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A Concise Synthesis of *Ortho*-Condensed Oxane-Oxene, Oxepene, Oxocene and Oxonene Ring Systems

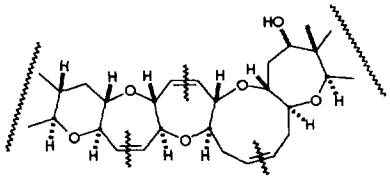
Eleuterio Alvarez, Mercedes Delgado, María Teresa Díaz, Liu Hanxing, Ricardo Pérez and Julio D. Martín*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna-CSIC, Carretera Vieja de La Esperanza, 2; 38206 La Laguna, Tenerife, Spain

Abstract: An efficient strategy for the synthesis of *trans*-fused oxabicyclic systems involving thioannulation followed by a Ramberg-Bäcklund olefination as the key step is described. Copyright © 1996 Elsevier Science Ltd

As a part of a program[1] aimed at the total synthesis of ciguatoxin,[2] and in an attempt to develop a general synthetic strategy for the synthesis of *trans*-fused unsaturated oxacycles, we focused on an approach in which unsaturated rings are introduced via thioannulation followed by a Ramberg-Bäcklund olefination.[3]

Figure 1: *Ciguatoxin (partial structure)*

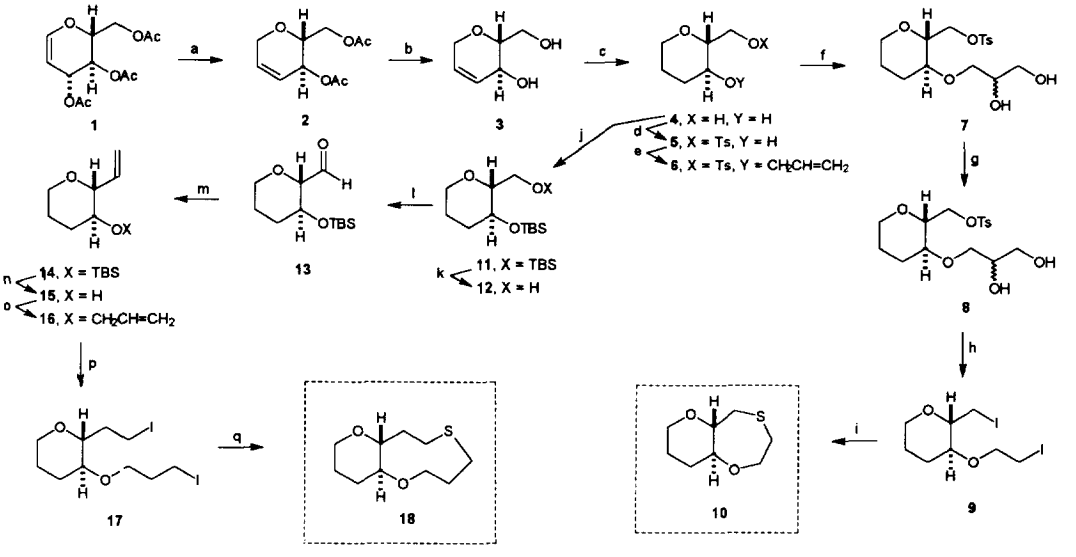


According to this strategy, cycloalkenes would be generated from the O-linked acyclic precursor via sulfur connection to form the 1,n-oxathiane and successive α-halogenation and oxidation at sulfur, followed by SO_2-extrusion reactions.[4] To assess the general applicability and scope of this method in terms of ring size, a number of *ortho*-condensed oxane:oxathiacycles were synthesized starting from the common tri-O-acetyl-D-glucal (Schemes 1-3).[5]

Compounds **10** and **18** (Scheme 1) were synthesized in 60% and 70% yield, respectively, by treatment of **9** and **17** with Na_2S/Al_2O_3, HMPA, at 100 °C.[6]

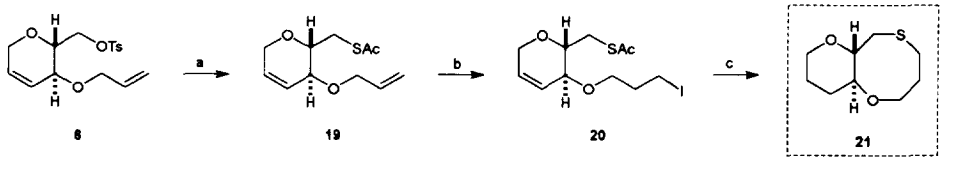
An alternative thioannulation pathway is shown in Scheme 2. The whole process involves treatment of the tosyl derivative **6** with NaH/AcSH to give **19**, which was further iodinated using $(Sia)_2BH$ followed by I_2/NaOH oxidation to yield iodide **20**.[7] Thioannulation to **21** proceeded smoothly by treatment of **20** with MeONa in MeOH at -25 °C under H_2 atmosphere (87% yield).

Scheme 1[a]



[a] *Reagents and Conditions*: (a) 1.2 equiv of Et_3SiH, 1.0 equiv of $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 2 h, 99%; (b) 1.0 equiv of NaOMe, MeOH, 30 min, 100%; (c) H_2, Pd/C 10% cat, MeOH, 8 h, 99%; (d) 1.0 equiv of TsCl, 1.5 equiv of NEt_3, DMAP cat, CH_2Cl_2, 0 °C, 8 h, 77%; (e) 1.5 equiv of NaH, 1.5 equiv of allyl bromide, *n*-Bu_4NI cat, DMF, 0 °C, 10 h, 93%; (f) cat OsO_4, 1.1 equiv of NMO, THF:H_2O (1:1), 25 °C, 4 h, 99%; (g) 1.5 equiv of $NaIO_4$, MeOH:H_2O (7:1), 0 °C, 30 min, then 2.0 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 95%; (h) 3.0 equiv of PPh_3, 3.0 equiv of imidazole, 2.0 equiv of I_2, benzene, 0 °C, 1 h, 75%; (i) 1.1 equiv of Na_2S-Al_2O_3, HMPA (0.01 M), 100 °C, 12 h, 60%; (j) 2.4 equiv of TBSCl, 5.0 equiv of imidazole, CH_2Cl_2, 25 °C, 6 h, 100%; (k) 7.0 equiv of TFA, THF:H_2O (1:1), 0 °C, 30 min, 81%; (l) 3.0 equiv of SO_3.Py complex, 5.0 equiv of NEt_3, DMSO:CH_2Cl_2 (1:1), 0 °C, 2 h, 85%; (m) 1.3 equiv of Ph_3PCH_2Br, 1.2 equiv of *n*-BuLi, toluene, 0 °C, 12 h, 54%; (n) 2.0 equiv of *n*-Bu_4NF, THF, 0 °C, 12 h, 100%; (o) 1.5 equiv of NaH, 1.3 equiv of allyl bromide, DMF, 0 °C, 2 h, 83%; (p) 3.0 equiv of $(Sia)_2BH$, THF, 0 °C, 12 h; then 2.2 equiv of I_2, MeOH, 3.0 equiv of NaOH, 25 °C, 2 h, 48%; (q) 1.1 equiv of Na_2S-Al_2O_3, HMPA (0.01 M), 100 °C, 24 h, 70%.

Scheme 2[a]

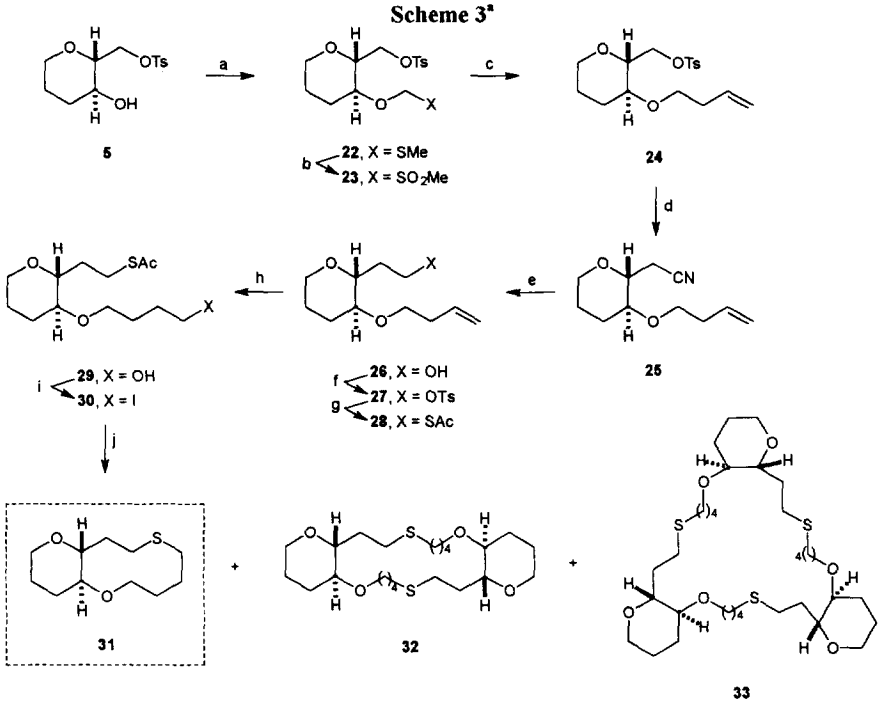


[a] *Reagents and Conditions*: (a) 2.5 equiv of AcSH, 2.0 equiv of NaH, DMF, 0 °C, 10 h, 81%; (b) 1.5 equiv of $(Sia)_2BH$, THF, 0 °C, 8 h, then 1.1 equiv of I_2, MeOH, 1.5 equiv of NaOH, 25 °C, 40 min, 58%; (c) 2.0 equiv of NaOMe, MeOH, 0-25 °C, 12 h, 87%.

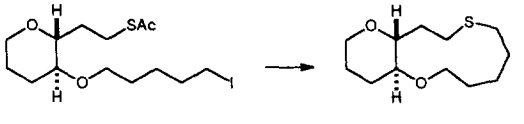
Cyclization of **30**, under similar conditions, gave in modest yield (40%) the oxathiacycle **31**, due to the formation of dimer **32** (40%)[8] and trimer **33** (12%)[8] (Scheme 3). However, thioannulation of the one-carbon higher homologous **34** was successful and provided **36** as a single isomer in high yield (89%). These results,

clearly reveal that the intramolecular transition state arrangement is affected not only by ring size but also by the conformation of the bicyclic skeleton.

Scheme 3[a]

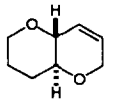
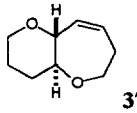
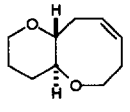
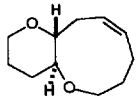


[a] *Reagents and Conditions*: (a) 50.0 equiv of DMSO, 25.0 equiv of Ac_2O, 12.5 equiv of AcOH, 25 °C, 2 days, 80%; (b) $RuCl_3$ cat, 4.0 equiv of $NaIO_4$, H_2O:CH_3CN:CCl_4 (3:2:2), 25 °C, 15 min, 100%; (c) 2.0 equiv of CH_2=$CHCH_2SiMe_3$, 2.0 equiv of $AlCl_3$, CH_2Cl_2, -78 °C → 20 °C, 6 h, 80%; (d) 3.0 equiv of NaCN, DMSO, 50 °C, 8 h, 95%; (e) 1.5 equiv of DIBAL, Et_2O, 0 °C, 6 h, then HCl (1.0 N), then 2.0 equiv of $NaBH_4$, MeOH, 0 °C, 30 min, 55%; (f) 1.1 equiv of TsCl, 1.5 equiv of NEt_3, DMPA cat, CH_2Cl_2, 8 h, 90%; (g) 2.5 equiv of AcSH, 2.0 equiv of NaH, DMF, 0 °C, 95%; (h) 3.0 equiv of $(Sia)_2BH$, THF, 0 °C, 12 h, then H_2O:NaOH (15%):H_2O_2 (30%) (2:5:5), 70%; (i) 2.0 equiv of I_2, 3.0 equiv of PPh_3, 3.0 equiv of imidazol, benzene, 0 °C, 95%; (j) 2.0 equiv of NaOMe, MeOH, 0-25 °C, 12 h, gave **31** (40%), **32** (40%) and **33** (12%).



Unsaturated oxabicycles **36-39** were formed from their respective oxathiacyclic precursors via the Ramberg-Bäcklund olefination process[3] (Table 1). Fortunately, SO_2-extrusion precludes undesired β-eliminations in entries 1 and 2. In entry 4, where the size of the unsaturated ring allows the possibility of *cis*- and *trans*-geometry of the double bond, a *cis*:*trans* mixture was obtained.

Table 1. Synthesis of Unsaturated Polyethers by SO_2-extrusion Reactions.

Entry	Oxathiane[a]	Product	Yield (%)
1	**10**	 **36**	40
2	**21**	 **37**	41
3	**18**	 **38**	37
4	**31**	 **39**	48

[a] *Reagents and Conditions:* (i) 1.5 equiv of NCS, CCl_4, 0 °C, 4-5 h; (ii) 1.5 equiv of MCPBA, CH_2Cl_2, 0-25 °C, 8-10 h; (iii) 1.2 equiv of ^{t}BuOK, THF, 0 °C, 4-5 h. Since the intermediate α-chloro sulfides and α-chloro sulfones are formed as mixtures of regio- and stereoisomers, it is convenient to use them in a crude form, and to withhold purification until the Ramberg-Bäcklund reaction itself has been completed.

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References and Notes.

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8. As expected, the symmetry of **32** and **33** was reflected in the ^{1}H and ^{13}C NMR spectra, which exhibited resonances for 20 hydrogens and 11 carbons, respectively. Dimer, **32**, FABMS, m/e, 455 $(M+Na)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (br d, J = 11.0 Hz, 1H), 3.70 (ddd, J = 9.0, 5.1, 5.1 Hz, 1H), 3.30 (m, 2H), 3.20 (ddd, J = 7.6, 7.6, 3.0 Hz, 1H), 2.98 (ddd, J = 10.5, 4.4, 4.4 Hz, 1H), 2.67 (ddd, J = 14.2, 9.7, 4.7 Hz, 1H), 2.54 (m, 3H), 2.22 (br d, J = 12.5 Hz, 1H), 2.10 (m, 1H), 1.66 (m, 7H), 1.30 (ddd, J = 17.5, 12.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 79.5 (d), 77.3 (d), 68.1 (t), 67.8 (t), 32.4 (t), 31.0 (t), 29.3 (t), 29.2 (t), 27.4 (t), 26.7 (t), 25.4 (t). Trimer, **33**, FABMS, m/e, 671 $(M+Na)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (br d, J = 10.9 Hz, 1H), 3.63 (m, 1H), 3.31 (m, 2H), 3.18 (ddd, J = 8.8, 8.8, 2.6 Hz, 1H), 3.63 (m, 1H), 3.31 (m, 2H), 3.18 (ddd, J = 8.8, 8.8, 2.6 Hz, 1H), 2.95 (ddd, J = 10.5, 9.2, 4.5 Hz, 1H), 2.68 (ddd, J = 9.5, 9.5, 4.8 Hz, 1H), 2.54 (m, 3H), 2.20 (br d, J = 15.0 Hz, 1H), 2.14 (m, 1H), 1.66 (m, 7H), 1.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 79.6 (d), 77.7 (d), 68.1 (t), 67.7 (t), 32.6 (t), 31.5 (t), 29.3 (t), 29.2 (t), 28.0 (t), 26.3 (t), 25.4(t).

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