Stereoselective Synthesis of Fully Protected (*S*)-1,7-Dioxaspiro[5,5]undec-4-ene Derivatives of Sugars

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Dedicated to Prof. L. Mangoni on his 70th birthday

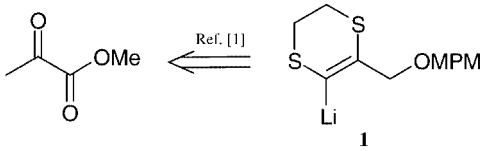
Keywords: Spiro compounds / Carbohydrates / Lactones / Dithiins

Perbenzylated 1,7-dioxaspiro[5,5]undec-4-ene derivatives of sugars are obtained in three steps, starting from fully protected glycono-1,5-lactones. The procedure is based on the attack of a lithiated dithiinyl reagent (**6**) on the starting δ-glyconolactone. The *C*-glycosidation leads to the sole thermodynamically more stable α-hemiacetal derivative, the spirocyclization of which is then accomplished with $BF_3{\cdot}Et_2O$. The fully protected unsaturated spiroacetals can be smoothly desulfurized for the purpose of any further elaborations of the free double bond.

Introduction

In a recent paper[1] we reported a new stereoselective synthesis of 1,6-dioxaspiro[4,5]dec-3-enes of common sugars, starting from the corresponding fully protected glyconolactones.

Under our conditions only the products having (*S*) configuration at the spiro carbon atom were formed in the *C*-glycosidation step, and that was likely due to the addition of a rather bulky 1,4-dithiinyl reagent **1** onto the carbonyl group of the starting glyconolactones. In fact, *C*-glycosidation reactions often suffer from poor facial selectivity of the nucleophile attack leading to mixtures of both diastereomeric *C*-glycosides.[2,3] Indeed, the (*S*) stereochemistry at the spirocentre represents an interesting synthetic outcome inasmuch as such a configuration is that shown by a wide group of natural products[4,5] containing a symmetrically disposed 1,7-dioxaspiro[5,5]undecene spiroacetal motif. Specifically, the calcium-binding ionophore[6] A 23187 and the group of potent anthelmintic antibiotics comprising the avermectins[7] and milbemycins[8] offer awe-inspiring examples of such structures.



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For these reasons we considered modifying our former synthetic approach in order to devise a new and reliable method for the preparation of 1,7-dioxaspiro[5,5]undec-4-ene derivatives of sugars, in which we are interested to perform a new synthesis of avermectin B_{1a}.

Results and Discussion

The procedure we reported to prepare 1,6-dioxaspiro[4,5-]dec-3-enes was based on the nucleophilic attack of 3-*C*-lithiated (5,6-dihydro-1,4-dithiin-2-ylmethoxy)(4-methoxyphenyl)methane (**1**) onto the carbonyl group of a δ-glyconolactone. The dithiinyl reagent **1**, devised in our laboratory, acts as an allylic alcohol anion equivalent and leads to three-carbon elongations of suitable electrophiles by introduction of a fully protected hydroxypropenyl moiety.

Hence, in order to synthesize 1,7-dioxaspiro[5,5]undec-4-ene derivatives of sugars we needed a new dithiinyl reagent, namely 3-{3-[(4-methoxybenzyl)oxy]propyl}-5,6-dihydro-1,4-dithiin-2-yl)lithium (**6**), that is a one-carbon homolog of **1**.

However, such a compound could not be prepared directly from methyl/ethyl acetoacetate[9] and a special synthetic path had to be devised.

The preparation turned out not to be as trivial as expected and more than one attempt at the synthesis was un-

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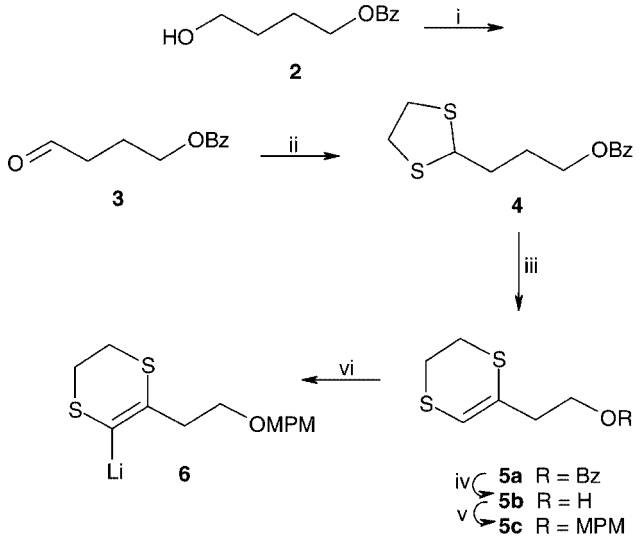
successful: eventually **6** was obtained, as outlined in Scheme 1, starting from the monobenzoyl ester of the commercially available 1,4-butanediol. The initial benzoic ester protection was chosen because of its resistance under the acidic conditions occurring during the ring-expansion step leading to dithiin **5a** from its parent dithiolane **4**. The benzoic ester was then removed and replaced by the 4-methoxybenzyl ether (MPM) protection which is more suitable for the spiro-ring closure conditions: as a matter of fact, the MPM protection is unaffected by butyllithium and, therefore, **5c** could be directly lithiated to afford the final dithiinyl reagent **6**.

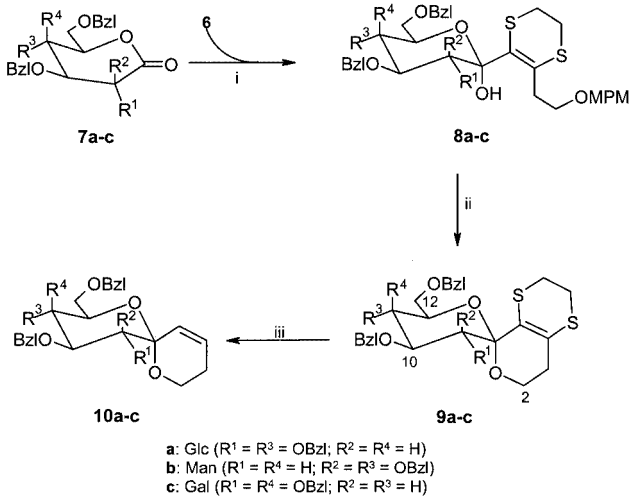


Scheme 1. Preparation of the lithiated reagent **6.** i. PCC, CH_2Cl_2, room temp.; ii. polymer-bound DPP /I_2, ethanedithiol, MeCN, room temp.; iii. NBS, $CHCl_3$, room temp.; iv. MeONa, MeOH, room temp.; v. NaH, MPMCl, DMF, room temp.; vi. BuLi, THF, −78 °C

The coupling of **6** with the fully protected δ-glyconolactones **7a**−**c**, in dry THF at −78 °C, led to the hemiacetals **8a,c**. The stereochemical outputs of the coupling reactions were confirmed via ^{1}H NMR experiments and found consistent with available literature data.[5,10] Indeed, the hemiacetal **8b**, coming from the corresponding protected δ-mannonolactone **7b**, could not be purified to get any of its physical data, likely due to the poor stability consequent to the Δ-2 effect and, from this, the equilibrium between the cyclic form and the open α,β-unsaturated ketone form. The cyclizations of the hemiacetals **8a,c**, and also of the coupling product coming from **7b**, occurred smoothly at room temperature, with $BF_3{\cdot}Et_2O$ in methylene dichloride affording the spiroacetals **9a**−**c** (Scheme 2). The stereochemistry of the six-membered ring closure is governed by thermodynamic factors,[1,3] leading to the more stable (*R*) derivatives, as ascertained by the ^{1}H NMR analysis of the desulfurized spiroacetals.

The dimethylenedisulfur bridge still present in the spiro compounds **9a**−**c** could be eventually removed by Raney-Ni in THF at room temperature.[11]

The (*S*) stereochemistry at the spirocarbon after sulfur removal was unambiguously assigned to all the spiroacetals



Scheme 2. Coupling and spirocyclization of sugars. i. THF, −78 °C; ii. $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp.; iii. Raney (Ni), THF, room temp.

10a−**c** on the basis of ^{1}H NMR comparison experiments which showed a NOE between 5-H and 11-H in both *gluco*- and *galacto*-spiroacetals (**10a,c**) (see Exp. Sect.). The NOE was instead absent in the *manno*-spiroacetal **10b**, thus ruling out the possibility of (*R*) configuration at the spiro centres.

If one considers that the dithiinyl compound **5c** is quite stable and can be stored for a long time in the refrigerator to be lithiated to afford **6** immediately before use, the whole procedure appears very convenient, being also characterized by clean and high-yielding reactions. The double bond in the final sulfur-free unsaturated spiroacetals can be easily saturated by catalytic hydrogenation, or hydroxylated under stereocontrolled conditions, to synthesise other more complex dioxaspiroacetal-based compounds.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra: Varian Inova 500, Bruker DRX-400, Varian Gemini 200 spectrometers, $CDCl_3$ unless otherwise specified, TMS internal standard. Bzl_i to Bzl_{iv} in the ^{1}H NMR data are used to indicate proton couplings in the same benzyl ring. Optical rotations (in $CHCl_3$): Jasco P-1010 (1.0-dm cell). Combustion analyses: Perkin−Elmer Series II 2400, CHNS analyzer. TLC analyses: silica gel Merck 60 F_{254} plates (0.2 mm layer thickness). Column chromatography: Merck Kieselgel 60 (70−230 mesh). Dry solvents were distilled immediately before use.

4-(Benzoyloxy)-1-butanol (2): Benzoyl chloride (6.43 mL, 55.5 mmol) was added in one portion, at 0 °C, to a magnetically stirred solution of 1,4-butanediol (4.9 mL, 55.5 mmol) in anhydrous pyridine (150 mL). After 2 h at room temperature the 1,4-butanediol was fully consumed (TLC monitoring). The solution was neutralized by addition of 2 N aq. HCl (250 mL) and the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL), dried (Na_2SO_4), and the solvents evaporated under reduced pressure to afford an oily residue that, after purification by column chromatography on silica gel, gave the pure monobenzoyl ester **2** (8.1 g, 75%) as an oil. $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.27; found C 68.13,

H 7.30. ^{1}H NMR (500 MHz): δ = 1.53 (br. s, 1 H, OH), 1.65−1.98 (m, 4 H, 2-H and 3-H), 3.75 (t, $J_{1,2}$ = 6.5 Hz, 2 H, 1-H), 4.38 (t, $J_{4,3}$ = 6.5 Hz, 2 H, 4-H), 7.38−7.61 (m, 3 H, H_{para} and H_{meta}), 8.07 (d, 2 H, H_{ortho}) ppm. ^{13}C NMR (300 MHz): δ = 25.1 (C-3), 29.1 (C-2), 62.3 (C-1), 64.6 (C-4), 128.2 (2 × C_{meta}), 129.4 (2 × C_{ortho}), 130.2 (C_{ipso}), 132.8 (C_{para}), 166.6 (C=O) ppm.

4-Benzoyloxybutanal (3): A solution of **2** (6.0 g, 30.9 mmol) in anhydrous CH_2Cl_2 (15 mL) was added in one portion, at room temperature, to a magnetically stirred suspension of pyridinium chlorochromate (PCC) (10.0 g, 46.4 mmol) and Celite 545 (10.0 g) in the same solvent (80 mL). The resulting dark-brown reaction mixture was kept at room temperature for 1.5 h and then diluted with anhydrous Et_2O and filtered through a sintered-glass septum funnel. The solvents were evaporated under reduced pressure and the crude residue was purified by column chromatography on silica gel (CH_2Cl_2) to give the pure aldehyde **3** (5.3 g, 90%), oily. $C_{11}H_{12}O_3$ (192.2): calcd. C 68.74, H 6.29; found C 68.95, H 6.31. ^{1}H NMR (300 MHz): δ = 2.05−2.30 (m, 2 H, 3-H), 2.75 (m, 2 H, 2-H), 4.30−4.51 (m, 2 H, 4-H), 7.38−7.65 (m, 3 H, H_{para} and H_{meta}), 8.05 (d, J_{ortho} = 7.9 Hz, 2 H, H_{ortho}), 9.82 (t, $J_{1,2}$ = 1.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (400 MHz): δ = 23.9 (C-3), 30.6 (C-2), 63.8 (C-4), 128.3 (2 × C_{meta}), 129.5 (2 × C_{ortho}), 130.2 (C_{ipso}), 133.0 (C_{para}), 166.6 (C=O), 201.0 (C-1) ppm.

2-[3′-(Benzoyloxy)propyl]-1,3-dithiolane (4): A solution of **3** (4.3 g, 22.6 mmol) in anhydrous acetonitrile (25 mL) was added via a syringe in one portion to a magnetically stirred suspension of polystyryl diphenylphosphane-iodine complex (22.6 mmol, prepared in situ) in the same solvent (150 mL), at room temperature and under dry nitrogen. After 10 min, 1 M ethanedithiol in the same solvent (23 mL) was also added in one portion. The benzoyloxybutanal was fully consumed (TLC monitoring) within 2 h. Solid K_2CO_3 (excess) was then added, and the suspension was stirred for a couple of minutes and finally filtered. The solid was washed with chloroform (3 × 100 mL) and the combined filtrates, after shaking with 5 N aq sodium thiosulfate (50 mL) and water until neutral, were evaporated under reduced pressure to leave a residue consisting of practically pure **4** (5.9 g, 98%), oily. $C_{13}H_{16}O_2S_2$ (268.4): calcd. C 58.18, H 6.01; found C 58.32, H 6.04. ^{1}H NMR (300 MHz): δ = 1.84−2.10 (m, 4 H, 1′-H and 2′-H), 3.12−3.37 (m, 4 H, 4-H and 5-H), 4.28−4.39 (m, 2 H, 3′-H), 4.54 (t, $J_{2,1'}$ = 6.3 Hz, 1 H, 2-H), 7.38−7.62 (m, 3 H, H_{para} and H_{meta}) 8.04 (d, J_{ortho} = 8.0 Hz, 2 H, H_{ortho}) ppm. ^{13}C NMR (300 MHz): δ = 28.1 (C-2′), 35.8, 38.3 (C-4 and C-5), 53.0 (C-2), 64.2 (C-3′), 128.2 (2 × C_{meta}), 129.4 (2 × C_{ortho}), 130.1 (C_{ipso}), 132.7 (C_{para}), 166.4 (C=O) ppm.

5,6-Dihydro-1,4-dithiin (5a): A solution of NBS (6.6 g, 37.4 mmol) in anhydrous $CHCl_3$ (100 mL) was added in one portion, at room temperature, to a magnetically stirred solution of pure 1,3-dithiolane **4** (5.0 g, 18.7 mmol) in the same solvent (500 mL). After 16 h at room temperature saturated aq. $NaHCO_3$ (200 mL) was added. The organic layer was separated and shaken with 5 N aq. sodium thiosulfate (150 mL), washed with water until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure. The oily residue, chromatographed on a silica gel column (petroleum ether/Et_2O, 9:1) afforded the pure 5,6-dihydro-1,4-dithiin **5a** (4.5 g, 90%), oily. $C_{13}H_{14}O_2S_2$ (266.3): calcd. C 58.62, H 5.30; found C 58.76, H 5.36. ^{1}H NMR (300 MHz): δ = 2.72 (dt, $J_{1',3}$ = 0.8, $J_{1',2'}$ = 6.6 Hz, 2 H, 1′-H), 3.98−3.26 (m, 4 H, 5-H and 6-H), 4.45 (t, $J_{2',1'}$ = 6.6 Hz, 2 H, 2′-H), 6.15 (s, 1 H, 3-H), 7.38−7.60 (m, 3 H, H_{para} and H_{meta}), 8.05 (d, J_{ortho} = 7.8 Hz, 2 H, H_{ortho}) ppm. ^{13}C NMR (200 MHz): δ = 24.3, 25.9 (C-5 and C-6), 37.0 (CH_2−C=), 61.6 (CH_2−O), 109.8 (C-3), 122.8 (C-2), 126.6 (2 × C_{meta}), 127.9 (2 × C_{ortho}), 128.6 (C_{ipso}), 131.2 (C_{para}), 164.7 (C=O) ppm.

5,6-Dihydro-1,4-dithiin 5b: Solid MeONa (0.6 g, 11.2 mmol) was added in one portion, with magnetic stirring and under nitrogen at room temperature, to a solution of **5a** (2.0 g, 7.5 mmol) in MeOH (15 mL). After 4 h the reaction was quenched with excess glacial acetic acid and most of the MeOH was removed under reduced pressure. The crude residue was redissolved by CH_2Cl_2 (100 mL), washed with water until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure. After purification by column chromatography on silica gel (CH_2Cl_2) pure **5b** was obtained (1.2 g, 98%), oily. $C_6H_{10}OS_2$ (162.2): calcd. C 44.41, H 6.21; found C 44.20, H 6.25. ^{1}H NMR (200 MHz): δ = 2.39 (t, $J_{1',2'}$ = 6.0 Hz, 2 H, 1′-H), 3.12−3.28 (m, 4 H, 5-H and 6-H), 3.73 (t, $J_{2',1'}$ = 6.0 Hz, 2 H, 2′-H), 6.01 (s, 1 H, 3-H) ppm. ^{13}C NMR (200 MHz): δ = 24.1, 25.9 (C-5 and C-6), 41.0 (CH_2−C=), 59.3 (CH_2−O), 109.4 (C-3), 123.1(C-2) ppm.

5,6-Dihydro-1,4-dithiin 5c: 4-Methoxybenzyl chloride (2.38 mL, 17.6 mmol) dissolved in dry DMF (40 mL) was added dropwise to a solution of pure **5b** (2.2 g, 13.5 mmol) and NaH (0.48 g, 20.3 mmol) in the same solvent (20 mL) that had been kept magnetically stirred and under nitrogen atmosphere for 30 min at room temperature. The stirring was continued for 15 h, and the reaction mixture was diluted with brine and extracted with Et_2O. The combined organic layers, after drying (Na_2SO_4) and evaporation of the solvents under reduced pressure, gave a crude product, which after chromatography on silica gel (petroleum ether/Et_2O, 9:1) afforded the pure oily **5c** (3.7 g, 96%). $C_{14}H_{18}O_2S_2$ (282.4): calcd. C 59.54, H 6.42; found C 59.57, H 6.45. ^{1}H NMR (200 MHz): δ = 2.45 (dt, $J_{1',3}$ = 0.8, $J_{1',2'}$ = 6.9 Hz, 2 H, 1′-H), 3.02−3.22 (m, 4 H, 5-H and 6-H), 3.55 (t, $J_{2',1'}$ = 6.9 Hz, 2 H, 2′-H), 3.81 (s, 3 H, OCH_3), 4.47 (s, 2 H, OCH_2MPM), 5.96 (d, $J_{3,1'}$ = 0.8 Hz, 1 H, 3-H), 6.88 (d, J_{ortho} = 8.1 Hz, 2 H, $H_{arom.}$), 7.28 (d, J_{ortho} = 8.1 Hz, 2 H, $H_{arom.}$) ppm. ^{13}C NMR (200 MHz): δ = 25.8, 27.5 (C-5 and C-6), 39.6 (CH_2C=), 55.1 (OCH_3), 68.4 (CH_2-O), 72.5 (OCH_2Ar), 110.2 (C-3), 113.6 (2 × C_{meta}), 122.1 (C-2), 129.2 (2 × C_{ortho}), 130.0 (C_{ipso}), 150.9 (C−OCH_3) ppm.

Compound 8a. Typical Coupling Procedure: 1.6 M BuLi in hexane (0.9 mL, 1.4 mmol) was added dropwise over 10 min to a stirred solution of **5c** (0.39 g, 1.2 mmol) in anhydrous THF (5 mL), at −78 °C and under N_2. After 40 min, D-gluconolactone **7a** (0.54 g, 1.0 mmol) dissolved in the same solvent (2 mL) was added dropwise via a cannula. The reaction mixture was kept at −78 °C for 3 h, then quenched with 10% aq. NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and the solvents evaporated under reduced pressure. Chromatography of the crude residue on silica gel (petroleum ether/EtOAc, 7:3) finally afforded the pure hemiacetal **8a** (0.74 g, 90%) as an oil. $[\alpha]_d^{25}$ = +5.4 (*c* = 1.8). $C_{48}H_{52}O_8S_2$ (821.0): calcd. C 70.22, H 6.38; found C 70.26, H 6.41. ^{1}H NMR (500 MHz, C_6D_6): δ = 1.72 (dd, $J_{1'a,2'a}$ = 2.4, $J_{1'a,1'b}$ = 12.9 Hz, 1 H, 1′-H_a), 2.32−2.38 (m, 2 H, CH_2S), 2.42−2.48 (m, 1 H, CH_aS), 2.83−2.92 (m, 1 H, CH_bS) 3.01−3.16 (m, 1 H, 2′-H_a), 3.22 (s, 3 H, OCH_3), 3.40−3.48 (m, 1 H, 2′-H_b), 3.62 (dd, $J_{6a,5}$ = 1.5, $J_{6a,6b}$ = 11.7 Hz, 1 H, 6-H_a), 3.92 (dd, $J_{6b,5}$ = 3.4, $J_{6b,6a}$ = 11.7 Hz, 1 H, 6-H_b), 3.98−4.06 (m, 2 H, 4-H and OCH_aMPM), 4.09−4.16 (m, 2 H, 3-H and OCH_bMPM), 4.19−4.22 (m, 1 H, 5-H), 4.34 (d, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 4.38−4.46 (m, 1 H, 1′-H_b), 4.58 (d, $J_{a,b}$ = 12.7 Hz, 1 H, Bzl_i-H_a), 4.63 (d, $J_{a,b}$ = 10.2 Hz, 1 H, Bzl_{ii}-H_a), 4.74 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{iii}-H_a), 4.80 (d, $J_{b,a}$ = 12.7 Hz, 1 H, Bzl_i-H_b), 4.87 (d, $J_{b,a}$ = 10.2 Hz, 1 H, Bzl_{ii}-H_b), 4.89 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{iv}-H_a), 4.94 (d, $J_{b,a}$ = 11.2 Hz, 1 H, Bzl_{iii}-H_b),

5.01 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_{iv}-H_b), 6.42 (br. s, 1 H, OH), 6.65 (d, J_{ortho} = 8.8 Hz, 2 H, $H_{arom.}$), 7.02−7.61 (m, 22 H, $H_{arom.}$) ppm. ^{13}C NMR (300 MHz): δ = 26.3 (CH_2C=), 31.3, 36.0 (2 × CH_2S), 55.1 (OCH_3), 67.8, 68.1, 68.5, 71.0, 73.2, 73.4, 74.9, 75.5, 75.9, 78.3, 81.6, 83.5 (4′-CH_2Bzl, CH_2O, OCH_2MPM, C-2, C-3, C-4, C-5, C-6), 99.3 (C-1), 113.6 (2 × C_{meta}MPM), 127.1−129.4 (22 × $C_{arom.}$, C_{ipso}MPM, 2 × C=), 137.8, 138.2, 138.5, 138.9 (4 × C_{ipso}), 159.2 (C−OMe) ppm.

Under the same conditions:

Compound 8c, from D-Galactonolactone 7c: (89%), oily. $[\alpha]_D^{25}$ = −1.02 (*c* = 1.1). $C_{48}H_{52}O_8S_2$ (821.0): calcd. C 70.22, H 6.38; found C 70.18, H 6.34. ^1H NMR (500 MHz, C_6D_6): δ = 1.89 (d, $J_{1'a,1'b}$ = 15.1 Hz, 1 H, 1′-H_a), 2.32−2.40 (m, 2 H, CH_2S), 2.41−2.48 (m, 1 H, CH_aS), 2.77−2.86 (m, 1 H, CH_bS), 3.14 (m, 1 H, 2′-H_a), 3.26 (s, 3 H, OCH_3), 3.46−3.54 (m, 1 H, 2′-H_b), 3.67 (dd, $J_{6a,5}$ = 5.4, $J_{6a,6b}$ = 8.8 Hz, 1 H, 6-H_a), 3.90 (t, $J_{6b,6a}$ = $J_{6b,5}$ = 8.8 Hz, 1 H, 6-H_b), 4.01 (m, 1 H, 4-H), 4.05 (d, $J_{a,b}$ = 11.3 Hz, 1 H, OCH_aMPM), 4.12 (dd, $J_{3,4}$ = 2.9, $J_{3,2}$ = 9.8 Hz, 1 H, 3-H), 4.16 (m, 2 H, 3-H and OCH_bMPM), 4.26 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_i-H_a), 4.33 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_i-H_b), 4.34−4.38 (m, 1 H, 1′-H_b), 4.39−4.44 (m, 1 H, 5-H), 4.48 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{ii}-H_a), 4.61 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_{ii}-H_b), 4.67 (d, $J_{a,b}$ = 10.7 Hz, 1 H, Bzl_{iii}-H_a), 4.68 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{iv}-H_a), 4.72 (dd, $J_{2,3}$ = 9.8, $J_{2,4}$ = 1.5 Hz, 1 H, 2-H), 4.91 (d, $J_{b,a}$ = 10.7 Hz, 1 H, Bzl_{iii}-H_b), 5.12 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_{iv}-H_b), 6.22 (br. s, 1 H, OH), 6.65 (d, J_{ortho} = 8.8 Hz, 2 H, $H_{arom.}$), 7.02−7.48 (m, 22 H, $H_{arom.}$). ^{13}C NMR (300 MHz): δ = 27.4 (CH_2−C=), 31.2, 36.0 (2 × CH_2S), 55.2 (OCH_3), 68.1, 68.4, 69.4, 72.6, 72.8, 73.1, 73.4, 74.2 (4 × CH_2Bzl, CH_2O, OCH_2MPM, C-5, C-6), 74.5, 78.6 81.0 (C-2, C-3, C-4), 99.8 (C-1), 113.7 (2 × C_{meta}MPM), 126.9, 129.4 (22 × $C_{arom.}$, C_{ipso}MPM, 2 × C=), 138.1, 138.5, 139.0, 139.6 (4 × C_{ipso}), 159.2 (C−OMe) ppm.

Spirocyclization of Hemiacetal 8a to Compound 9a. Typical Procedure: A solution (3% v/v in CH_2Cl_2) of $BF_3{\cdot}Et_2O$ (0.2 mL) was added carefully to a magnetically stirred solution of hemiacetal **8a** (0.81 g, 1.0 mmol) in CH_2Cl_2 (14 mL) at room temperature. After 1 h, the reaction was quenched with Et_3N (0.03 mL, 0.2 mmol) and the organic layer was washed with water and dried (Na_2SO_4). The solvents were evaporated under reduced pressure to afford a crude residue, and chromatography on a silica-gel column (petroleum ether/EtOAc, 8:2) afforded the pure spiroacetal **9a** (0.58 g, 87%), oily. $[\alpha]_D^{25}$ = −28.0 (*c* = 0.7). $C_{40}H_{42}O_6S_2$ (682.9): calcd. C 70.35, H 6.20; found C 70.38, H 6.17. ^1H NMR (500 MHz, C_6D_6): δ = 1.55 (dd, $J_{3,2}$ = 1.4, $J_{3a,3b}$ = 16.3 Hz, 1 H, 3-H_a), 2.30−2.42 (m, 2 H, CH_2S), 2.44−2.58 (m, 3 H, 3-H_b and CH_2S), 3.45 (dd, $J_{2a,3b}$ = 4.9, $J_{2a,2b}$ = 10.7 Hz, 1 H, 2-H_a), 3.65 (dd, $J_{12,8}$ = 1.5, $J_{12a,12b}$ = 11.2 Hz, 1 H, 12-H_a), 3.74 (ddd, $J_{2b,3a}$ = 1.4, $J_{2b,3b}$ = 9.3, $J_{2b,2a}$ = 10.7 Hz, 1 H, 2-H_b), 3.84 (dd, $J_{12,8}$ = 3.9, $J_{12b,12a}$ = 11.2, 1 H, 12-H_b), 3.90 (t, $J_{9,8}$ = $J_{9,10}$ = 9.8 Hz, 1 H, 9-H), 4.05 (ddd, $J_{8,12a}$ = 1.4, $J_{8,12b}$ = 3.9, $J_{8,9}$ = 9.8 Hz, 1 H, 8-H), 4.48 (d, $J_{a,b}$ = 12.2 Hz, 1 H, Bzl_i-H_a), 4.68 (d, $J_{b,a}$ = 12.2 Hz, 1 H, Bzl_i-H_b), 4.70 (d, $J_{a,b}$ = 11.3 Hz, 1 H, Bzl_{ii}-H_a), 4.82 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{iii}-H_a), 4.88−4.95 (m, 4 H, Bzl_{ii}-H_b and Bzl_{iii}-H_b and Bzl_{iv}-$H_{a,b}$), 7.02−7.43 (m, 20 H, $H_{arom.}$) ppm. ^{13}C NMR (300 MHz): δ = 27.6 (C-3), 29.6, 31.3 (2 × CH_2S), 58.3 (C-2), 68.6 (C-12), 72.2, 73.3, 74.9, 75.3, 75.6, 78.1, 81.3, 83.3 (4 × CH_2Bzl, C-8, C-9, C-10, C-11), 98.2 (C-6), 115.7 (C-4), 119.4 (C-5), 127.5−128.2 (20 × $C_{arom.}$), 138.2−138.7 (4 × C_{ipso}) ppm.

The following spiroacetals were also obtained under the same conditions:

Compound 9b from 8b: 87%, oily. $[\alpha]_D^{25}$ = −22.6 (*c* = 0.4). $C_{40}H_{42}O_6S_2$ (682.9): calcd. C 70.35, H 6.20; found C 70.39, H 6.19. ^1H NMR (500 MHz, C_6D_6): δ = 1.72 (dd, $J_{3a,2b}$ = 1.6, $J_{3a,3b}$ = 16.2 Hz, 1 H, 3-H_a), 2.10−2.19 (m, 1 H, CH_aS), 2.28−2.38 (m, 2 H, 3-H_b and CH_bS), 2.41−2.48 (m, 1 H, CH_aS), 2.81−2.88 (m, 1 H, CH_bS), 3.28 (dd, $J_{2a,3b}$ = 4.7, $J_{2a,2b}$ = 11.0 Hz, 1 H, 2-H_a), 3.67−3.73 (m, 1 H, 2-H_b), 3.76 (d, $J_{12a,12b}$ = 10.5 Hz, 1 H, 12-H_a), 3.84 (d, $J_{11,10}$ = 2.6 Hz, 1 H, 11-H), 3.94−4.01 (m, 2 H, 8-H and 12-H_b), 4.31 (dd, $J_{10,11}$ = 2.6, $J_{10,9}$ = 9.4 Hz, 1 H, 10-H), 4.42 (t, $J_{9,10}$ = 9.4 Hz, 1 H, 9-H), 4.51 (d, $J_{a,b}$ = 12.0 Hz, 1 H, Bzl_i-H_a), 4.55 (d, $J_{b,a}$ = 12.0 Hz, 1 H, Bzl_i-H_b), 4.61 (d, $J_{a,b}$ = 12.1 Hz,1 H, Bzl_{ii}-H_a), 4.65 (d, $J_{a,b}$ = 11.5 Hz, 1 H, Bzl_{iii}-H_a), 4.85 (d, $J_{a,b}$ = 11.0 Hz, 1 H, Bzl_{iv}-H_a), 4.88 (d, $J_{b,a}$ = 11.0 Hz, 1 H, Bzl_{iv}-H_b), 4.91 (d, $J_{b,a}$ = 11.5 Hz, 1 H, Bzl_{iii}-H_b), 4.99 (d, $J_{b,a}$ = 12.1 Hz, 1 H, Bzl_{ii}-H_b), 7.00−7.65 (m, 20 H, $H_{arom.}$) ppm. ^{13}C NMR (300 MHz): δ = 27.8 (C-3), 31.3, 31.9 (2 × CH_2S), 58.1 (C-2), 69.4 (C-12), 72.6, 73.7, 74.2, 74.6 (4 × CH_2Bzl), 74.8, 75.3, 80.2, 81.8 (C-8, C-9, C-10, C-11), 97.4 (C-6), 122.3 (C-4), 125.5 (C-5), 127.2−128.5 (20 × $C_{arom.}$), 138.8, 139.0, 139.1, 139.3 (4 × C_{ipso}) ppm.

Compound 9c from 8c: 88%, oily. $[\alpha]_D^{25}$ = −29.1 (*c* = 1.3). $C_{40}H_{42}O_6S_2$ (682.9): calcd. C 70.35, H 6.20; found C 70.39, H 6.16. ^1H NMR (500 MHz, C_6D_6): δ = 1.57 (dd, $J_{3a,2b}$ = 1.5, $J_{3a,3b}$ = 16.1 Hz, 1 H, 3-H_a), 2.27−2.34 (m, 1 H, CH_aS), 2.36−2.42 (m, 1 H, CH_bS), 2.44−2.57 (m, 3 H, CH_2S and 3-H_b), 3.44 (dd, $J_{2a,3b}$ = 4.5, $J_{2a,2b}$ = 10.6 Hz, 1 H, 2-H_a), 3.68 (dd, $J_{12a,8}$ = 5.4, $J_{12a,12b}$ = 8.8 Hz, 1 H, 12-H_a), 3.76−3.84 (m, 2 H, 2-H_b and 12-H_b), 3.97 (dd, $J_{9,8}$ = 1.2, $J_{9,10}$ = 2.7 Hz, 1 H, 9-H), 4.11 (dd, $J_{10,9}$ = 2.7, $J_{10,11}$ = 10.0 Hz, 1 H, 10-H), 4.17 (ddd, $J_{8,9}$ = 1.2, $J_{8,12a}$ = 5.4, $J_{8,12b}$ = 6.8 Hz, 1 H, 8-H), 4.22 (d, $J_{a,b}$ = 11.8 Hz, 1 H, Bzl_i-H_a), 4.27 (d, $J_{b,a}$ = 11.8 Hz, 1 H, Bzl_i-H_b), 4.48 (d, $J_{a,b}$ = 11.8 Hz, 1 H, Bzl_{ii}-H_a), 4.59 (d, $J_{b,a}$ = 11.8 Hz, 1 H, Bzl_{ii}-H_b), 4.65 (d, $J_{a,b}$ = 11.8 Hz, 1 H, Bzl_{iii}-H_a), 4.88 (d, $J_{11,10}$ = 10.0 Hz, 1 H, 11-H), 4.91 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{iv}-H_a), 5.02 (d, $J_{b,a}$ = 11.2 Hz, Bzl_{iv}-H_b), 5.13 (d, $J_{b,a}$ = 11.8 Hz, 1 H, Bzl_{iii}-H_b), 7.02−7.48 (m, 20 H, $H_{arom.}$) ppm. ^{13}C NMR (300 MHz): δ = 27.7 (C-3), 29.0, 31.2 (2 × CH_2S), 58.3 (C-2), 68.6 (C-12), 70.4, 72.9, 73.3, 74.0 (4 × CH_2Bzl), 74.5, 75.5, 78.0, 80.8 (C-8, C-9, C-10, C-11), 98.7 (C-6), 119.9 (C-4), 126. 7 (C-5), 127.0−128.2 (20 × $C_{arom.}$), 137.9, 138.7, 139.0, 139.2 (4 × C_{ipso}) ppm.

Compound 10a. Typical Desulfurization Procedure: A solution of spiroacetal **9a** (0.1 g, 0.15 mmol) in THF (3 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (1.5 g, wet) in the same solvent (2 mL) at room temperature. The suspension was stirred for 35 min (TLC monitoring) and the solid was then filtered off and washed with EtOAc. The filtrate was neutralized with saturated aq. Na_2CO_3 and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure to afford a crude residue. Chromatography of the latter on a silica gel column (petroleum ether/EtOAc, 8:2) gave the pure sulfur-free spiroacetal **10a** (0.07 g, 79%) as an oil. $[\alpha]_D^{25}$ = +29.3 (*c* = 0.5). $C_{38}H_{40}O_6$ (592.7): calcd. C 77.00, H 6.80; found C 77.06, H 6.84. ^1H NMR (500 MHz, C_6D_6): δ = 1.18−1.37 (m, 1 H, 3H_a), 1.98−2.09 (m, 1 H, 3H_b), 3.41 (d, $J_{11,10}$ = 9.8 Hz, 1 H, 11-H), 3.55 (dd, $J_{2a,3b}$ = 5.76, $J_{2a,2b}$ = 10.7 Hz, 1 H, 2-H_a), 3.68 (dd, $J_{12a,8}$ = 1.95, $J_{12a,12b}$ = 10.7 Hz, 1 H, 12-H_a), 3.72−3.81 (m, 2 H, 2-H_b and 12-H_b), 3.87 (t, $J_{9\cdot8}$ = $J_{9,10}$ = 9.3 Hz, 1 H, 9-H), 4.09 (m, 1 H, 8-H), 4.31 (dd, $J_{10,9}$ = 9.3, $J_{10,11}$ = 9.8 Hz, 1 H, 10-H), 4.34 (dd, $J_{a,b}$ = 12.2 Hz, 1 H, Bzl_i-H_a), 4.45 (d, $J_{a,b}$ = 12.2 Hz, 1 H, Bzl_i-H_b), 4.55 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{ii}-H_a), 4.68 (dd, $J_{b,a}$ = $J_{a,b}$ = 11.2 Hz, 2 H, Bzl_{ii}-H_b and Bzl_{iii}-H_a), 4.82 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{iv}-H_a), 4.92 (d, $J_{b,a}$ = 11.2 Hz, 1 H, Bzl_{iv}-H_b), 4.98 (d, $J_{b,a}$ = 11.2 Hz, 1 H, Bzl_{iii}-H_b), 5.50 (td, $J_{5,3}$ = 1.0, $J_{5,4}$ = 10.26 Hz, 1 H,

5-H), 5.70 (dd, $J_{4,3a}$ = 5.8, $J_{4,5}$ = 10.2 Hz, 1 H, 4-H), 7.01−7.18 (m, 20 H, $H_{arom.}$) ppm, [5-H, 11 H: NOE effect]. ^{13}C NMR (400 MHz): δ = 24.6 (C-3), 58.6 (C-2), 69.3 (C-12), 71.5, 73.8, 75.3, 75.7, 76.1, 78.7, 83.3, 83.6 (4 × CH_2Bzl, C-8, C-9, C-10, C-11), 96.1 (C-6), 127.9−129.0 (C-4, 20 × $C_{arom.}$), 130.8 (C-5), 138.5, 138.6, 138.8, 139.6 (4 × C_{ipso}) ppm.

The following desulfurized spiroacetals were also obtained under the same conditions:

Compound 10b from 9b: 77%, oily. $[\alpha]_d^{25}$ = +18.4 (*c* = 0.1). $C_{38}H_{40}O_6$ (592.7): calcd. C 77.00, H 6.80; found C 70.04, H 6.85. ^1H NMR (500 MHz, C_6D_6): δ = 1.15−1.25 (m, 1 H, 3-H_a), 1.82−1.92 (m, 1 H, 3-H_b), 3.35 (dd, $J_{2a,3b}$ = 6.3, $J_{2a,2b}$ = 10.7 Hz, 1 H, 2-H_a), 3.63−3.68 (m, 2 H, 10-H and 12-H_a), 3.72−3.78 (m, 2 H, 2-H_b and 12-H_b), 3.96−4.02 (m, 1 H, 8-H), 4.15−4.23 (m, 2 H, 9-H and 11-H), 4.34 (d, $J_{a,b}$ = 12.2 Hz, 1 H, Bzl_i-H_a), 4.39−4.52 (m, 5 H, Bzl_i-H_b and Bzl_{ii}-H_a and Bzl_{iii}-H_a and Bzl_{iv}-$H_{a,b}$), 4.84 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_{ii}-H_b), 4.86 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{iii}-H_b), 5.57 (dd, $J_{4,3a}$ = 5.8, $J_{4,5}$ = 10.3 Hz, 1 H, 4-H), 6.16 (dd, $J_{5,3b}$ = 1.4, $J_{5,4}$ = 10.3 Hz, 1 H, 5-H), 6.99−7.35 (m, 20 H, $H_{arom.}$) ppm, [5-H, 11 H: no NOE effect]. ^{13}C NMR (200 MHz): δ = 29.6 (C-3), 57.6 (C-2), 69.5 (C-12), 72.3, 72.6, 73.2, 74.8 (4 × CH_2Bzl), 74.9, 75.0, 78.5, 81.4 (C-8, C-9, C-10, C-11), 95.5 (C-6), 126. 5 (C-4), 127.3−128.1 (20 × $C_{arom.}$), 128.5 (C-5), 138.2−138.6 (4 × C_{ipso}) ppm.

Compound 10c from 9c: 78%, oily. $[\alpha]_d^{25}$ = +10.1 (*c* = 0.1). $C_{38}H_{40}O_6$ (592.7): calcd. C 77.00, H 6.80; found C 77.04, H 6.85. ^1H NMR (500 MHz, C_6D_6): δ = 1.20−1.32 (m, 1 H, 3-H_a), 2.08−2.18 (m, 1 H, 3-H_b), 3.56 (dd, $J_{2a,3b}$ = 5.9, $J_{2a,2b}$ = 10.7 Hz, 1 H, 2-H_a), 3.75 (dd, $J_{12a,8}$ = 5.8, $J_{12a,12b}$ = 8.8 Hz, 1 H, 12-H_a), 3.78−3.86 (m, 2 H, 2-H_b, and 12-H_b), 3.98 (br. s, 1 H, 9-H), 4.14 (br. s, 1 H, 10-H), 4.20−4.25 (m, 2 H, 8-H and 11-H), 4.26 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_i-H_a), 4.32 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_i-H_b), 4.48 (d, $J_{a,b}$ = 11.7 Hz, 1 H, Bzl_{ii}-H_a), 4.55 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{iii}-H_a), 4.60 (d, $J_{b,a}$ = 11.7 Hz, 1 H, Bzl_{ii}-H_b), 4.62 (d, $J_{a,b}$ = 11.2 Hz, 1 H, Bzl_{iv}-H_a), 4.78 (d, $J_{b,a}$ = 11.2 Hz, 1 H, Bzl_{iii}-H_b), 5.08 (d, $J_{b,a}$ = 11.2 Hz, Bzl_{iv}-H_b), 5.58 (dd, $J_{5,3b}$ = 1.9, $J_{5,4}$ = 10.2 Hz, 1 H, 5-H), 5.68 (dd, $J_{4,3a}$ = 5.8, $J_{4,5}$ = 10.2 Hz, 1 H, 4-H), 7.01−7.45 (m, 20 H, $H_{arom.}$) ppm, [5-H, 11 H: NOE effect]. ^{13}C NMR (200 MHz): δ = 29.6 (C-3), 58.2 (C-2), 68.8 (C-12), 69.7, 73.2, 73.4, 74.5 (4 × CH_2Bzl), 74.9, 75.3, 79.2, 80.3 (C-8, C-9, C-10, C-11), 95.9 (C-6), 127.2−128.2 (20 × $C_{arom.}$), 128.5 (C-4), 130.0 (C-5), 138.0, 138.2, 138.4, 138.8 (4 × C_{ipso}) ppm.

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