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A Novel Route to Monoanomeric Spiroketals

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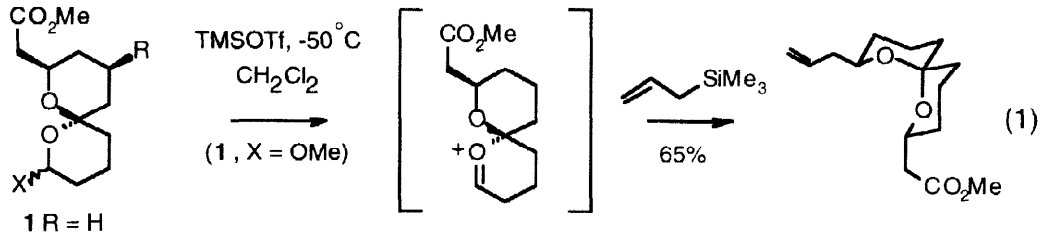
Abstract: A series of spiroketal C2-acetals was treated with an alkylsilane reagent in the presence of either TMSOTf or $BF_3.OEt_2$ to effect C2-substitution. Regioselective alkylation was successful, but in each case a monoanomeric spiroketal was the unexpected major product. The sequence provides a model for the synthesis of the CD subunit of altohyrtin A. © 1998 Elsevier Science Ltd. All rights reserved.

Following the independent isolations of the altohyrtin,[1] spongistatin,[2] and cinachyrolide[3] cytotoxic macrolides, a number of groups have focused their attention on the synthesis of monoanomeric spiroketals.[4] Although rare in nature, and less thermodynamically stable than bis-anomeric spiroketals, these structures are prominent features of the aforementioned natural products. In connection with our own efforts in this area, we have been investigating C2-substitutions on the 1,7-dioxaspiro[5.5]undecane ring system using C2-acetal and hemiacetal substrates. Recently,[5] we demonstrated that compound **1** (X=OMe) can be alkylated under Lewis acid conditions with complete stereoselectivity to give a diequatorial, bis-anomeric product (eq.1). These findings are consistent with a mechanism involving net equatorial nucleophilic addition to a dioxaoxonium ion intermediate. We now report that these results are not general, and that the stereochemistry of these alkylations can be substantially influenced by ring substituents. This observation was made during alkylation studies on the spiroketal derivatives **2** (X=OH, OPNB, OMe), which led to a novel synthesis of monoanomeric spiroketals, and has provided a model for the synthesis of the CD subunit of altohyrtin A.



1 R = H
2 R = OBn

The racemic synthesis of compounds **2** from epoxide **3** is outlined in Scheme 1. A key step in this sequence was a chelation-controlled [2+2] cycloaddition[6] of TMS-ketene to aldehyde **6**, which gave the β-lactone derivative **7** stereoselectively (99% ds at -60°C).[7] Low temperature ozonolysis of compound **7** provided ketoaldehyde **8**, which spontaneously cyclized to a mixture of spirolactols **2a** (3:1 α:β) upon treatment with K_2CO_3 in MeOH, presumably *via* the hydroxy ester **9**.[8] From spirolactol **2a**, standard conditions gave the p-nitrobenzoate **2b** (p-$NO_2C_6H_4COCl$, Et_3N, Et_2O, 87%) which could be converted to the diastereomerically pure methyl acetal **2c** (MeOH, CH_3CN, TMSOTf, -37°C, 88%).[9]

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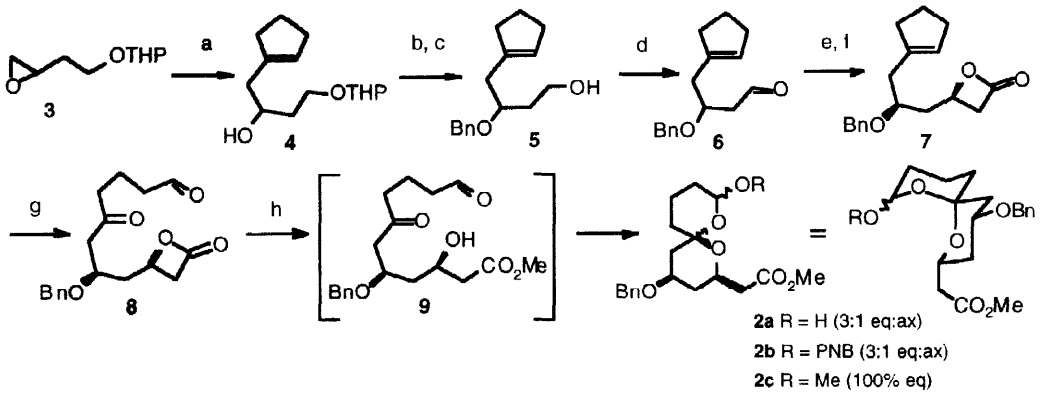
Scheme 1



Reagents: (a) Cyclopentenylmagnesium bromide, THF, CuI, -40°C → -20°C (75%); (b) NaH, BnBr, THF-DMF (84%); (c) p-TsOH, MeOH (93%); (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then Et_3N; (e) TMS-ketene, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, -60°C; (f) $KF \cdot 2H_2O$, CH_3CN, r.t. (94% from **5**); (g) O_3, -78°C, 3:1 MeOH-CH_2Cl_2, then Me_2S, 12h (91%); (h) K_2CO_3, MeOH, r.t., 2 min (93%).

Derivatives **2a-2c** were each treated with allyltrimethylsilane in the presence of either $BF_3 \cdot OEt_2$ or TMSOTf (see Table 1). The instability of both anomers of **2b** to silica gel prevented their separation by column chromatography. For this reason, both Spirolactols **2a** and their p-nitrobenzoates **2b** were reacted as their C2-anomeric mixtures (see entries 1-4). Most surprisingly, the major product in each reaction was not compound **12**, expected from our earlier work (see eq.1), but a 5:1 mixture of spiroketals **11** and **10**.[10] Methyl acetal **2c** (entry 5), formed as a single C2-α-diastereomer, also gave a 5:1 mixture of spiroketals **11** and **10**, along with a minor amount (17%) of the substituted tetrahydropyran derivative **13**.[11] Spiroketal **12** was not detected in this product mixture.

Because spiroketals **10** and **11** were inseparable by column chromatography, structure proof required minor synthetic manipulation. Thus, hydride reduction of the mixture of **10** and **11** gave the corresponding diastereomeric alcohols, from which the major component, compound **14**, could be isolated by column chromatography. Conversion of compound **14** to the saturated diol **15**[12] then allowed stereochemical confirmation by NOE difference experiments. Irradiation of the axial C3-proton at 4.29 ppm resulted in an enhancement of both axial proton signals at C5 (3.95 ppm) and C9 (2.63 ppm), while irradiation of the axial C11 proton at 3.49 ppm gave an enhancement of the axial C9 signal only.

Although an S_N2 mechanism has been considered to explain these results, evidence strongly suggests an S_N1 path, with a C2-oxonium ion as the intermediate. In the course of our recent work on the synthesis of the CD spiroketal subunit of altohyrtin A,[13] we have found that in cases where the C2-p-nitrobenzoate anomers can be separated by column chromatography, both α and β diastereomers gave an identical product mixture. This, then, raises the question as to which oxonium ion is the reactive intermediate in the reactions of compounds **2**. Half-chairs **A** and **B** (Scheme 2) represent two possibilities. Axial nucleophilic addition to oxonium ion **A** would give spiroketal **10**, which could isomerize to **11** by a Lewis acid-catalyzed inversion of the spiroketal carbon. However, this contradicts our earlier findings[5] which indicate a preference for net equatorial addition to these ions (see eq.1). Oxonium ion **B** presumably exists in equilibrium with **A**. Net

equatorial addition to this ion, from the less-hindered face, would give spiroketal **11** directly. Future work in this area will hopefully provide mechanistic clarification.

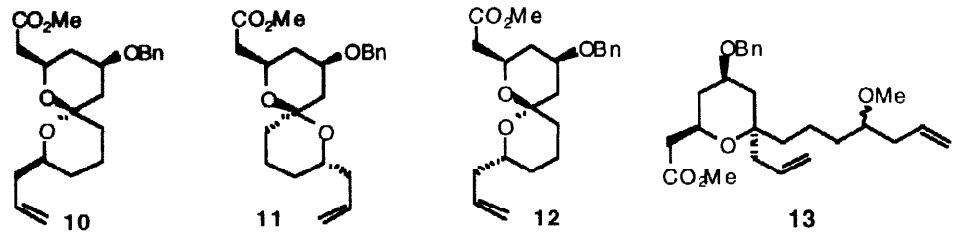
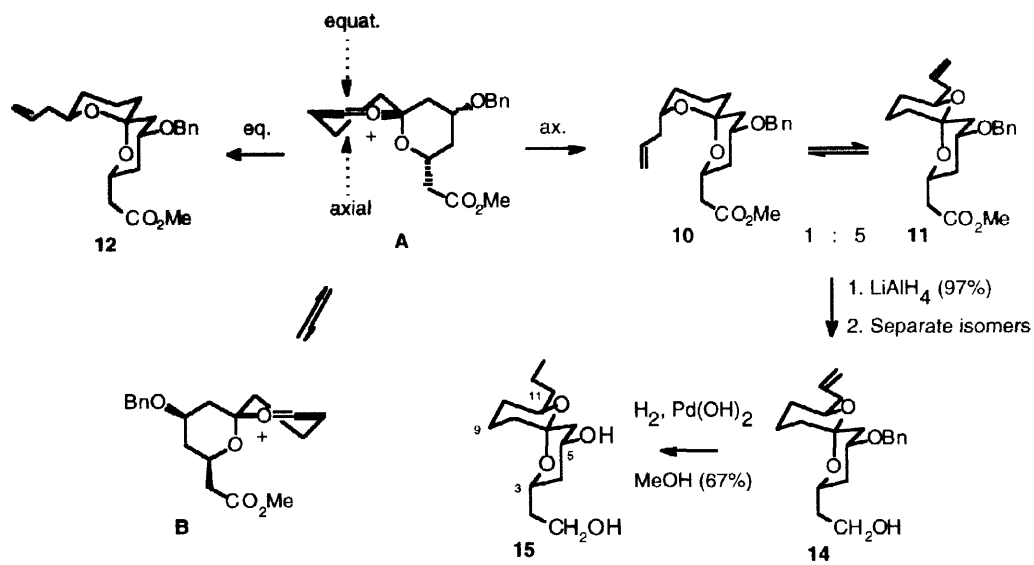


Table 1.[a] Substitution Reactions of Compounds **2a-2c**

Entry	S. M.	L.A.(eq)	Silane eq.	t (°C)	t (h)	yield[b]	**10:11:12**
1	**2a**	BF_3•OEt_2 (2)	2.0	-42	2.0	75%	1 : 5 : 1
2	**2a**	BF_3•OEt_2 (1.2)	1.2	-42→ -20	2.5	71%	1 : 5 : 1
3	**2b**	BF_3•OEt_2 (2)	2.0	-78	0.5	77%	1 : 5 : 1
4[c]	**2b**	TMSOTf (1.2)	1.2	-38	0.5	86%	1 : 5 : 1
5	**2c**	TMSOTf (3)	2.5	-42→ -20	3.0	51%	1 : 5 : -

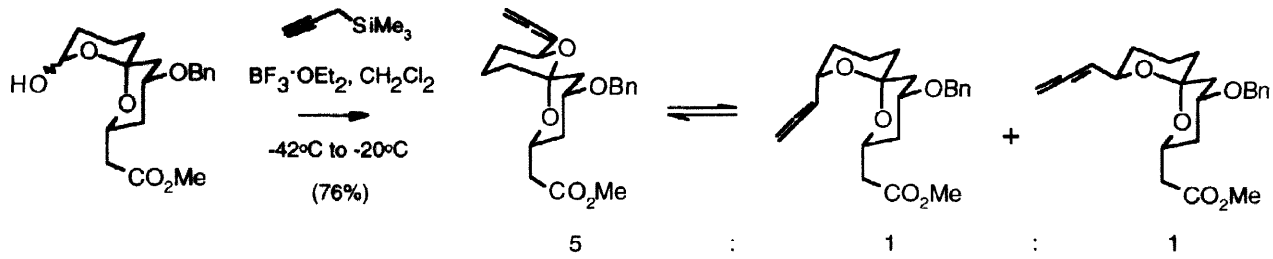
[a]All reactions were conducted at a concentration of 0.05 M in CH_2Cl_2, unless otherwise stated; [b]All yields refer to isolated yields of spiroketal products only; [c]Reaction was conducted in CH_3CN.

Scheme 2



To see if the reaction is general for other nucleophiles, the mixture of spirolactols **2a** was treated with propargyltrimethyl silane in the presence of BF_3•OEt_2 (Scheme 3). Three C2-allenyl substituted spiroketals were formed in a ratio identical to their allyl relatives, with the monoanomeric spiroketal once again being the major product. Evidently, an sp^2 hybridized substituent at C2, instead of sp^3, does not alter the 5:1 preference for the monoanomeric form in these structures. This particular observation formed the basis of our approach to the CD subunit of altohrtin A.[13]

Scheme 3



In summary, the stereoselectivity of C2-substitutions on the 6,6-spiroketal framework has been studied, and found to be sensitive to substituent effects. The precise nature of these substituent effects (i.e. electronic, conformational) will be a topic for future investigation.

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References and Notes:

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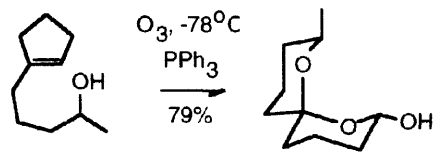
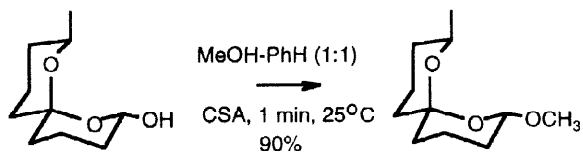
6. Zemribo, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159-4162.
7. White, D.; Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1997**, *38*, 2223-2226.
8. A general route to spirolactols has since been developed in our lab, in which cyclopentene ozonolysis is conducted in the presence of the free alcohol (see below).



9. We have since found a direct route to methyl acetals from spirolactols (see below).



10. During the course of this work, a similar equilibrium mixture of spiroketals, prepared by acid-catalyzed ring closure of an open-chain keto-diol, was reported by Heathcock and Hayes. See: reference 4a.
11. For a mechanistic explanation for the formation of tetrahydropyran **13** from **2c**, see reference 5.
12. ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.92 (3H, t, J = 6.0 Hz), 1.06 (1H, dd, J = 11.7, 9.0 Hz), 1.15-1.87 (12H), 1.94 (1H, m), 1.98 (1H, m), 2.63 (1H, ddd, J = 12.4, 4.6, 2.1 Hz), 3.45 (1H, m), 3.76-3.88 (2H), 3.95 (1H, m), 4.30 (1H, m); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 14.19, 19.14, 29.69, 30.84, 34.83, 37.61, 38.51, 40.82, 45.02, 61.67, 64.35, 68.85, 69.51, 97.97
13. See the following paper in this issue.