# Synthesis of Unsaturated Trans-Fused Polyether Frameworks via O-linked Oxacycles: A Convergent Approach

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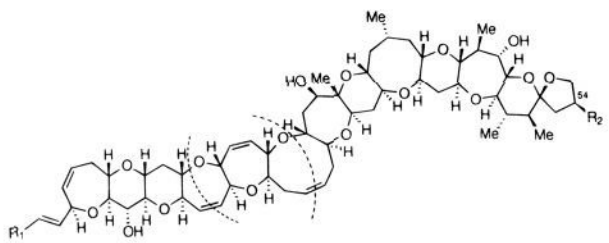
As a part of a program[1] aimed at the total synthesis of ciguatoxin (**1**), and in an attempt to develop a general, mild methodology for the convergent assemblage of previously synthesized pieces with concomitant generation of unsaturated rings, following the disconnections indicated in **1**, we have designed the strategy shown in Scheme 1 as a potential route to these systems. According to this strategy, the cycloalkene **2**



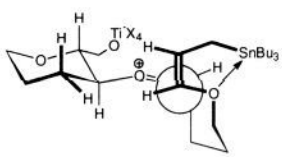
**1**

would be generated from the O-linked oxacyclic precursor **6** via thioannulation and successive α-halogenation and oxidation at sulfur, followed by a Ramberg−Bäcklund reaction.[2] The skeleton and functional groups of compound **6**, the key intermediate, are typical of an end product of the Yamamoto[3] allylic tin aldehyde (acetal) condensation, several of which have already been used[1] in the synthesis of oxacyclic models in the course of this program. Further retrosynthetic analysis provided, via **7**, two oxacyclic subunits **8** and **9**, for use in the construction of **2**.

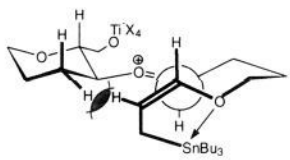
To assess the general applicability and scope of this method in terms of ring size and substitution, a number of α-vinyl β-oxyalkenyl ethers were prepared and subjected to the described sequence, giving a series of trans-fused unsaturated oxacyclic systems.[4−7]

A simple application of this technology to a convergent design is outlined in Scheme 2. Both **19**[8] (optically active) and **20** were readily prepared from commercially available starting materials using known procedures. The two pieces were joined under carefully controlled acetalization conditions, giving acetal **21** in 94% yield. Treatment of **21** with *s*-BuLi and $Bu_3SnCl$ gave the desired organometallic derivative **22** (81%), which underwent facile Lewis acid cyclization (2.0 equiv of $TiCl_3(O^i$-Pr), $CH_2Cl_2$, −78 °C, 20 min) to give the trans-substituted O-linked ether **23** in 73% yield.[9]

It is noteworthy that this reaction behaves selectively in two ways. Firstly, it is group selective. Ether **23** is formed predominantly, probably due to preferential complexing of the Lewis acid with the less hindered oxygen of the acetal.[10] Secondly, the cyclization is stereoselective. The newly generated *vic*-methine protons are trans ($J$ = 9.0 Hz), which can be accounted for by examining the synclinal transition structures **A** and/or **B** where the back side of the oxocarbenium ion plane is blocked by the sterically bulky Ti-complexed oxymethyl appendage, forcing the γ-carbon of the allylstannyl system to approach from the front side of the plane. The absolute



**A**



**B**

configuration of the two new stereogenic centers created was unequivocally determined as 4′(*R*), 5′(*S*) as follows. The primary OH group in **23** was oxidized under Swern conditions[11] to give the corresponding aldehyde, which was submitted to retro-Michael reaction by base treatment to afford **24**,[12] $[\alpha]^{25}_D$ = −6.6° ($CHCl_3$), in 58% overall yield. This asymmetric induction was to be expected as transition structure **A** is the less sterically crowded of the two possibilities and, in consequence, preferable to option **B**.

This sequence appeared ideal for our needs, *since the cyclization reproduces the strict R/S alternation of the stereogenic centers in the carbon skeleton of ciguatoxin and related polyethers* (see general structure **2**). The next few steps leading to the final molecule **31** make use of standard chemical procedures. Thus, hydroboration of **23** followed by oxidative workup gave the diol **25** (81%), which was further iodinated[13] to afford diiodide **26** (93%). Treatment of **26** with $Na_2S/Al_2O_3$[14] (HMPA, 80 °C, 12 h) gave the cyclized sulfide **30** in 63% yield. An alternative pathway involves treatment of the tosyl derivative

(1) For our recent stereoselective synthesis of several ciguatoxin frameworks, see: Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848−2876.

(2) For extensive reviews of the Ramberg−Bäcklund reaction, see: Clough, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, Y., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861−886. Block, E.; Putman, D.; Schwan, A. In *Sulfur-centered Reactive Intermediates in Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D., Eds.; NATO-ASI Series, Life Sciences; Plenum Press: London, 1990; pp 257−267. Guziec, F. S.; Sanfilippo, L. J. *Tetrahedron* **1988**, *44*, 6241−6285. Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1−71.

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(4) All new compounds exhibited satisfactory spectral and exact mass data. Yields have not been maximized and refer to spectroscopically and chromatographically homogeneous materials.

(5) One of the great strengths of the reaction is that there is no ambiguity about the position of the newly introduced double bond; it is fixed by the position of the sulfone group in the heterocycle and does not isomerize under the reaction conditions.

(6) More details on the preparation of these compounds and their precursors can be found in the supplementary material.

(7) Thus, the present methodology constitutes an alternative to the ring-closing olefin metathesis recently reported by Grubbs, who cyclized several substituted diene ethers to unsaturated oxygen heterocycles: (a) Fu, G. C; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427. (b) Fu, G. C; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800−3801. (c) Fu, G. C; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.

(8) Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040−3054.

(9) The reaction also produces a 7% yield of the cis-fused isomer (not shown).

(10) (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695−10704. (b) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10988−10999. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458−6467. (d) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115.

(11) (a) Mancuso, A. J.; Hwang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.

(12) The 4(*S*), 5(*R*) enantiomer of **24**, $[\alpha]^{25}_D$ = 6.5° ($CHCl_3$), was prepared in eight steps from tri-*O*-acetyl-D-glucal. See supplementary material for details.

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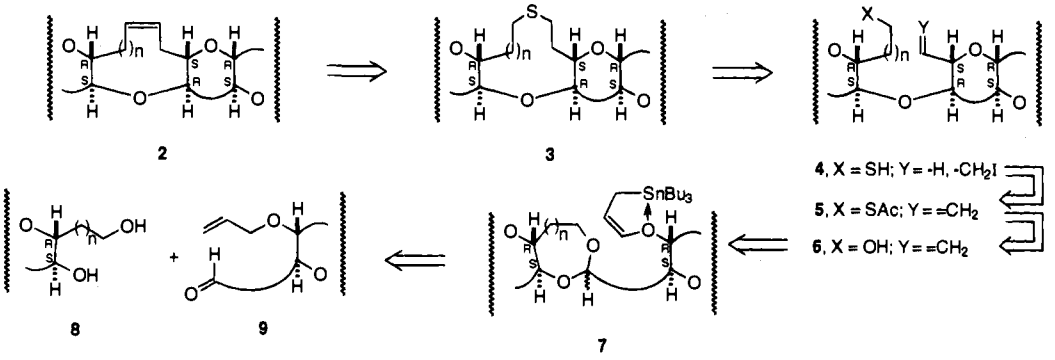
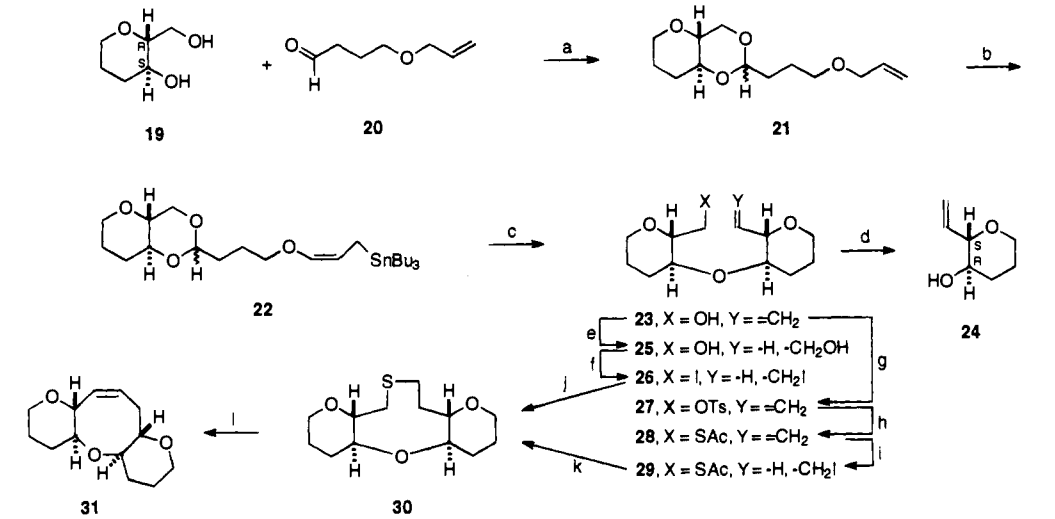
**Scheme 1**




**Scheme 2**[a]

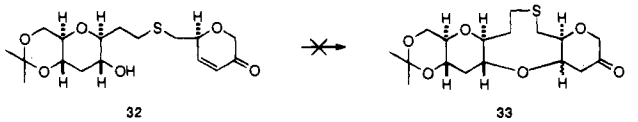



[a] Reagents and conditions: (a) 0.05 equiv of CSA, benzene, reflux, 12 h, 94%; (b) 1.2 equiv of *s*-BuLi, 1.2 equiv of $Bu_3SnCl$, THF, −78 °C, 20 min, 81%; (c) 2.0 equiv of $TiCl_3(O^iPr)$, $CH_2Cl_2$, −78 °C, 20 min, 73%; (d) (i) Swern oxidation, 90%; (ii) 2.0 equiv of LiOH, THF−$H_2O$ (3:1), 50 °C, 6 h, 64%; (e) 2.2 equiv of $BH_3$−THF, THF, 0 °C, 1 h, NaOH−$H_2O_2$, 81%; (f) 4.0 equiv of $I_2$, 5.0 equiv of $Ph_3P$, 2.4 equiv of imidazole, 10−15 °C, 4 h, 93%; (g) 1.1 equiv of TsCl, 3.0 equiv of $Et_3N$, DMAP catalyst, $CH_2Cl_2$, 0 °C, 30 min, 79%; (h) 3.4 equiv of NaH, 4.3 equiv of AcSH, $CH_2Cl_2$, 25 °C, 12 h, 89%; (i) 1.2 equiv of $(Sia)_2BH$, THF, 0 °C, 6 h, 1.2 equiv of $I_2$, NaOH−MeOH, 52%; (j) 1.1 equiv of $Na_2S$−$Al_2O_3$, HMPA (0.01 M), 80 °C, 12 h, 63%; (k) 2.0 equiv of MeONa, MeOH, $H_2$ atmosphere, 25 °C, 12 h, 78%; (l) (i) 1.5 equiv of NCS, $CCl_4$, 0 °C, 2 h; (ii) 1.5 equiv of MCPBA, $CH_2Cl_2$, 0−25 °C, 3 h; (iii) 1.2 equiv of $^t$BuOK, THF, 0 °C, 1.5 h, 52%.

**27** with NaH/AcSH to give **28** (89%), which was further hydroborated using $(Sia)_2BH$ followed by $I_2$/NaOH oxidation[15] to yield iodide **29** (52%). The cyclization to **30** proceeded smoothly by treatment of **29** with MeONa in MeOH at −25 °C under an $H_2$ atmosphere[16] (78%). Finally, compound **30** was converted to **31** via the Ramberg−Bäcklund olefination process in 52% yield.

As an alternative to the thioannulation process, we explored the intramolecular hetero-Michael cyclization of **32**[17] to give **33**. Unfortunately, the intramolecular 1,4-addition did not prove fruitful under acidic or basic conditions, affording complex mixtures of products, none of which was the desired compound **33**.

These results and the efficient thioannulation achieved via O-linked oxacycles probably involve entropy, a proposition which is borne out by NOE experiments on derivatives of **23** and **25**−**29**, showing preferred solution conformers in which the reacting centers are in close spacial proximity. Similar analysis of the S-linked derivative **32** suggests a fully extended zig-zag conformation making the intramolecular coupling difficult.




To sum up, this synthesis provides a new technology for the construction of unsaturated medium-size polyethers using organosulfur and organotin chemistry and follows a highly economical strategy for intermolecular coupling of oxacyclic subunits.

**Acknowledgment.** Financial support from the MEC, Spain (PB92-0487), and the EU (Contract CI1-CT92-0049) is gratefully acknowledged.

**Supplementary Material Available:** Experimental details for the preparation of **13**, **16** and **32**, $^1$H and $^{13}$C NMR spectra of all new compounds, 1D $^1$H, NOE difference and ROESY spectra for **23** and **32**, tables containing synthesis data for α-vinyl α-oxalkenyl ethers and unsaturated polyethers, and an illustration of the predicted preferred solution conformations **23A** and **23B** and related derivatives (111 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JA9426507

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(16) Zervas, L.; Photaki, I.; Chelis, N. *J. Am. Chem. Soc.* **1963**, *85*, 1337−1341.

(17) Full details of the synthesis of **32** can be found in the supplementary material.