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# Synthetic Studies Towards Ciguatoxin via Acetal/γ-Oxovinyl Stannane Condensation: A Convergent Approach

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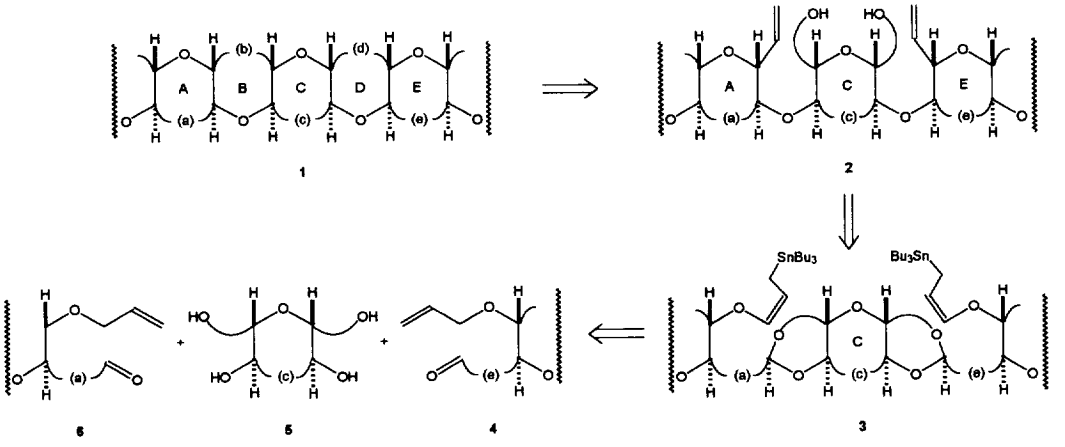
**Abstract**: A two-directional approach converting acetals to O-linked oxacycles, by way of intramolecular allyl tin-acetal condensation, is described.


The chemistry published by Nicolaou[1] and others[2] has single-handedly made it possible for most natural *trans*-fused polyethers[3] to be synthesized. Nonetheless, for greater ease of access from the synthetic point of view, the size and complexity of natural compounds do require efficient convergent methodologies, as yet to be designed, since synthesis is envisaged as a better source of these substances than the frequently laborious process of culturing the microorganisms which produce them.

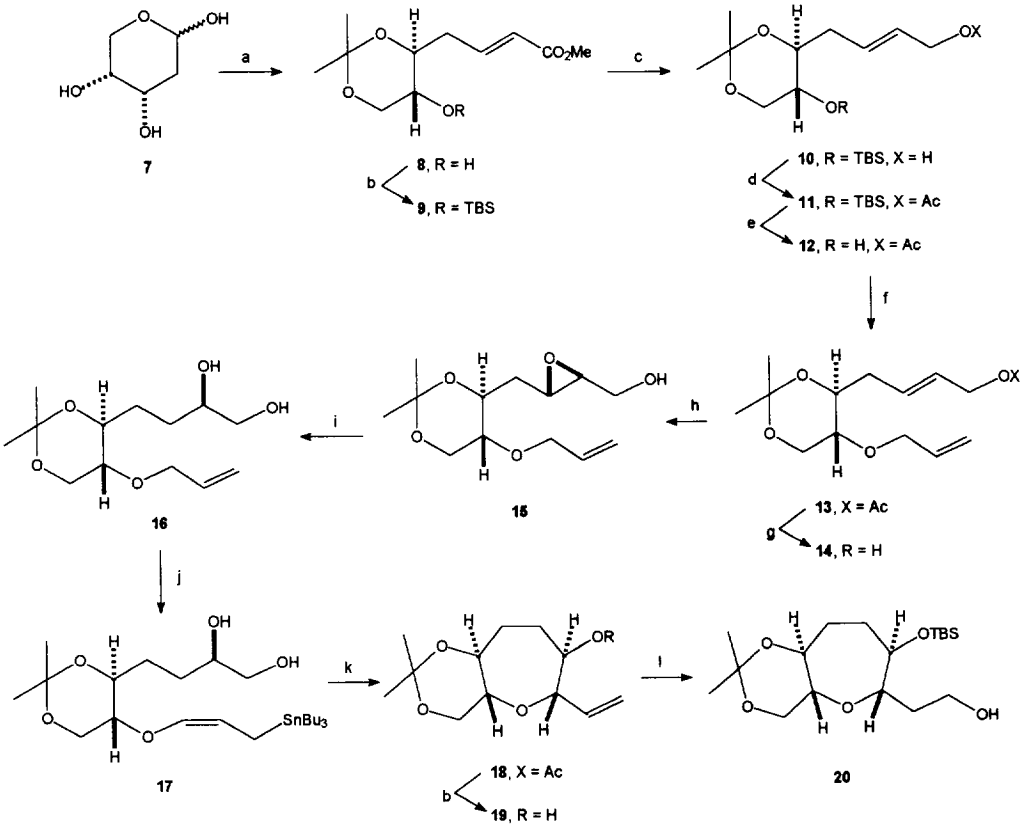
We have recently reported[4] that intramolecular acetal/γ-oxovinyl stannane condensation efficiently produces ring closure to give O-linked oxacycles. This cyclization was of particular interest in the context of *trans*-fused polyether synthesis, since it reproduces the strict R/S alternation of the stereogenic centres in the carbon skeleton of ciguatoxin and related compounds.[5,6] As an extension of this methodology, and in an attempt to demonstrate the generality and scope of these reactions in the construction of *trans*-fused polyethers, we have designed the two-directional strategy shown in Scheme 1 as a potential route to these systems.

To exemplify the concepts involved in this strategy, we detail here the construction of the O-linked oxatricyclic system **25**, starting from the $C_9$-oxepanyl subunit **21** (Scheme 3).[7] Synthesis of key intermediate **20**[8] is briefly summarized in Scheme 2. Thus, 2-deoxy-D-ribose **7** was converted into olefin **9** (91% overall yield) by a Wittig reaction followed by sequential and selective protection involving acetonide formation and silylation. Subsequent reduction led to the alcohol **10**, which was converted to the allyl ether **14** by standard chemistry (70% overall yield). Sharpless epoxidation of alcohol **14** with (+)-diethyl tartrate gave the epoxy alcohol **15**, which was further reduced to the diol **16** by treatment with DIBAL in benzene (56% overall yield).

## Scheme 1



## Scheme 2[a]

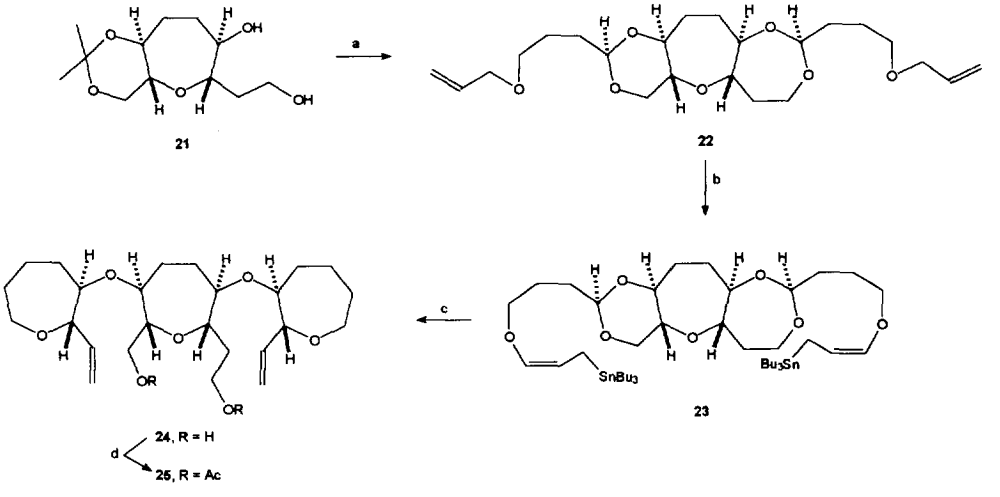


[a] *Reagents and conditions*: (a) 1.2 equiv of $Ph_3PCHCO2Me$, THF, 80 °C, 4 h, 100%; 1.5 equiv of $(CH_3O)_2C(CH_3)_2$, CSA catalyst, $CH_2Cl_2$, 40 °C, 12 h, 93%; (b) 1.4 equiv of TBSOTf, 2.0 equiv of $Et_3N$, $CH_2Cl_2$, 0-25 °C, 1 h, 98%; c) 2.5 equiv of DIBAL, $Et_2O$, 0-25 °C, 5 h, 81%; (d) 1.2 equiv of $Ac_2O$, DMAP catalyst, $CH_2Cl_2$, 25 °C, 6 h, 96%; (e) 1.5 equiv of *n*-$Bu_4NF$, THF, 25 °C, 2 h, 87%; (f) 1.5 equiv of NaH, 2.2 equiv of allyl bromide, DMF, 0-25 °C, 5 h, 83%; (g) 1.5 equiv of $K_2CO_3$, acetone:MeOH (4:1), 25 °C, 6 h, 98%; (h) 0.12 equiv of (+)-DET, 0.1 equiv of $(i\text{-}PrO)_4Ti$, 3.0 equiv of TBHP, MS 4A, $CH_2Cl_2$, -20 °C, 24 h, 94%; (i) 2.0 equiv of DIBAL, $C_6H_6$, 10-25 °C, 5 h, 60%; (j) 3.2 equiv of *sec*-BuLi, 1.2 equiv of *n*-$Bu_3SnCl$, THF, -78 °C, 15 min, 62%; (k) 1.5 equiv of *n*-$Bu_4NIO_4$, $CH_2Cl_2$, 0-25 °C, 3 h, then add 2.0 equiv of $BF_3.OEt_2$, -78 °C, 15 min, 95%; (l) 2.2 equiv of $BH_3$.THF, THF, 0-25 °C, 12 h, NaOH-$H_2O_2$, 70%.

Lithiation of **16** with *sec*-BuLi and trapping with *n*-$Bu_3SnCl$ gave **17** in 62% yield. The cyclization to give **18** was accomplished by *vic*-diol fragmentation with *n*-$BuNIO_4$ followed by treatment of the resulting aldehyde with $BF_3.OEt_2$ to afford **18** in 95% yield.[9] Silylation of **18** followed by hydroboration using borane-THF complex followed by oxidative work-up led to compound **20** (70% yield).

The coupling of diol **21** with 5-allyloxypentanal and elaboration of the resulting diacetal to compound **25**[10] are summarized in Scheme 3.

**Scheme 3**




*Reagents and conditions*: (a) 2.2 equiv of 5-allyloxypentanal, 2.0 equiv of CSA, $CH_2Cl_2$, 25 °C, 4 h, 87%; (b) 2.4 equiv of *sec*-BuLi, 2.2 equiv of *n*-$Bu_3SnCl$, THF, -78 °C, 15 min, 50%; c) 4.0 equiv of $TiCl_3(O^iPr)$, $CH_2Cl_2$, -78 °C, 20 min, 15% (d) 2.5 equiv of $Ac_2O$, pyridine, 25 °C, 12 h, 100%.

Bis-acetal **22** was prepared under carefully controlled conditions in 50% yield. Lithiation of **22** with *sec*-BuLi and treatment with *n*-$Bu_3SnCl$ gave **23** which, under Lewis acid conditions [$TiCl_3(OiPr)$, $CH_2Cl_2$, -78 °C] underwent cyclization to give the *trans*-substituted O-linked polyether **24**, albeit in modest yield (~ 15%).

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**References and Notes**

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7. All new compounds exhibited satisfactory spectral and exact mass data. Yields have not been maximized and refer to spectroscopically and chromatographically homogeneous materials.
8. Selected spectral data for compound **20**: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.00 (dd, J = 7.6, 6.1 Hz, 1H), 3.92 (dd, J = 11.8, 5.8 Hz, 1H), 3.83 (dd, J = 7.6, 5.8 Hz, 1H), 3.77 (br t, J = 5.2 Hz, 2H), 3.37 (ddd, J = 11.2, 6.0, 2.1 Hz, 1H), 3.31 (m, 2H), 2.61 (br s, 1H), 2.01 (m, 3H), 1.86 (m, 1H), 1.65 (m, 1H), 1.45 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 109.3 (s), 83.1 (d), 77.8 (d), 77.6 (d), 70.8 (d), 66.4 (t), 61.5 (t), 34.1 (t), 32.8 (t), 27.4 (t), 26.5 (q), 25.8 (q), 25.2 (q), 19.9 (s), -4.1 (q), -4.7 (q).
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10. Selected spectral data for compound **25**: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddd, J = 17.0, 10.5, 5.3 Hz, 1H), 5.92 (ddd, J = 17.0, 10.5, 5.3 Hz, 1H), 5.31 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 5.29 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 5.15 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H), 5.13 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H), 4.15 (m, 3H), 4.07 (ddd, J = 11.8, 11.8, 6.5 Hz, 1H), 4.00 (ddd, J = 12.6, 4.6, 4.6 Hz, 1H), 3.94 (ddd, J = 12.6, 4.5, 4.5 Hz, 1H), 3.82 (m, 2H), 3.56 (m, 4H), 3.32 (m, 4H), 2.22 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.93 (m, 2H), 1.80-1.37 (m, 14H); $^{13}$C NMR ($CDCl_3$) δ 170.8 (s), 170.1 (s), 138.1 (d), 138.0 (d), 114.8 (t), 114.6 (t), 84.2 (d), 84.2 (d), 83.6 (d), 83.6 (d), 77.3 (d), 75.3 (d), 74.3 (d), 71.6 (d), 71.3 (t), 70.7 (t), 64.0 (t), 60.8 (t), 31.3 (t), 31.2 (t), 31.2 (t), 29.9 (t), 29.7 (t), 28.9 (t), 26.6 (t), 21.1 (q), 21.0 (t), 21.0 (t), 21.0 (q).

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