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MODEL STUDIES TOWARDS THE SYNTHESIS OF APLYSIATOXIN SPIRO-CONFORMATIONAL CONTROL IN THE REACTIVITY OF C_2-OXIDIZED SPIROKETALS.[1]

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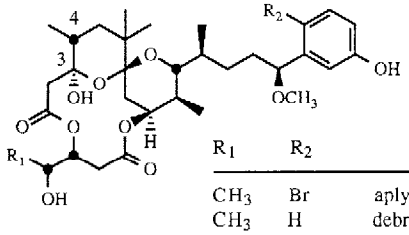
Summary: The strategy of pre-forming a highly functionalized C_2-oxidized spiroketal prior to utilizing the steric and stereoelectronic biases of the ring system to direct the introduction of further functionality is an attractive method for complex spiroketal synthesis By such an approach, aplysiatoxin-oscillatoxin models have been constructed, in which non-chair conformations have been discovered

Our group has recently reviewed the different synthetic strategies towards spiroketal ring formation and the subsequent chemistry thereof [3a] With few exceptions,[4] the strategy used in complex spiroketal synthesis involves the construction of fully-functionalized acyclic precursors with the correct functionality level and relative stereochemistry prior to spirocyclization. This approach overlooks the use of the inherent steric and stereoelectronic biases present in spiroketals to direct the introduction of functionality and the establishment of stereochemistry. Our approach involves initial rapid synthesis of a spiroketal by furan oxidation, followed by exploitation of the steric and stereoelectronic biases of the ring system to direct the introduction of further functionality and relative stereochemistry This approach has been employed in the synthesis of C_2-oxidized spiroketals of the 1,7-dioxaspiro[5 5]undecane type which model the spiroketal substructure of the aplysiatoxins 1 [5] The results of this study are presented herein.

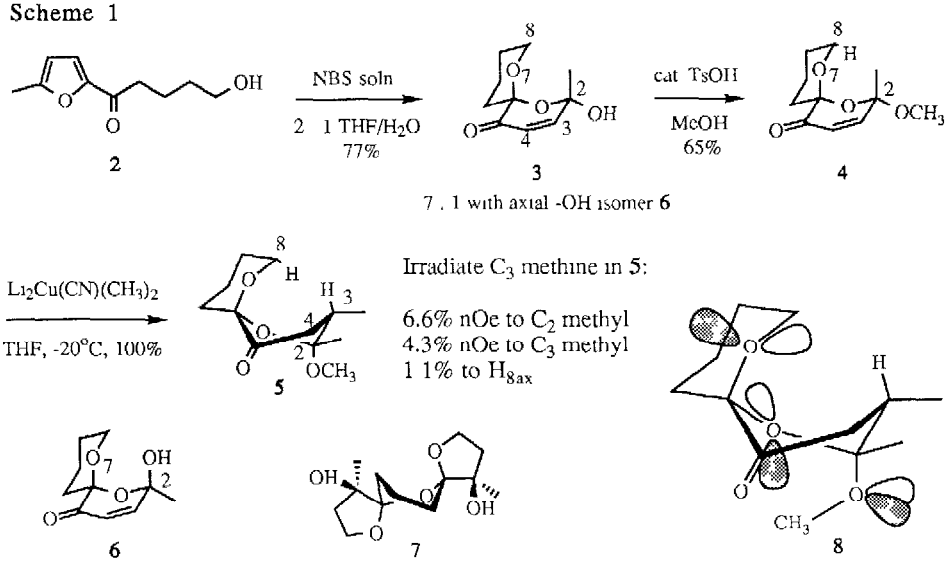


R_1	R_2		
CH_3	Br	aplysiatoxin	**1a**
CH_3	H	debromoaplysiatoxin	**1b**
H	H	oscillatoxin A	**1c**

In preparing C_2-oxidized spiroketals, we made use of the 2-furyl ketone oxidation-rearrangement method previously developed by our group (Scheme 1).[3b] Oxidation-rearrangement of 2-furyl ketone **2** in 2 : 1 tetrahydrofuran/water at 0 °C was effected by addition of a solution of NBS in 2 · 1 THF/H_2O, providing hemispiroketal *3* in *77%* yield as a slowly equilibrating *7* : 1 mixture of C_2 diastereomers. To circumvent the slow

equilibration between hemiketal forms, the crude reaction product was treated with methanol and catalytic TsOH at 25°C for 30 minutes, giving a single spiroketal product in 65% yield. On the basis of 300 MHz 1D ^{1}H NMR nuclear Overhauser enhancement of the C_2 methyl signal on irradiation of H_{8ax}, the structure was assigned as **4**.[6] Due to the similarity of ^{1}H and ^{13}C NMR spectra to those of the major isomer of **3**, the structure previously reported[3b] as **6**, in which the C_2 hydroxyl group was assigned as axial, is hereby corrected. We attribute the predominance of hemispiroketal **3** and the exclusive formation of **4** to the minimization of destabilizing dipole interactions between the axial C-O7 bond at the spiro center and an axial C_2-OH bond. We anticipated that cuprate addition to **4** would occur on the face of the olefin away from the C-O7 bond at the spiro center. A face-selective addition was not achieved using a Gilman-type methyl cuprate, which gave the two isomeric addition products with low selectivity. However, addition of a higher order methyl cuprate[7] to **4** proceeded quantitatively, giving a single isomer by ^{1}H NMR which has been assigned as **5**. Structural elucidation by ^{1}H NMR decoupling revealed anomalously large vicinal coupling constants between H_3 and H_4 and $H_{4'}$ (7.6 and 10.7 Hz), suggesting that the tetrahydropyranone ring existed in a non-chair conformation. A study by Descotes and coworkers[8] reported complete spectral and X-ray crystallographic studies of trioxadispiroketal **7** containing a central tetrahydropyran ring found to reside in a twist-boat conformation. The study reported anomalously large vicinal ^{1}H coupling constants at analogous positions on the twist-boat ring to those in **5**. In addition, we carried out 1D ^{1}H NMR NOE in studies in $CDCl_3$ and found that irradiation of H_3 resulted in enhancement of the H_{8ax}, C_2 methyl, and C_3 methyl signals. These data are consistent with the twist-boat conformation shown in **5**. We propose that one reason for such a conformational change on conjugate methyl addition to **4** is the introduction of a third stabilizing anomeric effect[9a] by virtue of an axial methoxy group. Structure **8** illustrates the oxygen lone pairs on the twist-boat spiroketal. Using this model, one can envision oxygen lone pair interactions with anti-periplanar C-O bonds. Another rationalization of this conformation is the preference for the C_2 methyl to reside in an equatorial position and thereby avoid unfavorable diaxial interactions with the C-O7 bond at the spiro center in a chair conformer.[9b]

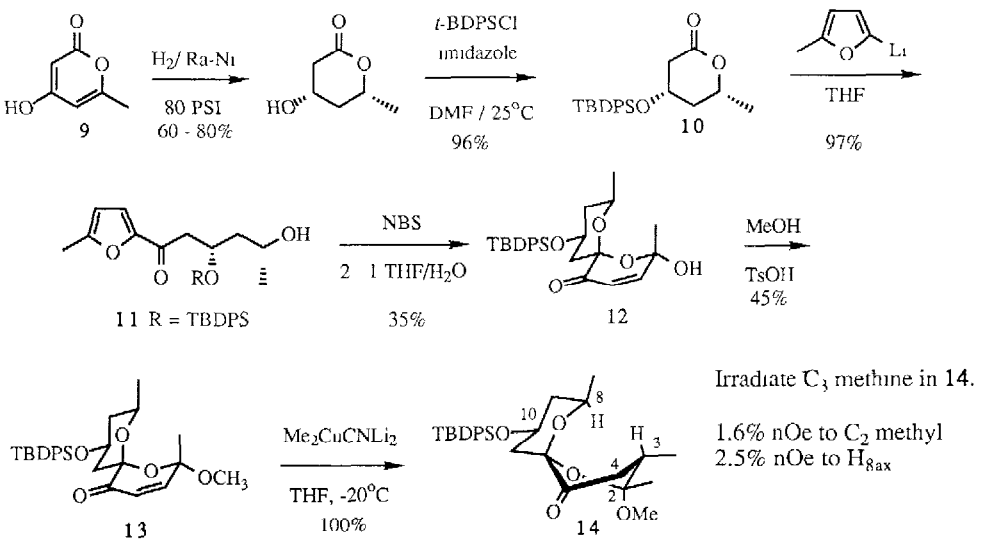
Scheme 1

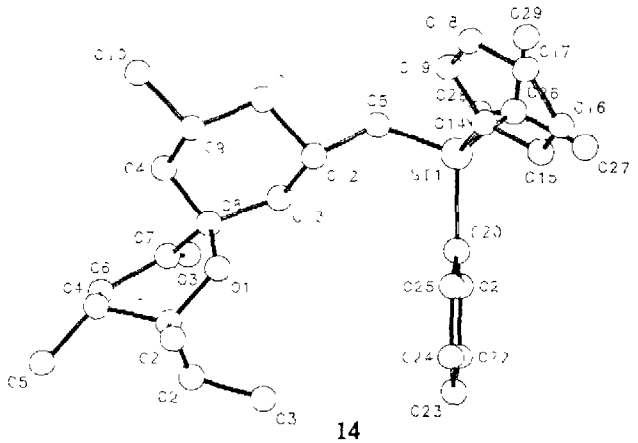


We next proceeded to a more functionalized model to see if controlled diastereofacial addition could be achieved at C_3 relative to substituents on the opposite ring (Scheme 2). Hydrogenation of the commercially available triacetic acid lactone **9** afforded the cis-oriented β-hydroxy lactone **10**[10] This was readily converted to its TBDPS ether under standard conditions. Addition of excess 5-methyl-2-furyllithium to lactone **10** led solely to monoaddition product **11**. Oxidation-rearrangement was performed with two equiv of NBS in THF/H_2O (2 . 1 v/v) and yielded an equilibrating mixture of hemispiroketals from which only the major isomer **12** could be obtained cleanly in 35% yield after chromatography. ^1H and ^{13}C NMR spectra were found to be similar in analogous signals to spiroketal **4**. Conversion to the methyl ketal **13** proceeded as before in 45% yield. Treatment with 6 equiv of $Me_2Cu(CN)Li_2$ produced a single product **14** in quantitative yield. ^1H NMR decoupling again revealed anomalously large vicinal coupling constants between H_3 and H_4 and H_4' (7.4 and 10 6 Hz), in close agreement with those found for **6**. 1D ^1H NMR NOE studies carried out in CD_2Cl_2 showed small transannular enhancements of H_{8ax} and the C_2 methyl on irradiation of the C_3 methine The structure of **14** was confirmed by X-ray crystallography.

Thus, the steric and stereoelectronic bias of the 2-alkoxy spiroketal ring arrangement leads to diastereoselective introduction of the C_3 methyl group on two spiroketals which model the spiroketal substructure of aplysiatoxin By rigorous NMR and X-ray analysis, we have been able to ascertain the stereochemical and conformational character of each spiroketal intermediate. This shows that the C_4 methyl group (aplysiatoxin numbering) can be introduced stereospecifically with respect to the substituents on the opposite ring

Scheme 2. Synthesis of an Aplysiatoxin-Oscillatoxin Model Substance





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2) Author to whom correspondence concerning X-ray data should be addressed

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