A Convergent Total Synthesis of the Macrolactone Disaccharide Toxin (−)-Polycavernoside A

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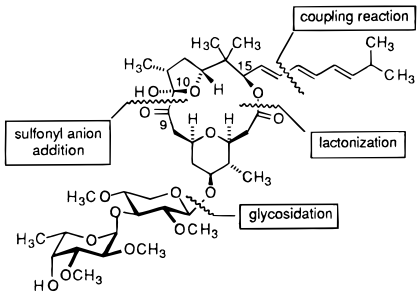
Received February 8, 1999

Polycavernoside A (**1**) was isolated in 1993[1] from a frequently ingested red alga that had suddenly developed seasonally dependent lethal properties.[2] Identification of the gross structural features of the causative toxin as a macrolide disaccharide was accomplished through recourse to detailed NMR analysis.[1] Arrival at its absolute stereochemistry awaited the independent synthesis of the D-fucose-L-xylose subunit by the Murai[3] and Paquette groups[4] and additional preliminary synthetic efforts in both laboratories.[5,6] Reinforcement was derived by the application of the Celmer model of macrolide stereostructure[7] to the unraveled form of the macrolactone.[6] The recently disclosed total synthesis of **1** by Murai[8] demonstrated the previous deductions to be correct.



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We describe herein our independent successful development of a stereoselective protocol for the expeditious construction of this structurally unique substance.

Our retrosynthetic analysis of polycavernoside A took early cognizance of the acyloxy triene unit in the northeastern quadrant. This undoubtedly sensitive functionality was destined therefore to be introduced late in the synthesis via an appropriate coupling reaction at the indicated site. Beyond reliance on the cyclization of a fully elaborated seco acid and stereoselective glycosidation, the critical C9−C10 bond that interlinks a selectively masked α-diketone would require early assembly under conditions that would not promote β-elimination with cleavage of the tetrahydropyran ring. We had previously determined that 1,3-dithiane technology cannot be satisfactorily applied here,[6] and recourse to a sulfonyl anion alternative was therefore projected.

To this end, lactone **2**, which is readily available from L-malic acid,[9] was treated with 3 equiv of allylmagnesium bromide at −78 °C, and the resulting lactol was directly reduced with triethylsilane in the presence of $SnCl_4$ to give **3** (Scheme 1). This methodology served to orient the allyl substituent equatorially in a highly diastereoselective manner. Once the conversion of **3** to **4** was achieved, the iodide was formed[10] and subjected to displacement with lithiated methyl phenyl sulfone to deliver **5**.

Attention was simultaneously directed toward elaborating **6**[6] into the companion electrophilic partner. Reduction with lithium borohydride generated the related diol, which was pivaloylated as in **7** and subsequently converted efficiently into aldehyde **8**. Wittig olefination of this intermediate followed by asymmetric dihydroxylation of the terminal olefin[11] expectedly set the appropriate C15 stereochemistry in **9** under reagent control. The next transformation required was the fully regioselective introduction of two different silyl-protecting groups. Once **10** was in hand, the pivaloyl functionality was reductively cleaved with Dibal-H to deliver a primary alcohol whose perruthenate oxidation[12] afforded the desired fully elaborated aldehyde **11**. Condensation of the lithium salt of **5** with **11** in THF at −78 °C gave rise to an alcohol which was directly oxidized with the Dess−Martin periodinane reagent[13] to provide **12**.

At this stage, the key question centered around the timing of the steps that would lead most efficaciously to **1**. Although many pitfalls were uncovered,[14] it did prove practical to deprotect the C15 hydroxyl in advance of cleavage of the allylic double bond (Scheme 2). This two-step sequence furnished **13**, making possible chemoselective oxidation of the aldehyde with buffered sodium chlorite[15] and macrocyclization under modified Yamaguchi conditions.[16] Interestingly, the macrolactone **14** was produced as a single diastereomer at C9 as a consequence of concomitant enolate equilibration. Subsequent exposure of **14** to the HF·pyridine reagent served to unmask the primary hydroxyl and enable the advanced aldehyde **15** to be generated. When this compound was added to an excess of the Takai reagent,[18] stereoselective iodovinylation as in **16** was achieved without detectable epimerization at C15. This newly introduced functionality proved to be adequately robust to withstand the conditions needed for the oxidative desulfonylation[19] of **16** to deliver the requisite α-diketone intermediate, as well as the DDQ oxidation[20] that made possible the arrival at **17**. The five-membered cyclic acetal was produced exclusively within the usual limits of spectroscopic detection. The stereochemical assignment to C10 in **17** was advanced on the basis of the strong NOE interaction illustrated which parallels that found in **1**.

Completion of the synthesis involved the NBS-promoted glycosidation[21] with the activated disaccharide **18**.[22] The protocol

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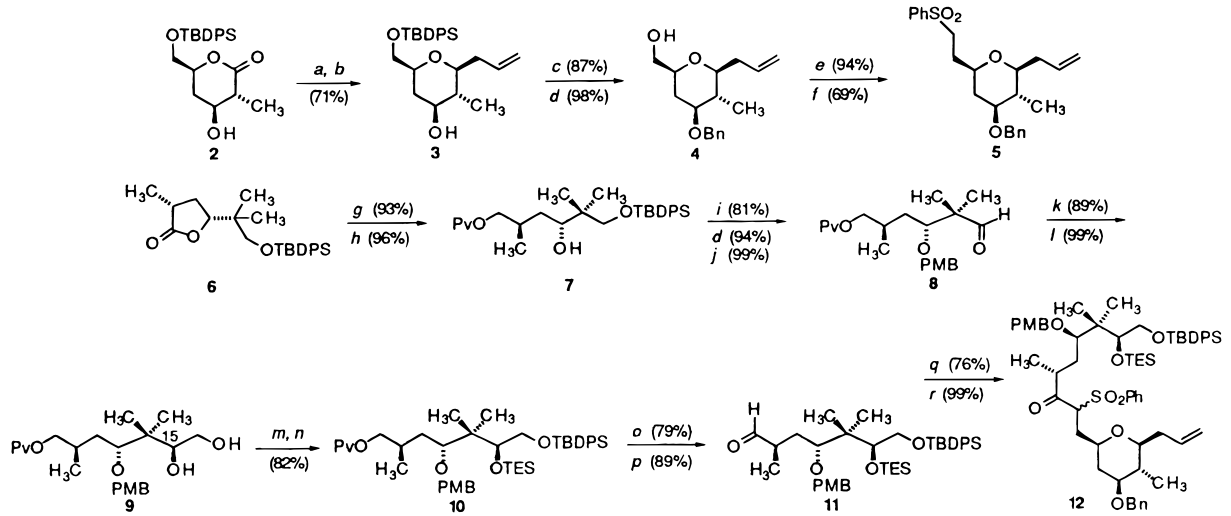
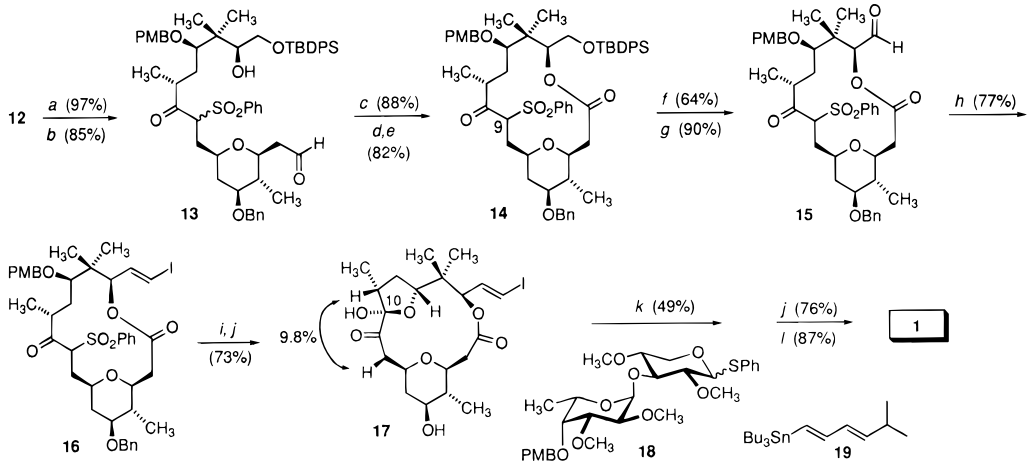
10.1021/ja990384x CCC: $18.00
Published on Web 04/27/1999

Scheme 1[a]



[a] CH_2=$CHCH_2MgBr$, THF, −78 °C. [b] Et_3SiH, $SnCl_4$, CH_2Cl_2, −78 °C → 20 °C. [c] NaH, BnBr, NaI, THF, reflux. [d] TBAF, THF. [e] Ph_3P, I_2, imid, C_6H_6. [f] $LiCH_2SO_2Ph$, THF, HMPA, rt. [g] $LiBH_4$, ether, CH_3OH. [h] PvCl, py, CH_2Cl_2. [i] 4-$CH_3OC_6H_4CH_2OC$(=NH)CCl_3, (TfOH), ether. [j] Swern. [k] Ph_3P=CH_2, THF. [l] OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH, H_2O, 0 °C. [m] TBDPSCl, imid, THF. [n] TESCl, imid, DMAP, DMF. [o] $(i\text{-Bu})_2AlH$, THF, −30 °C. [p] TPAP, NMO, 4 Å MS, CH_2Cl_2. [q] *n*-BuLi, **5**, THF, −78 °C. [r] Dess−Martin periodinane, CH_2Cl_2.

Scheme 2[a]



[a] (TsOH), CH_3OH, CH_2Cl_2. [b] OsO_4, NMO, THF, H_2O; $NaIO_4$. [c] NaClO2, NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH, H_2O, 0 °C. [d] 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 25 °C. [e] DMAP, toluene, 110 °C. [f] Hf•py, THF, py. [g] Dess−Martin periodinane, CH_2Cl_2. [h] $CrCl_2$, CHI_3, THF. [i] KO-*tert*-Bu, Davis oxaziridine, THF, 0 °C. [j] DDQ (excess), CH_2Cl_2, H_2O. [k] NBS, 4 Å MS, **18**, CH_3CN, −20 °C → 0 °C. [l] $PdCl_2(CH_3CN)_2$, **19**, DMF, rt, 4 h.

delivered exclusively the β-anomer in 49% yield at 50% conversion. Deprotection of the glycoside with DDQ proceeded uneventfully. Recourse was made to Stille coupling[23] in order to complete the synthesis. The first indications that this step would be more difficult than usual came from the lack of success realized in promoting carbon−carbon formation to dienylstannane **19**[24] with $Pd_2(dba)_3/AsPh_3$[25] or various Cu(I) salts.[26] However, when recourse was made to bis(acetonitrile)dichloropalladium(II) in DMF at 25 °C,[27] the target **1** was obtained exclusively in 80% yield. The fully synthetic material was identified by direct comparison of its 500 MHz ^1H and 125 MHz ^{13}C NMR spectra in CD_3CN to those of authentic polycavernoside A. In addition, a negative optical rotation, $[\alpha]^{25}_D$ −34.5 (*c* 0.06, CH_3CN), in close accord with the reported value was recorded.[28] Finally, we call attention to the fact that the late-stage conjoining of **17**, **18**, and **19** might well be exploited to prepare new analogues of **1** for biological evaluation.

Acknowledgment. This contribution is dedicated to the memory of Donald L. Fields, a true scientific innovator and loyal friend. This research was made possible by financial support from Eli Lilly and Company. L.B. is the recipient of a postdoctoral fellowship from the Ministère de l'Enseignement Supérieure et de la Science (FCAR, Québec, Canada).

Supporting Information Available: Spectroscopic data for the advanced intermediates **5**, **11**−**17** and **1**, procedural details for the macrocyclization, glycosidation, and Stille coupling steps, and copies of the ^1H and ^{13}C NMR spectra of synthetic and natural (−)-**1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990384X

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