Communications to the Editor

Total Synthesis of the Marine Toxin Polycavernoside A via Selective Macrolactonization of a Trihydroxy Carboxylic Acid

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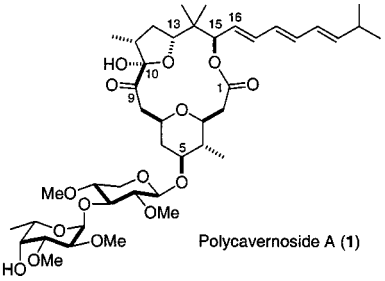
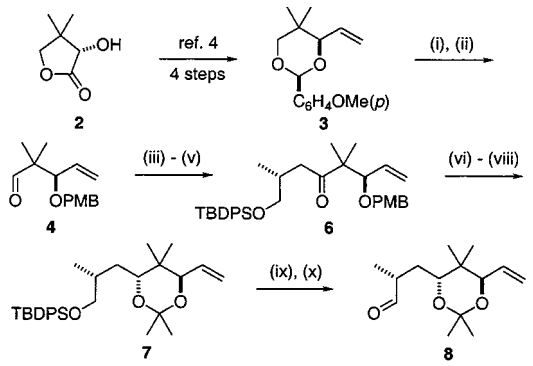
Naturally occurring macrolactones (macrolides) are found in a wide variety of ring sizes, yet little is known of the propensity of their precursor seco acids for forming a particular ring size when more than one macrocyclization pathway is available.[1] There does, nevertheless, appear to be a preponderance of macrolides with 14- and 16-membered rings, reflecting a bias by the synthase which fabricates these systems toward rings of this size. Our plan for the total synthesis of polycavernoside A (**1**), a macrolide isolated by Yasumoto from the red alga *Polycavernosa tsudai* and shown to possess lethal toxic properties,[2] incorporated a step which hinged critically upon macrolactonization of a trihydroxy carboxylic acid to create a 14-membered ring. We now report the successful realization of a scheme leading to a total synthesis of **1** which accomplishes this key reaction in highly selective fashion.[3]



Our strategy from the outset envisioned assembly of the aglycon of **1** from subunits which would be coupled first at the C9−C10 bond before closure of the macrocycle by lactonization. An important feature of this route was concealment of the C9 ketone and a C16 aldehyde, the latter for eventual elaboration of the conjugated triene chain of **1**, as alkenes until exposure via ozonolysis at a late stage of the synthesis. Construction of the C10−C16 portion of **1** commenced from (*S*)-pantolactone (**2**) which was transformed to olefin **3** by the method of Mukaiyama (Scheme 1).[4] Reduction of the benzylidene acetal with DIBAL-H gave a *p*-methoxybenzyl ether in which the liberated primary alcohol was oxidized to aldehyde **4**. Julia coupling of **4** with the lithio anion of (*S*)-sulfone **5** afforded a mixture of stereoisomers which were oxidized to a pair of keto sulfones. Reductive cleavage of the sulfonyl substituent with samarium diiodide[5] then gave **6** as a single stereoisomer. Removal of the *p*-methoxybenzyl ether from **6** and reduction of the resulting *β*-hydroxy ketone with tetramethylammonium triacetoxyborohydride[6] yielded the anti-1,3-diol, subsequently protected as its acetonide **7**. The primary silyl ether of **7** was unmasked to expose a primary alcohol which was oxidized to aldehyde **8**.

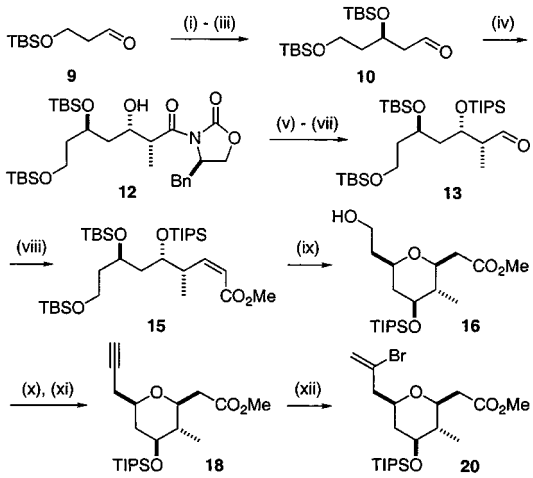
Synthesis of the C1−C9 subunit of **1** began with the protected aldehyde **9**. This was first subjected to Brown asymmetric

Scheme 1[a]



[a] (i) (*i*-Bu)$_2$AlH, CH_2Cl_2, −78 °C → rt, 100%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt, 96%; (iii) (*S*)-TBDPSOCH$_2$CH(CH$_3$)CH$_2$SO$_2$Ph (**5**), *n*-BuLi, THF, −50 °C; (iv) Dess−Martin periodinane, CH_2Cl_2, rt; (v) SmI_2, THF, −78 °C, 90% from **4**; (vi) DDQ, CH_2Cl_2−H_2O (10:1), 0 °C → rt, 89%; (vii) $Me_4NBH(OAc)_3$, AcOH−MeCN (1:1), −20 °C; (viii) $Me_2C(OMe)_2$, PPTS (cat.), CH_2Cl_2, rt, 76% for 2 steps; (ix) *n*-Bu_4NF, THF, rt, 94%; (x) Dess−Martin periodinane, CH_2Cl_2, rt, 76%.

Scheme 2[a]



[a] (i) CH_2=$CHCH_2MgBr$, (−)-Ipc$_2$BOMe, Et_2O, −100 °C → −78 °C, 82%, 85% ee; (ii) TBSCl, imidazole, DMF, rt, 90%; (iii) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 93%; (iv) (4*R*)-Benzyl-3-propionyloxazolidin-2-one (**11**), *n*-Bu_2BOTf, Et_3N −78 °C → rt; (v) MeNH(OMe)·HCl, Me_3Al, CH_2Cl_2, 0 °C → rt, 75% from **10**; (vi) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C → 0 °C, 100%; (vii) (*i*-Bu)$_2$AlH, THF, −78 °C, 81%; (viii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (**14**), KHMDS, 18-crown-6, THF, −78 °C → rt, 94%; (ix) PPTS, MeOH−THF, 55 °C, then K_2CO_3, 70%; (x) Dess−Martin periodinane, CH_2Cl_2, rt, 85%; (xi) $MeCOC(N_2)PO(OMe)_2$ (**17**), K_2CO_3, MeOH, rt, 84%; (xii) 9-Br-9-BBN (**19**), CH_2Cl_2, 0 °C → rt, 77%.

(1) For a review of marine macrolides, see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(2) Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147.

(3) For total syntheses of **1**, see: (a) Fujiwara, K.; Murai, A.; Yotsu-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770. (b) Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619.

(4) The synthesis of ent-**3** from (*R*)-pantolactone has been reported very recently: Shiina, I.; Shibata, J.; Ibuka, R.; Imai, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 113.

(5) Molander, G. A.; Hahn G. *J. Org. Chem.* **1986**, *51*, 1135.

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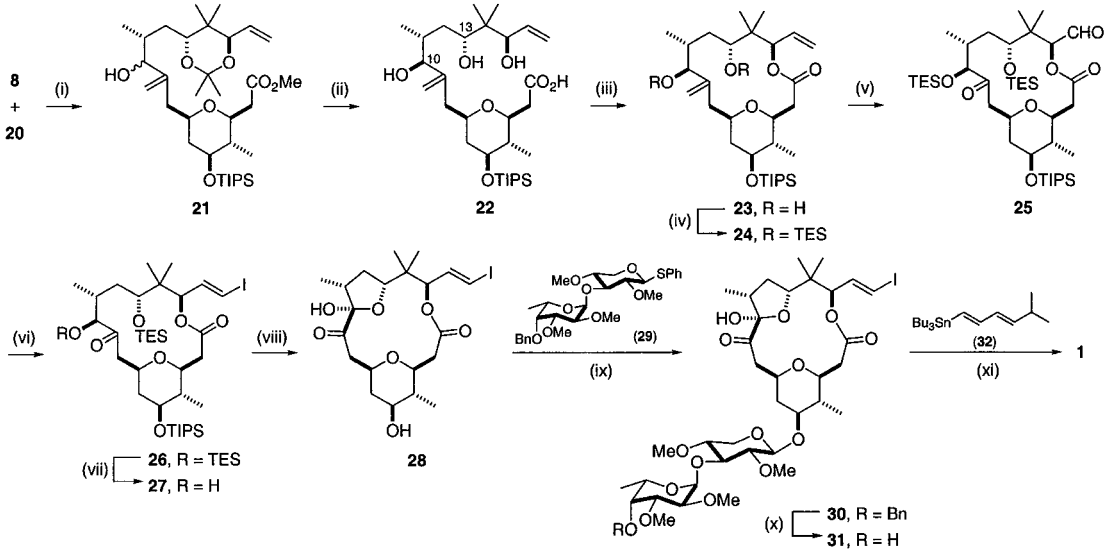
Scheme 3[a]



[a] (i) $CrCl_2$, $NiCl_2$ (cat.), DMF, rt, 79%, dr = 1:1; (ii) PPTS, MeOH, 35 °C, then NaOH, rt, 86%; (iii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt, then DMAP, PhMe, Δ, 75%; (iv) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (v) O_3, CH_2Cl_2−MeOH (3:1), −78 °C, then Ph_3P, −78 °C → rt, 81%; (vi) CHI_3, $CrCl_2$, THF, 0 °C → rt, 76%; (vii) PPTS, MeOH−CH_2Cl_2 (4:1), rt, 88%; (viii) Dess−Martin periodinane, pyr-CH_2Cl_2, 0 °C, then HF·pyr, THF, rt, 88%; (ix) **29**, NBS, MeCN, −35 °C → rt, 27%; (x) DDQ, CH_2Cl_2−H_2O (20:1), rt, 70%; (xi) **32**, $PdCl_2(MeCN)_2$, DMF, rt, 74%.

allylation using (−)-diisopinylcampheylmethoxyborane (Scheme 2),[7] and the resulting (*S*) homoallylic alcohol[8] was protected as its *tert*-butyldimethylsilyl ether before ozonolysis of the terminal alkene furnished aldehyde **10**. Condensation of **10** with the di-*n*-butylboron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**11**)[9] afforded aldol product **12**, a substance that could not be purified without causing retroaldol fragmentation. Oxazolidinone **12** was therefore transformed directly to its easily purified Weinreb amide by reaction with trimethylaluminum and *N*-methoxymethylamine hydrochloride.[10] After protection of the secondary alcohol of this amide as its triisopropylsilyl ether, reduction with DIBAL-H yielded aldehyde **13**. Condensation of **13** with the Gennari−Still phosphonate **14**[11] gave the expected cis α,β-unsaturated ester **15**, and subsequent removal of both *tert*-butyldimethylsilyl ethers under acidic conditions produced a diol which underwent clean cyclization in the presence of methanolic potassium carbonate to produce tetrahydropyran **16**. Oxidation of primary alcohol **16** to an aldehyde, followed by exposure to Ohira's reagent (**17**),[12] furnished alkyne **18** which was reacted with 9-bromo-9-borabicyclo[3.3.1]nonane (**19**)[13] to give vinyl bromide **20**.

Coupling of aldehyde **8** with bromide **20** was carried out under Nozaki−Hiyama−Kishi conditions[14] and gave allylic alcohol **21** as a 1:1 mixture of epimers (Scheme 3). These were separated by column chromatography, and the less polar (10*S*) alcohol was treated with acidic methanol and then saponified to yield trihydroxy carboxylic acid **22**. Macrolactonization of **22** under Yamaguchi conditions[15] afforded exclusively **23** resulting from closure at the C15 hydroxyl group, with no trace of lactones derived from the hydroxyl substituents at either C10 or C13. The structure of **23** was fully confirmed by X-ray crystallographic analysis. A molecular modeling study of the cationic acyl DMAP adduct derived from acid **22**, a putative intermediate in the lactonization, revealed that the reactive conformer leading to **23** is >8.5 kcal mol^{-1} lower in energy than alternative assemblies leading to possible nine- and twelve-membered lactones (Figure 1). Although analogous theoretical treatment of the epimeric (10*R*) acyl DMAP complex indicated a difference in energy between competing lactonization pathways, the (10*R*) epimer corresponding to trihydroxy acid **22** yielded only 46% of the 14-membered lactone together with 16% of the 12-membered macrocycle derived from lactonization at the C13 hydroxyl group.

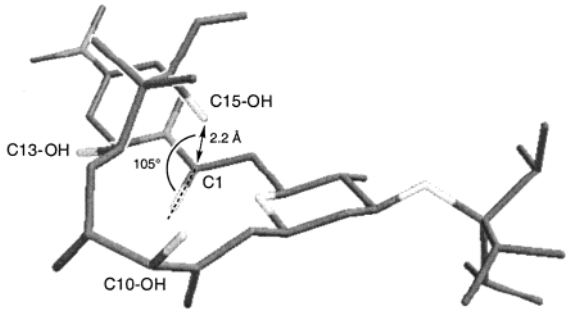


Figure 1. Energy-minimized conformation (Spartan, PM3) of the prelactonization complex from **22** and DMAP. The model is constrained to mimic a Burgi−Dunitz approach trajectory of the C15 hydroxyl at the activated acyl group.

Dihydroxy lactone **23** was protected as its bis-triethylsilyl ether **24** before ozonolysis to furnish keto aldehyde **25**. A Takai reaction[16] of **25** with iodoform gave iodoalkene **26** in which the C10 alcohol was unmasked selectively with acidic methanol. Oxidation of α-hydroxy ketone **27** to a diketone, followed by exposure to hydrogen fluoride, resulted in removal of both silyl groups with concomitant cyclization to hemiketal **28**. The latter was identical in all respects to the substance prepared independently by Murai[3a] and Paquette[3b] in the course of their syntheses of **1**.[17] The C10 epimer of **23** was successfully elaborated to **28**

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(15) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(16) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(17) Data for **28**: $[\alpha]^{22}_D$ −35.6 (*c* 0.09, $CHCl_3$); lit.[3a] $[\alpha]^{22}_D$ −38 (*c* 0.12, $CHCl_3$).

in 23% overall yield by the same route described for **23**. Glycosidation of alcohol **28** with 3-[4-*O*-benzyl-2,3-di-*O*-methyl-α−L-fucopyranosyl]-2,4-di-*O*-methyl-1-thiophenyl-*β*-D-xylopyranose (**29**)[18] gave glycoside **30** as a single *β*-anomer, albeit in low yield. Oxidative debenzylation of **30** followed by Stille coupling of vinyl iodide **31** with dienylstannane **32**[3b] furnished polycavernoside A (**1**), identical by comparison of the ^{1}H NMR spectra with those of the natural material.

In summary, a convergent and efficient route to polycavernoside A has been achieved which employs a remarkably selective macrolactonization of trihydroxy carboxylic acid **22**. Modeling studies provide a plausible explanation for this selectivity.

(18) Disaccharide **29** is the thiophenyl anomer of the sugar used in Murai's synthesis of **1**.[3a]

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Supporting Information Available: Experimental procedures and characterization data for all compounds; X-ray crystallographic data for **23**; molecular modeling data and energy calculations for lactonization of **22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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