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The low temperature addition of dilithiomethylphenyl sulfone to 2,3-*O*-isopropylidene-D-erythronolactone, and to 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone gives the lactols **2** and **3a**, respectively. Dehydration of lactol **2** in the presence of boron trifluoride etherate produces tetrahydrofuranylidene sulfones **5** and **6** in good yields. The reaction of lactol **3a** under the same reaction conditions proceeds with formation of the 1',5'-anhydro derivative **7** via competing intramolecular substitution.

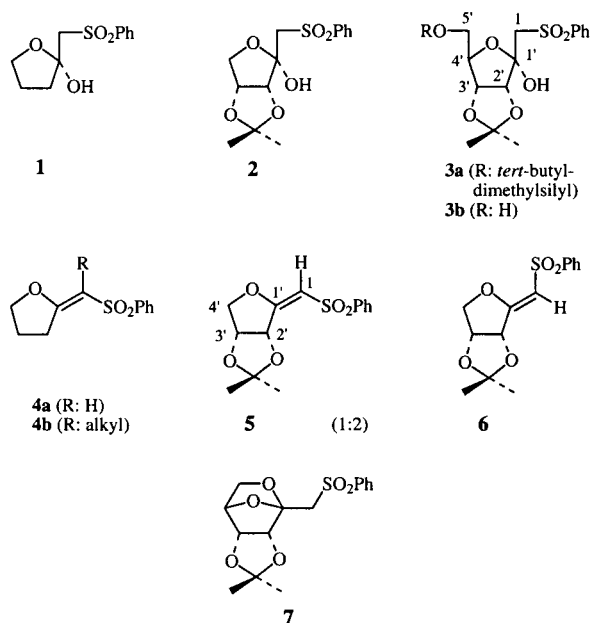
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The synthesis of branched-chain carbohydrates having an olefinic bond at the branching atom has been stimulated by their use as starting compounds for addition reactions at the exocyclic methylene group in the route to bioactive compounds [2]. Recent work in this area has led to the development of alternative methods for the synthesis of several α -methylene- γ -lactones [3]. On the other hand, tetrahydrofuran derivatives possessing an *exo*-methylene group adjacent to the ring oxygen were obtained earlier from aldonolactones with the titanocene methylidene complexes and dicyclopentadienyl-dimethyltitanium [4], from cyano-substituted endocyclic enol ethers *via* stereocontrolled reduction-isomerization [5], and by the addition of stabilized carbanions to iodolactones [6] and to 4-bromobutyrate derivatives [7].

As part of our work directed to the development of synthetic methods leading to functionalized heterocycles as precursors of branched-chain carbohydrates, we have reported recently on the regio- and stereoselective formation of 2-(benzenesulfonylmethylidene)tetrahydrofurans from hydroxyketosulfones. We found that the thermal dehydration of α' -benzenesulfonyl- γ -hydroxyketones affords the desired tri- and tetrasubstituted *E*-1-(benzenesulfonyl)-1-tetrahydrofuranylidenes **4** (R = H, R = benzyloxyethyl, *n*-hexyl; and *n*-pentyl) with remarkable regio- and stereoselectivity [8]. These reactions were reported to proceed *via* the corresponding nonisolable intermediate hemiacetals of type **1** and the extent of the observed stereocontrol was explained in terms of the stereoelectronic interaction between the vinylic sulfonyl group and the oxygen atom at the five-membered ring, which is neither decreased nor reversed when the vinylic hydrogen in **4a** is substituted by larger groups. However, initial attempts to explore the applicability of this methodology to the synthesis of tetrahydrofuranylidenes derived from sterically hindered γ -lactones under the same dehydration conditions were unsuccessful [9]. In connection with our efforts on the phenylsulfonyl-methylenation of aldonolactones we report herein the synthesis of both stereoisomeric tetrahydrofuranylidene sulfones **5** and **6** from 2,3-*O*-isopropylidene-D-erythronolactone, and the formation of

the 1',5'-anhydro derivative **7** from 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone.

α' -Benzenesulfonyl- γ -hydroxyketones are readily formed by the addition of dilithiomethylphenyl sulfone to γ -butyrolactone in tetrahydrofuran at -60° , and the equilibrium between the open-chain sulfonyl hydroxyketones and the lactols is shifted towards the former [10]. However, under identical reaction conditions the addition of dilithium methylphenyl sulfone to other sterically hindered five-membered lactones such as 2,3-*O*-isopropylidene-D-erythronolactone and 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone leads exclusively to lactols **2** and **3a** in good yields (92 and 75% respectively) after column chromatography and recrystallization from isopropyl alcohol. Two rationales may explain the observed results. First, the structural rigidity imparted by their bicyclic nature may prevent lactols **2** and **3a** from opening to the corresponding sulfonyl hydroxyketone derivatives. Second, the conformational bias of the lactone



rings in 2,3-*O*-isopropylidene-D-erythronolactone, and 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone seems to favor the preferential formation of the lactols with the hydroxyl group in the α -position. Structure assignments of the isolated compounds were based on infrared-, ^1H nmr, ^{13}C nmr, 2D ^1H - ^1H and ^{13}C - ^1H correlation, mass spectral and elemental analysis. In recent reports, the stereoselective addition of other organometallic compounds such as phenyllithium to both 2,3-*O*-isopropylidene-D-erythronolactone, and to 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone has been described for the preparation of 1-deoxy-1-phenyl- β -D-ribofuranose [11], and 1-deoxy-1-phenyl- β -D-glucopyranose [12].

In contrast to α' -benzenesulfonyl- γ -hydroxyketones which undergo facile thermal cyclization-dehydration in toluene at 130° , lactols **2** and **3a** are very stable. They fail to undergo thermal dehydration even after refluxing several hours in xylenes at 180° . Not surprisingly, mineral acid catalysis gave no reaction with exception of the recovery of partially unprotected starting material in the case of both lactols. For circumvention of this difficulty, dehydration reactions were carried out with boron trifluoride diethyl etherate in acetonitrile at -40° . Under these conditions, treatment of lactol **2** with 1 equivalent of the Lewis acid leads to a 1:2 mixture of the desired tetrahydrofuranilidene sulfones **5** and **6** in 75% overall yield. The *E*:*Z* mixture is easily separable by column chromatography on silica gel. Both separated stereoisomers equilibrated to a thermodynamic mixture by standing in chloroform solution for several hours. *Ab initio* Calculations (HF/6-31G**/HF/3-21G*) performed on both isomers showed **6** to be slightly more stable than **5** by 0.8 Kcal/mol [13].

The structural assignment of both stereoisomers is based on key spectral features of this compound class. The ^1H nmr spectrum of the parent *E*-tetrahydrofuranilidene sulfone **4a** shows a characteristic signal for the allylic oxolane proton H_2 at δ 3.12 ppm as a consequence of the deshielding effect of the anisotropic sulfonyl group. The strong enol ether absorption band at 1636 cm^{-1} in the infrared, and structural analysis by single-crystal X-ray diffraction provided further experimental evidence supporting this assignment [14]. In the ^1H nmr spectrum of the *E*-isomer **5** the allylic oxolane proton H_2 resonates at δ 5.94 and it shows coupling to H_3 ($J = 5.6\text{ Hz}$), and to the vinylic proton H_1 ($J = 1.0\text{ Hz}$), which appears at δ 5.86 ppm. On the other hand, the resonance of the allylic proton H_2 of the *Z*-isomer **6** appears as a clean doublet of doublets centered at δ 5.09 ppm ($J = 4.8\text{ Hz}$ and $J = 1.0\text{ Hz}$), as expected for resonances of protons attached to carbons bearing oxygen atoms. The observed difference of 0.85 ppm in the chemical shifts of the allylic oxolane protons H_2 of both stereoisomers **5** and **6** is attributed to the relative position of the deshielding vinylic sulfonyl group, and is in close agreement with previous assignments for *E*-tetrahydrofuranilidene sulfones [8]. Also, stereoisomers

5 and **6** show their distinctive strong and sharp enol ether infrared absorption bands at 1639 cm^{-1} and 1648 cm^{-1} , respectively. COSY and APT experiments were used to assign the ^{13}C nmr resonances at δ 113.4 (hemiacetal) and 104.2 ppm (vinylic C_1) in isomer **5**. For tetrahydrofuranilidene sulfone **6** the corresponding ^{13}C nmr signals appear at δ 114.2 and 102.6 ppm. In tetrahydrofuranilidene sulfone **5** the dihedral angles predicted by the *ab initio* molecular models for its equilibrium conformation ($\Phi = 24.7^\circ$ and 8.9°) would require larger values for the observed vicinal cis coupling constants of H_3 ($J_{3,4,\beta} = 4.5\text{ Hz}$, $J_{3,2} = 5.6\text{ Hz}$) at the first glance. However, smaller than expected coupling constants between protons on vicinal oxygenated carbon atoms in rigid systems are not unusual as described in previous reports for some marine natural products and other compounds [15]. Here, weakening of the coupling strength of vicinal protons was explained in terms of the electronegativity effects of vicinal oxygen atoms. Accordingly, the same trends in chemical shifts, dihedral angles and coupling constants are observed for isomer **6**. Since the dihedral angle between H_3 and H_4 are 100.8° (*E*-isomer) and 98.6° (*Z*-isomer), the resonances of protons $\text{H}_{4\alpha}$ in **5** and **6** appear as clean doublets (geminal coupling) at δ 4.42 ($J = 10.7\text{ Hz}$), and δ 4.55 ($J = 11.1\text{ Hz}$), respectively as expected for a five-membered ring. While the dehydration of lactol **2** with boron trifluoride diethyl etherate in acetonitrile at -40° gives the desired tetrahydrofuranilidene sulfones **5** and **6** in good yields, 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactol **3a** produces the 1',5'-anhydro compound **7** in 85% yield. Under the acidic reaction conditions used cleavage of the labile protecting *tert*-butyldimethylsilyl group and subsequent intramolecular substitution prevent dehydration of **3a** to occur, and only minor amounts of the corresponding tetrahydrofuranilidene sulfones can be observed in the infrared spectrum of the crude reaction product. The modification of reaction conditions and the use of other protecting devises that are more resistant to the acid conditions required are now in progress.

In conclusion, the phenylsulfonyl-methylenation of γ -lactones has been expanded to sterically hindered derivatives such as D-erythronolactone by the use of boron trifluoride diethyl etherate in acetonitrile as the dehydrating agent. In contrast to the regio- and stereoselective thermal dehydration of α' -benzenesulfonyl- γ -hydroxyketones the reaction with boron trifluoride diethyl etherate yields both easily separable stereoisomeric tetrahydrofuranilidene sulfones.

EXPERIMENTAL

General.

Melting points were determined on an Electrothermal apparatus and are uncorrected. Commercially available reagents and solvents were used without further purification. 2,3-*O*-Isopropylidene-D-ribofuranolactone and 2,3-*O*-isopropylidene-D-erythronolactone were purchased from Aldrich and tetrahydro-

furan was distilled from sodium metal in the presence of benzophenone under dry argon; Acetonitrile was refluxed over phosphorus pentoxide and distilled with a Vigreux column. *N,N*-Dimethylformamide was purified by fractional distillation *in vacuo*. Infrared spectra were determined on a Perkin-Elmer 1620 FT-IR spectrophotometer in carbon tetrachloride solutions. The ^1H and ^{13}C nmr spectra were recorded on either a Bruker DRX 500 or a Varian 200 MHz spectrometers at a nominal frequency of 500.13 and 199.97 MHz for hydrogen, and 50.28 for carbon, respectively. The 7.26 ppm resonance of residual chloroform and 77.0 ppm of deuteriochloroform were used as internal references. The exact coupling constants were determined *via* nmr simulations using the IvorySoft gnmr package (v. 3.6, Cherwell Scientific Publishing, Ltd., The Magdalen Centre, Oxford Science Park, Oxford OX4 4GA). Electron impact mass spectra were obtained on a VG Fisons Autospec spectrometer (70 eV) equipped with a direct insertion probe attachment. Combustion analysis were performed by Oneida Research Services, Whitesboro, NY 13492. Thin-layer chromatography and flash chromatography were carried out using Riedel-de-Haen silica gel 60 F 254 sheets and E. Merck silica gel grade 9385 (230-400 mesh), respectively.

E-2-(Benzenesulfonylmethylidene)-3,4-*O*-isopropylidene-tetrahydrofuran (**5**) and *Z*-2-(Benzenesulfonylmethylidene)-3,4-*O*-isopropylidene-tetrahydrofuran (**6**).

To a magnetically stirred solution of lactol **2** (2.0 g, 6.4 mmoles) in dry acetonitrile (80 ml) was added dropwise boron trifluoride diethyl etherate (0.84 ml, 6.6 mmoles) at -40° and under argon. After stirring at -40° for 1 hour, the solution was warmed to room temperature and quenched by the addition of saturated aqueous potassium carbonate (40 ml). The reaction mixture was extracted with diethyl ether (3 x 30 ml), dried with magnesium sulfate and concentrated under reduced pressure. Purification of the crude reaction product by flash column chromatography on silica gel (ethyl acetate/hexane 2:3) and recrystallization from isopropyl alcohol afforded **5** (494 mg, 26%) as colorless crystals, mp 113-116 $^\circ$; ir: 3068, 2992, 2955, 1639, 1447, 1374, 1328, 1263, 1213, 1184, 1157, 1143, 1085 cm^{-1} ; ^1H nmr: δ 8.02 (d, 2H, *J* = 7.6 Hz, ArH_o), 7.55 (t, 1H, *J* = 7.3 Hz, ArH_p), 7.48 (dd, 2H, *J* = 7.6 Hz, *J* = 7.3 Hz, ArH_m), 5.94 (dd, 1H, *J* = 5.6 Hz, *J* = 1.0 Hz, H_2), 5.86 (br s, 1H, H_1), 4.90 (dd, 1H, *J* = 5.6 Hz, *J* = 4.5 Hz, H_3), 4.42 (d, 1H, *J* = 10.7 Hz, $\text{H}_{4\alpha}$), 4.24 (dd, 1H, *J* = 10.7 Hz, *J* = 4.5 Hz, $\text{H}_{4\beta}$), 1.40 (s, 3H), 1.21 (s, 3H); ^{13}C nmr: δ 170.4 (C_1), 143.1 (ArCSO_2), 132.6 (ArC_p), 128.6 (ArC_m), 127.4 (ArC_o), 113.4 (O-C-O), 104.2 (C_1), 78.8 (C_2), 77.4 (C_3), 75.7 (C_4), 26.4 (CH_3), 25.7 (CH_3); ms: *m/z* (ion, relative intensity) 296.4 (M^+ , 9), 281.4 (100).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{S}$: C, 56.74; H, 5.44; S, 10.82. Found: C, 56.41; H, 5.41; S, 10.75

The slower eluting stereoisomeric tetrahydrofuranylidene **6** (931 mg, 49%) was obtained after recrystallization from isopropyl alcohol as colorless crystals, mp 126-127 $^\circ$; ir: 3068, 2993, 2960, 1648, 1446, 1384, 1325, 1286, 1225, 1152, 1107, 1086 cm^{-1} ; ^1H nmr: δ 7.95 (d, 2H, *J* = 7.7 Hz, ArH_o), 7.56 (t, 1H, *J* = 7.4 Hz, ArH_p), 7.47 (dd, 2H, *J* = 7.7 Hz, *J* = 7.4 Hz, ArH_m), 5.70 (d, 1H, *J* = 1.0 Hz, H_1), 5.09 (dd, 1H, *J* = 4.8 Hz, *J* = 1.0 Hz, H_2), 4.74 (dd, 1H, *J* = 4.8 Hz, *J* = 4.2 Hz, H_3), 4.55 (d, 1H, *J* = 11.1 Hz, $\text{H}_{4\alpha}$), 4.41 (dd, 1H, *J* = 11.1 Hz, *J* = 4.2 Hz, $\text{H}_{4\beta}$), 1.31 (s, 3H), 1.16 (s, 3H); ^{13}C nmr: δ 167.3 (C_1), 142.6 (ArCSO_2), 132.8 (ArC_p), 128.7 (ArC_m), 127.0 (ArC_o), 114.2 (O-C-O), 102.6 (C_1), 81.0 (C_2), 76.7 (C_3), 77.4 (C_4), 26.9 (CH_3),

26.1 (CH_3); ms: *m/z* (ion, relative intensity) 296.4 (M^+ , 12), 281.4 (100).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{S}$: C, 56.74; H, 5.44; S, 10.82. Found: C, 56.38; H, 5.40; S, 10.83.

1'-(Benzenesulfonylmethylene)-2',3'-*O*-isopropylidene- α -D-ribofuranose (**3b**).

2,3-*O*-Isopropylidene-D-ribofuranolactone (2.5 g, 13.3 mmoles), *tert*-butyldimethylsilyl chloride (2.4 g, 15.9 mmoles), and imidazole (2.26 g, 33.2 mmoles) were dissolved in dimethylformamide (5.0 ml) and stirred at 35° for 15 hours to afford 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone (3.8 g, 95%). To a magnetically stirred solution of methyl phenyl sulfone (1.81 g, 11.6 mmoles) in dry tetrahydrofuran (50 ml) was added *n*-butyllithium (9.2 ml of a 2.5 *M* solution in hexanes, 23.1 mmoles) at -60° , warmed up to 0° , stirred for 0.5 hour and cooled again to -60° . At this temperature a solution of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone (3.5 g, 11.6 mmoles) was added. Then, the solution was stirred three hours at -60° , and two additional hours at -35° . The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (20 ml). After extraction with ethyl acetate the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. Purification of the crude reaction mixture on silica gel (acetone/hexane 1:2) afforded **3a** (3.3 g, 62%) as colorless crystals, mp 40-42 $^\circ$; ir: 3464, 3070, 2955, 2930, 2858, 1471, 1448, 1383, 1374, 1255, 1212, 1141, 1081, 1022 cm^{-1} ; ^1H nmr: δ 7.95 (m, 2H, ArH), 7.49 (m, 3H, ArH), 5.31 (s, 1H, OH), 4.68 (d, 1H, *J* = 5.8 Hz, H_2), 4.46 (d, 1H, *J* = 5.8 Hz, H_3), 4.11 (t, 1H, *J* = 3.8 Hz, H_4), 3.67 (m, 4H, H_{5a} , H_{5b} , CH_{1a} , CH_{1b}), 1.38 (s, 3H), 1.25 (s, 3H), 0.95 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C nmr: δ 141.1 (ArCSO_2), 133.3 (ArC_p), 128.8 (ArC_o), 128.2 (ArC_m), 112.7 (C_1), 104.4 (OCO), 86.8 (C_2), 86.5 (C_5), 81.6 (C_3), 64.2 (C_4), 59.9 (C_1), 26.3 (CH_3), 25.6 (CMe_3), 24.9 (CH_3), 18.0 (CH_3), -5.7 (CSi). Subsequent heating in isopropyl alcohol and recrystallization from the same solvent yielded **3b** as colorless crystals, mp 121-122 $^\circ$; ir: 3411, 2995, 2949, 1448, 1381, 1320, 1260, 1211, 1167, 1135, 1080, 1011 cm^{-1} ; ^1H nmr: δ 7.96 (d, 2H, *J* = 7.8 Hz, ArH_o), 7.66 (t, 1H, *J* = 7.4 Hz, ArH_p), 7.56 (dd, 2H, *J* = 7.7 Hz, *J* = 7.6 Hz, ArH_m), 5.90 (br s, 1H, OH), 4.87 (d, 1H, *J* = 5.7 Hz, H_2), 4.49 (d, 1H, *J* = 5.7 Hz, H_3), 4.23 (m, 1H, H_4), 3.69 (m, 4H, H_{1a} , H_{1b} , H_{5a} , H_{5b}), 2.22 (br s, 1H, OH), 1.37 (s, 3H), 1.25 (s, 3H); ^{13}C nmr: δ 140.3 (ArCSO_2), 133.9 (ArC_p), 128.2 (ArC_m), 129.0 (ArC_o), 112.8 (O-C-O), 104.5 (C_1), 59.6 (C_1), 87.6 (C_2), 87.2 (C_4), 81.4 (C_3), 63.7 (C_5), 26.2 (CH_3), 24.6 (CH_3); ms: *m/z* (ion, relative intensity) 343.7 (M^+ , 2), 77.2 (100).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_7\text{S}$: C 52.31; H 5.85; S 9.31. Found: C, 52.08; H, 5.74; S, 9.01.

1',5'-Anhydro-1'-(benzenesulfonylmethylene)-2',3'-*O*-isopropylidene- β -D-ribofuranose (**7**).

Under the same reaction conditions used for the conversion of lactol **2** into *E*-2-(benzenesulfonylmethylidene)-3,4-*O*-isopropylidene-tetrahydrofuran (**5**) and *Z*-2-(Benzenesulfonylmethylidene)-3,4-*O*-isopropylidene-tetrahydrofuran (**6**), lactol **3a** afforded after silica gel flash chromatography on silica gel (acetone/hexane 1:3) and recrystallization from isopropyl alcohol 1',5'-anhydro compound **7** (270 mg, 67%) as a colorless solid, mp 143-144 $^\circ$; ir: 3069, 2980, 2938, 2899, 1448, 1382, 1373, 1340, 1267, 1210, 1150, 1087, 1050 cm^{-1} ; ^1H nmr: δ 7.94 (d, 2H, *J* = 7.0 Hz, ArH_o), 7.61 (t, 1H, *J* = 7.2 Hz, ArH_p), 7.54 (dd, 2H, *J* = 7.2 Hz, *J* = 7.0 Hz, ArH_m), 4.58 (d, 1H, *J* = 3.2 Hz, H_4), 4.32 (m, 2H, H_{5a} , H_{5b}), 3.88

(d, 1H, J = 14.7 Hz, CH_{1a}), 3.74 (d, 1H, J = 14.7 Hz, CH_{1b}), 3.35 (m, 2H, H₂, H₃), 1.35 (s, 3H), 1.23 (s, 3H); ¹³C nmr: δ 140.5 (ArCSO₂), 133.7 (ArC_p), 128.8 (ArC_m), 128.4 (ArC_o), 112.6 (C_{1'}), 104.2 (OCO), 81.7 (C_{2'}), 79.8 (C_{4'}), 77.8 (C_{3'}), 64.7 (C_{5'}), 54.2 (C₁), 25.8 (CH₃), 25.3 (CH₃); ms: m/z (ion, relative intensity) 326.4 (M⁺, 1.0), 68.2 (100).

Anal. Calcd. for C₁₅H₁₈O₆S: C, 55.20; H, 5.56; S, 9.83 (Calcd.). Found: C 55.05; H 5.49; S, 9.70.

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