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TETRAHEDRON

New Approach to the Stereoselective Synthesis of the [4.5] Spiroketal Moiety of Papulacandins

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Abstract: An efficient approach for the stereoselective construction of the spiroketal moiety of papulacandins, based on the condensation of the protected derivative of D-arabino-1,4-lactone **2** with the α-lithiated carbanion of β-phenylsulfonyl dihydrofuran **1**, is described.
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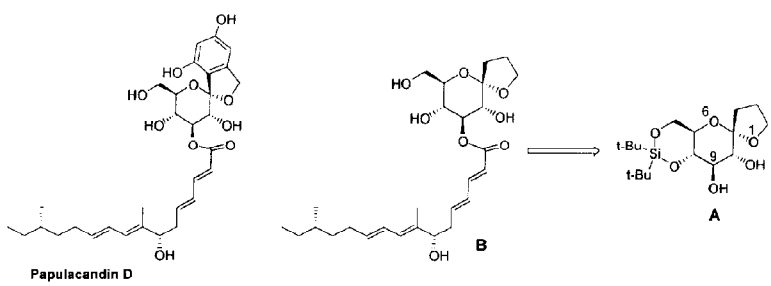
Keywords: papulacandin; spiroketal; D-arabino-1,4-lactone; α,β–unsaturated sulfones.

Papulacandins A, B, C and D, isolated from *Papularia sphaerosperma*,[1] with strong *in vitro* activity against *Candida Albicans* and various other yeasts[2] are recognized as attractive targets in the search for antifungal agents. Most of these compounds have shown acceptable inhibition of β-1,3-glucan synthase[3] and whole cell activity, though little or no efficacy in animal models was found. All the papulacandins contain both a β-*C*-glucoside and an α-*O*-glucoside as key components in their structures. The synthetically challenging features of the spiroketal nucleus coupled with the aim to improve the *in vivo* activity, make these compounds interesting synthetic targets.



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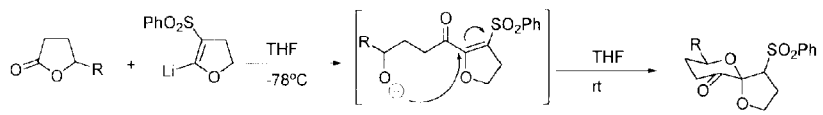
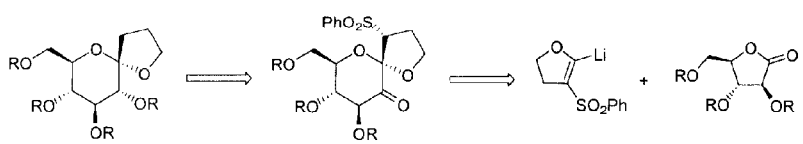
Efforts to extend the structure activity relationship studies and understand the role of the aromatic moiety[4] suggested the synthesis of compound **A**. Compound **A** should be a suitable precursor for esterification at the C-9 position and conversion to the direct analog of papulacandin D devoid of an aromatic ring (**B**). The previous approaches for the construction of the spiroketal nucleus present in natural papulacandins can be summarised as the following: a) hetero-Diels-Alder[5] reaction, b) palladium-catalyzed coupling of a stannyl glucal with an aryl halide[6], and c) condensation of an aryl lithium with protected gluconolactone[7]. A few years ago we reported a convergent and stereoselective one-step procedure for the synthesis of functionalized 1,6-dioxaspiro[4.5]decanes based on the condensation of γ-lactones with the α-lithiated carbanion of β-phenylsulfonyl dihydrofurans[8] (Scheme 1). The process takes place by initial α-acylation at -78°C to give the alkoxy intermediate, which evolves slowly at rt by intramolecular conjugate addition to the α,β-unsaturated sulfone moiety to provide stereoselectively 1,6-dioxaspiro[4.5]decanes in good yields (50-74%).



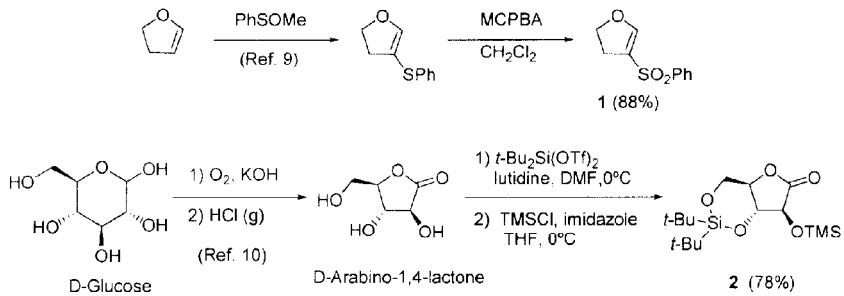
Scheme 1

We wish to report herein that this method can be efficiently applied to the synthesis of the polyhydroxylated spiroketal moiety present in papulacandins using protected D-arabino-1,4-lactones as electrophiles (Scheme 2). Two important features distinguish this approach from the previously reported. First, the spiroketalization takes place under basic conditions (instead of acid conditions), which could be an advantage for the selection of the hydroxyl protecting groups. Second, the starting sugar would be a γ-lactone derived from D-arabinose instead of a δ-lactone derived from D-glucose.



Scheme 2

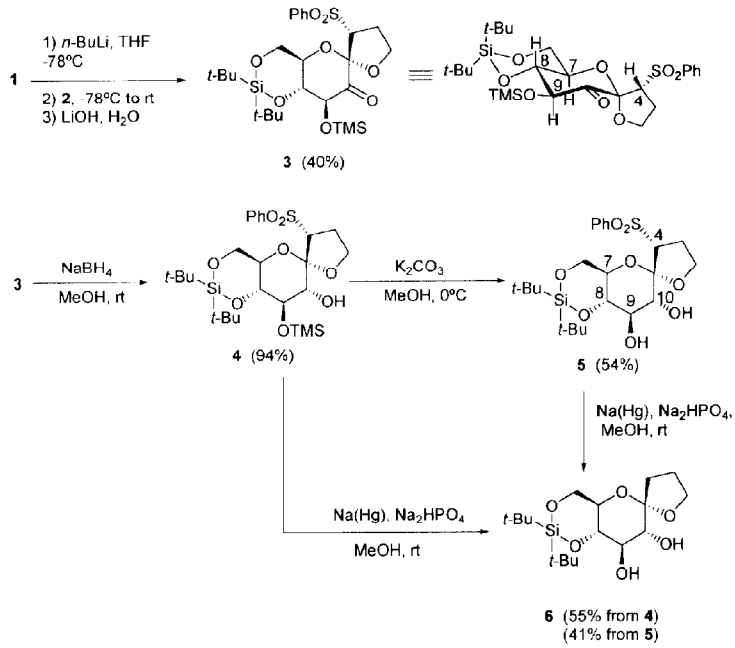
The required β-phenylsulfonyl dihydrofuran **1**[8] was readily prepared from dihydrofuran by sulfenylation at the β-position with phenyl methyl sulfoxide in the presence of trifluoracetic anhydride[9] and subsequent MCPBA oxidation (88% overall yield). Meanwhile, after several attempts we found that the protected D-arabino-1,4-lactone **2**, bearing the 3,5-diol protected as a cyclic di-*tert*-butylsilylether and the hydroxyl group at C-2 protected as TMS derivative, was a suitable substrate for the condensation reaction. γ-Lactone **2** was prepared in gram quantities in two steps from D-arabino-1,4-lactone[10] by reaction with di-*tert*-butylsilyl *bis*(trifluoromethanesulfonate) and 2,6-lutidine (CH_2Cl_2, 0°C, 85% yield)[11] and further quantitative silylation with trimethylsilyl chloride and imidazole of the remaining hydroxyl group[12] (Scheme 3).



Scheme 3

α-Deprotonation of the β-phenylsulfonyl dihydrofuran **1** with *n*-BuLi (THF, -78°C), followed by reaction with **2** (THF, rt) and quenching of the reaction by addition of aqueous LiOH afforded spiroketal **3** as a single isomer in 40% yield after flash chromatography[13] (Scheme 4). The stereochemical assignment of **3** was unequivocally established from its ^{1}H-NMR data (table 1), especially from the typically *anti* values for the coupling constants $J_{7,8}$ and $J_{8,9}$ (9.7 Hz both) and the high chemical shift of H_4 (δ_4= 4.58 ppm) characteristic of its location in 1,3-*syn*-parallel arrangement with respect to the carbonyl group[14].

Interestingly, reduction of **3** with $NaBH_4$ in MeOH was fully stereoselective leading to the desired equatorial alcohol **4** ($J_{9,10}$= 9.0 Hz) in 94% yield. Selective deprotection of the silyl ether at C-9 was achieved by reaction of **4** with K_2CO_3 in MeOH at 0°C, to afford diol **5** (54%)[15]. Finally, reductive elimination of the sulfonyl group by treatment of **5** with Na(Hg) in MeOH afforded the dihydroxy spiroketal **6** in 41% yield. We found that the conversion of compound **4** into the desired target **6** could be performed more efficiently in one step by directly subjecting **4** to the conditions of the reductive elimination with Na(Hg) (55% yield).



Scheme 4

Table 1: Significant δ (in ppm) and J (in Hz) of the ^{1}H-NMR spectra of spiroketals **3-6** (in $CDCl_3$).

Spiroketal	δ_4	δ_7	δ_8	δ_9	δ_{10}	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$
3	4.58	3.90	3.48	4.45	-	9.7	9.7	-
4	4.12	3.60	3.61	3.95	3.31	9.6	10.1	9.0
5	4.04	3.62	3.61	3.95	3.52	9.6	9.6	8.8
6	2.20, 1.85	3.75	3.75	4.04	3.46	*	9.2	8.5

* Not evaluated due to the coincidence of chemical shifts of H-7 and H-8.

In summary, the spiroketal moiety of papulacandins has been readily prepared in three steps from β-phenylsulfonyl dihydrofuran **1** and D-arabino-1,4-lactone **2** in a completely stereoselective manner. Esterification at C-9 and conversion into direct analogues of papulacandin D is underway and will be reported along with the biological data in due course.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were adquired at 200 or 300 MHz and 50 or 75 MHz respectively. Chemical shifts are reported in ppm, relative to the solvent used: $CDCl_3$ (7.26 ppm and 77 ppm), CD_3OD (3.40 ppm and 49.9 ppm), D_2O (4.6 ppm). Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded with electron impact (EI, 70 eV) or FAB. Mass data are reported in mass units (m/z), and the values in brackets report the relative intensity from the base peak (as 100%). Reaction were usually carried out under argon atmosphere in anhydrous solvents. The following reaction solvents were dried before use: THF from sodium-benzophenone, CH_2Cl_2 from P_2O_5, and DMF from molecular sieve 4Å. Analytical thin-layer chromatography (TLC) was performed Merck silica gel 60-F_{254} plates. Flash column chromatography was performed using silica gel Merck-60 (230-400 mesh). 3-(Phenylthio)-4,5-dihydrofuran and D-arabino-1,4-lactone were prepared according to the procedures described in references 9 and 10 respectively.

3-(Phenylsulfonyl)-4,5-dihydrofuran (**1**). To a cooled solution of 3-(phenylthio)-4,5-dihydrofuran (2.65 g, 14.9 mmol) in CH_2Cl_2 (20 mL) at 0°C was slowly added a solution of MCPBA (22.4 g, 29.8 mmol) in CH_2Cl_2 (44 mL). After stirring for 30 min at 0°C, saturated aqueous solutions of Na_2SO_3 (50 mL) and $NaHCO_3$ (50 mL) were added and stirring was continued for 15 min. The mixture was extracted with CH_2Cl_2 (3 x 75 mL) and the organic layer was dried (Na_2SO_4) and concentrated. The residual yellow oil was purified by flash chromatography (eluent: ethyl acetate-hexane 1:4) to give dihydrofuran **1**[8] (3.10 g, 99%) as a colourless liquid. IR ($CHCl_3$): 1600, 1300, 1165, 1155, 970. ^{1}H-NMR ($CDCl_3$) δ: 7.98-7.86 (m, 2H), 7.72-7.52 (m, 3H), 7.25 (t, 1H, J=1.8 Hz), 4.62 (t, 2H, J=9.7Hz), 2.80 (dt, 2H, J=9.7, 1.8Hz).

*(2S, 3R, 4R)-3,5-O-(di-*tert*-butylsilylene)-D-arabino-1,4-lactone*. To a cooled solution of D-arabino-1,4-lactone[10] (100 mg, 0.67 mmol) in a mixture of dry CH_2Cl_2 (10 mL) and dry DMF (2 mL) at 0°C under argon were added 2,6-lutidine (299 μL, 2.57 mmol, 3.8 equiv) and di-*tert*-butylsilyl *bis*(trifluoromethanesulfonate) (516 μL, 1.41 mmol, 2.1 equiv). The solution was stirred at 0°C for 30 min and warmed to rt for 1h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (eluent: ethyl acetate-hexane 1:8) to give the title lactone (164 mg, 85%) as a yellow oil. $[\alpha]_D^{20}$ −7.4 (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) υ_{max}: 3660, 3500, 1800, 1480, 1225, 1100, 840. ^{1}H-NMR ($CDCl_3$) δ: 4.74 (d, 1H, J=9.7Hz), 4.45 (ddd, 1H, J=8.6, 4.3, 1.6Hz), 4.28 (dd, 1H, J=9.7, 8.6Hz), 4.15-3.92 (m, 2H), 1.06, 1.05, 1.00 (s, 18H). ^{13}C-NMR ($CDCl_3$) δ: 171.9, 79.8, 74.9, 72.2, 66.2, 27.2, 27.1, 27.0, 22.6, 20.5, 20.4.

*(2S, 3R, 4R)-3,5-O-(di-*tert*-butylsilylene)-2-O-(trimethylsilyl)-D-arabino-1,4-lactone* **(2)**. To a cooled solution of *(2S, 3R, 4R)*-3,5-*O*-(di-*tert*-butylsilylene)-D-arabino-1,4-lactone (290 mg, 1mmol) in dry THF (6 mL) at 0°C under argon was added imidazole (274 mg, 4.02 mmol, 4.0 equiv) and the mixture was stirred at 0°C for 30 min. Then, trimethylsilyl chloride (255 μL, 2.01 mmol, 2 equiv) was added and the reaction mixture was warmed to rt for 3 h. Saturated NH_4Cl aqueous solution (3 mL) was added and the mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (2 x 50 mL), dried ($MgSO_4$) and concentrated to give lactone **2** (359 mg, 99%) as a yellow oil. $[\alpha]_D^{20}$ –5.7 (*c* 5.42, $CHCl_3$); IR (neat) υ_{max}: 1810, 1465, 1250, 1090, 820. ^{1}H-NMR ($CDCl_3$) δ: 4.60 (d, 1H, J=9.6Hz), 4.45 (ddd, 1H, J=8.1, 4.2, 1.6Hz), 4.33 (dd, 1H, J=9.6, 8.8Hz), 4.13-3.93 (m, 2H), 1.06, 1.05, 1.00 (s, 18H), 0.29 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ: 171.8, 80.1, 74.4, 72.0, 66.4, 27.7, 27.5, 27.3, 27.1, 22.6, 20.6, 20.3, 20.1, 2.2, 2.1.

*(4R, 5R, 7R, 8R, 9S)-7,8-*O*-(di-*tert*-butylsilylene)-8,9-dihydroxy-7-hydroxymethyl-4-phenylsulfonyl-9-O-(trimethylsilyl)-1,6-dioxaspiro[4.5]decan-10-one* **(3)**. To a solution of 3-(phenylsulfonyl)-4,5-dihydrofuran **1** (1.18 g, 5.6 mmol) in dry THF (25 mL) at -78°C under argon was added a solution of *n*-BuLi (2.5 M in hexane, 2.5 mL, 6.2 mmol, 1.1 equiv) and the mixture was stirred at -78°C for 15 min. Then, γ-lactone **2** (3.03 g, 8.5 mmol, 1.5 equiv) was added and the reaction mixture was slowly warmed to rt and stirring was continued for 16h. A 1M aqueous solution of LiOH (6 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (eluent: ethyl acetate-hexane 1:4) to give the spiroketal **3** (1.28 g, 40%) as a white solid. Mp: 41-42°C. $[\alpha]_D^{20}$ +20.8 (*c* 7.4, $CHCl_3$); IR (neat) υ_{max}: 1750, 1470, 1250, 1090, 690, 640. ^{1}H-NMR ($CDCl_3$) δ: 7.85 (m, 2H), 7.62-7.40 (m, 3H), 4.58 (t, 1H, J=9.3Hz), 4.45 (d, 1H, J=9.7Hz), 4.25 (m, 2H), 4.08-3.83 (m, 2H), 3.88 (t, 1H, J=10.1Hz), 3.48 (t, 1H, J=9.7Hz), 2.85-2.70 (m, 1H), 2.55-2.40 (m, 1H), 1.06, 1.05, 1.00 (s, 18H), 0.29 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ: 194.1, 138.8, 133.7, 129.5, 128.5, 105.1, 79.1, 78.2, 68.3, 68.2, 66.2, 64.9, 27.7, 27.6, 27.5, 24.9, 22.7, 21.7, 20.4, 19.8, 1.84, 1.00. MS (FAB): 571 (M^+ + 1, 1), 529 (7), 473 (7), 413 (7), 300 (12).

*(4R, 5R, 7R, 8R, 9R, 10R)-7,8-*O*-(di-*tert*-butylsilylene)-8,9,10-trihydroxy-7-hydroxymethyl-4-phenylsulfonyl-9-O-(trimethylsilyl)-1,6-dioxaspiro[4.5]decane* **(4)**. To a suspension of $NaBH_4$ (14 mg, 0.35 mmol, 2.0 equiv) in methanol (1 mL) at 0°C under argon was added spiroketal **3** (101 mg, 0.18 mmol) and the mixture was warmed to rt for 3 h. Then, CH_2Cl_2 (3 mL) and water (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (eluent: ethyl acetate-hexane 1:4) to give the spiroketal **4** (95 mg, 94%) as a white solid. Mp: 52-53°C. $[\alpha]_D^{20}$ +15.4 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) υ_{max}: 3660, 3500, 1470, 1250, 1090, 750, 650. ^{1}H-NMR ($CDCl_3$) δ: 7.90 (m, 2H), 7.63 (t, 1H, J=7.4Hz), 7.52 (t, 2H, J=7.9Hz), 4.12 (dd, 1H, J=10.1, 9.3Hz), 4.05-3.90

(m, 3H), 3.95 (dd, 1H, J=10.1, 9.0Hz), 3.84 (dd, 1H, J=10.1, 9.9Hz), 3.74-3.56 (m, 1H), 3.61 (t, 1H, J=9.6Hz), 3.31 (dd, 1H, J=9.0, 4.7Hz), 2.55-2.41 (m, 1H), 2.39-2.25 (m, 1H), 2.43 (d, 1H, J=4.7Hz), 1.06, 1.05, 1.00 (s, 18H), 0.29 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ: 139.0, 133.7, 129.5, 128.6, 105.4, 77.4, 76.5, 72.3, 67.8, 66.6, 66.2, 65.4, 27.7, 27.6, 27.5, 25.5, 22.7, 21.1, 20.4, 19.8, 2.2. MS (FAB): 573 (M^+ + 1, 2), 531 (30), 529 (4), 513 (3), 483 (5), 445 (4).

*(4R, 5R, 7R, 8R, 9R, 10R)-7,8-O-(di-*tert*-butylsilylene)-8,9,10-trihydroxy-7-hydroxymethyl-4-phenylsulfonyl-1,6-dioxaspiro[4.5]decane* (**5**). To a solution of spiroketal **4** (550 mg, 0.96 mmol) in methanol (15 mL) at 0°C under argon was added K_2CO_3 (498 mg, 2.9 mmol, 3.0 equiv) and the suspension was stirred at 0°C for 4 h. Then, CH_2Cl_2 (10 mL) and saturated NH_4Cl aqueous solution (10 mL) were added and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (eluent: ethyl acetate-hexane 1:4) to give spiroketal **5** (259 mg, 54%) as a white solid. Mp: 92-93°C. $[\alpha]_D^{20}$ +19.6 (*c* 3.65, $CHCl_3$); IR ($CHCl_3$) υ_{max}: 3420, 1470, 1305, 1150, 1080, 830, 650. ^{1}H-NMR ($CDCl_3$) δ: 7.89 (m, 2H), 7.65 (t, 1H, J=7.4Hz), 7.53 (t, 2H, J=7.9Hz), 4.07-3.93 (m, 4H), 4.04 (dd, 1H, J=10.0, 9.6Hz), 3.85 (dd, 1H, J=9.9, 9.8Hz), 3.74-3.57 (m, 1H), 3.61 (t, 1H, J=9.6Hz), 3.52 (dd, 1H, J=8.8, 6.5Hz), 3.46 (s, 1H), 2.90 (d, 1H, J=6.7Hz), 2.57-2.43 (m, 1H), 2.37-2.25 (m, 1H), 1.06, 1.05, 1.00, 0.99 (s, 18H). ^{13}C-NMR ($CDCl_3$) δ: 138.9, 133.9, 129.4, 128.7, 105.4, 77.4, 76.7, 72.2, 67.4, 66.3, 66.2, 65.3, 27.5, 27.4, 25.3, 22.7, 20.7, 20.6, 19.9. MS (FAB): 483 (M^+ - OH, 10), 465 (12), 441 (12), 361 (15). HRMS (FAB) calc for $C_{23}H_{35}O_7SSi$ (M^+ - OH): 483.1873, found (M^+ - OH): 483.1863.

*(5S, 7R, 8R, 9R, 10R)-7,8-O-(di-*tert*-butylsilylene)-8,9,10-trihydroxy-7-hydroxymethyl-1,6-dioxaspiro[4.5] decane* (**6**). To a solution of spiroketal **4** or **5** (0.09 mmol) in methanol (1 mL) at rt was added Na_2HPO_4 (53 mg, 0.37 mmol, 4.1 equiv) and 2 g of powdered Na(Hg) (6%) and the mixture was stirred at rt for 2 h. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (eluent: ethyl acetate-hexane 1:4) to give the desulfonylated spiroketal **6** (18 mg, 55% from spiroketal **4** and 14mg, 41% from spiroketal **5**) as a white solid. Mp: 56-57°C. $[\alpha]_D^{20}$ +18.1 (*c* 3.6, $CHCl_3$); IR ($CHCl_3$) υ_{max}: 3410, 1460, 1390,1160, 1080. ^{1}H-NMR ($CDCl_3$) δ: 4.10-3.90 (m, 4H), 4.04 (dd, J=9.2, 8.5Hz), 3.84-3.68 (m, 3H,), 3.78 (s, 1H), 3.46 (dd, 1H, J=8.5, 8.4Hz), 2.63 (d, 1H, J=8.2Hz), 2.25-2.13 (m, 1H), 2.10-1.92 (m, 1H), 1.92-1.78 (m, 2H), 1.06, 1.05, 1.00, 0.99 (s, 18H,). ^{13}C-NMR ($CDCl_3$) δ: 107.5, 78.0, 77.7, 74.2, 69.0, 66.9, 33.9, 27.5, 27.4, 27.0, 23.6, 22.7, 20.6, 19.9. MS (FAB): 343 (M^+ - OH, 10), 325 (23), 285 (7), 231 (15). HRMS (FAB) calc for $C_{17}H_{31}O_5Si$ (M^+ - OH): 343.1941, found (M^+ - OH): 343.1943.

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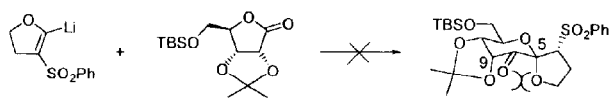
11 Unexpectedly our attempts to prepare the benzylidene acetal of the 3,5-diol of D-arabino-1,4-lactone were unsuccessful under all conditions tried (benzaldehyde/HCl, benzaldehyde/$ZnCl_2$, benzaldehyde/camforsulfonic, and benzaldehyde dimethyl acetal/*p*-toluenesulfonic acid).

12 Probably due to the deactivation induced by the contiguous carbonyl group, the reactivity of the hydroxyl group at C-3 proved to be rather low. We recovered the starting material in the attempts to prepare the TBDMS (TBDMSCl/imidazole/DMAP or TBDMSOTf/2,6-lutidine), TES (TESCl/imidazole/DMPA) or MOM derivatives (MOMCl/di-*iso*-propyl ethyl amine).

13 In contrast the reaction of **1** with protected D-ribono-1,4-lactones gave a complex mixture of products, in which the corresponding spiroketals were not detected (see scheme below). Taking into account that the spiroketal formation by intramolecular addition of the alkoxide to the vinylsulfone moiety is a thermodynamically controlled process (ref. 8), the absence of the spiroketals from D-ribose derivatives could be explained by the presence of a strong 1,3-diaxial interaction between the oxygenated substituents at C-5/C-9 (see scheme below).



14 δ_4 is much lower (about 0.9 ppm less) in related spiroketals of opposite configuration at C-4 (ref. 8).

15 Unexpectedly, all the attempts to perform the desilylation at C-9 from ketone **3** were unsuccessful, recovering the starting material (aqueous HCl at rt, AcOH/THF/H_2O 8:8:1 at reflux, or citric acid/MeOH at rt) or giving complex mixtures of products (TBAF in THF at rt, 20% HF in acetonitrile at rt, or K_2CO_3 in methanol at rt).