15H, *H*ar); 5.16 (d, 1H, $J = 11.4$ Hz, CH_2Ph); 4.80 (d, 1H, $J = 11.4$ Hz, CH_2Ph); 4.64–4.54 (m, 4H, CH_2Ph); 4.28 (ddd, 1H, $J = 11.0$, 8.8, 5.0 Hz, H_3); 4.04 (m, 1H, H_5); 3.92 (dd, 1H, $J = 10.4$, 4.7 Hz, H_{6a}); 3.87–3.78 (m, 3H, H_{6b}, H_4 and $H_{5'}$); 3.49 (m, 2H, $H_{6'a,b}$); 2.28 (dd, 1H, $J = 12.9$, 5.4 Hz, H_{2eq}); 2.05 (ddddd, 1H, $J = 13.2$, 13.2, 13.2, 4.1, 4.1 Hz, $H_{3'a}$); 1.72–1.58 (m, 2H, $H_{2'a}$ and H_{2ax}); 1.47 (m, 1H, $H_{3'b}$); 1.35 (ddd, 1H, $J = 13.2$, 13.2, 4.4 Hz, $H_{2'b}$); 1.32 (m, 1H, $H_{4'eq}$); 1.25 (dddd, 1H, $J = 12.6$, 12.6, 12.6, 3.9 Hz, $H_{4'ax}$). NMR (^{13}C, CD_3OD, 75 MHz), δ (ppm): 140.7, 140.5 and 140,4 (*C*ar); 129.5, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 128.5 (15*C*Har); 98.4 (C_1); 80.1 (C_4); 79.2 (C_3); 75.7 (*C*H_2Ph); 74.1 (*C*H_2Ph); 72.4 (C_5); 72.3 (*C*H_2Ph); 72.2 ($C_{5'}$); 70.8 (C_6); 66.8 ($C_{6'}$); 42.2 (C_2); 35.6 ($C_{2'}$); 27.9 ($C_{4'}$); 19.8 ($C_{3'}$). HRMS: $C_{32}H_{38}O_6Na$ calcd, 541.2566; found, 541.2569.