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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF POLYCAVERNOSIDE A. ENANTIOSELECTIVE SYNTHESIS OF THE DISACCHARIDE COMPONENT

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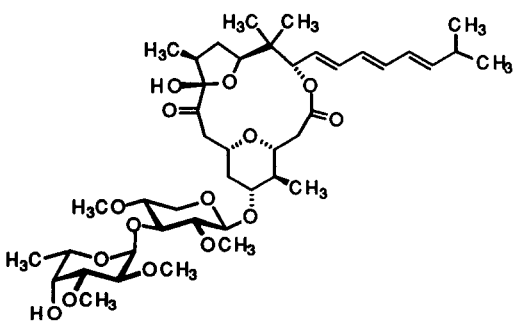
Abstract: Adaptation of the Mukaiyama-Nicolaou protocol to the coupling of a monounprotected thioglycoside to a glycosyl fluoride is capable of delivering the unusual disaccharide present in the title toxin.

In the early spring the red alga *Polycavernosa tsudai* is particularly unsuited for human consumption because of its incorporation at that time of the maximum concentration of a powerful toxin recently identified as polycarvernoside A (**1**).[2] The unusual molecular architecture of this macrolide disaccharide consists of a heretofore unprecedented 3,5,7,13,15-pentahydroxy-9,10-dioxotricosanoic acid-derived aglycone and a glycosidic residue in which a 2,3-di-*O*-methyl-α-L-fucopyranose is linked 1 → 3 to a 2,4-di-*O*-methyl-β-D-xylopyranose. An enantioselective total synthesis of this unique substance would provide confirmation of the absolute configurational assignment and make possible the preparation of structural variants that could lend insight into its mechanism of action.



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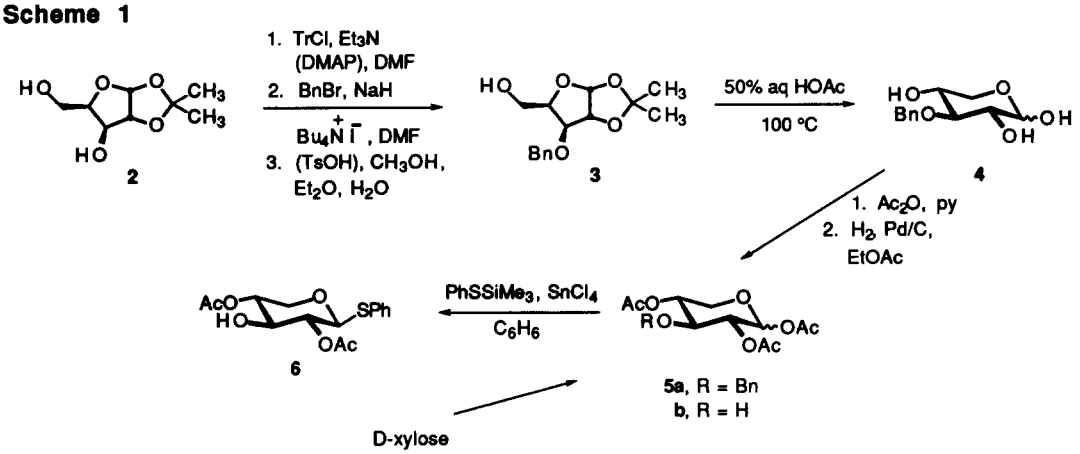
The sensitive functionality that adorns the aglycone and the desire to implement a convergent synthesis led us to view the primary disconnection to reside between the aglycone and the disaccharide. Herein is described our successful acquisition of the disaccharide in its activated thioglycoside form. Companion efforts to prepare the aglycone will be reported in due course.[3,4]

Scheme 1



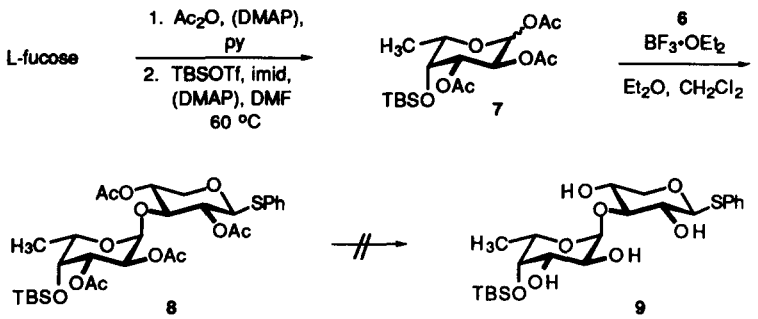
The acceptor glycoside **6** was approached from two directions (Scheme 1). Commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose (**2**) was initially transformed into **3** by sequential tritylation[5] of the primary carbinol, O-benzylation, and detritylation[6] (81% overall). Upon warming **3** in 50% aqueous acetic acid, hydrolysis of the isopropylidene unit occurred, making possible equilibration to the pyranose form **4**. Direct acetylation gave rise to **5a** (85% for 3 steps), hydrogenolysis of which furnished **5b** (97%). Treatment of **5b** with phenylthiotrimethylsilane and $SnCl_4$ in dry benzene[7] made **6** available without complication (60%).

A more expeditious route to **5b** took advantage of the selectivity with which D-xylose undergoes controlled acetylation. In our hands, the yield of this triacetate (21%) was not improved in relation to that realized in the developmental stages.[8]

Existing literature reports suggested that both **7** and **13** might be suitable glycosyl donors. Acetate **7** proved to be readily accessible by means of a two-step sequence involving selective acetylation of the equatorial hydroxyls in L-fucose, followed by silylation of the lone remaining axial OH group (Scheme 2). The selective formation of **8** in the presence of boron trifluoride etherate[9] (41% conversion, 96% efficiency) requires that C-O bond formation occur exclusively via axial addition to the oxonium ion intermediate. Despite the success of this coupling, the conversion of **8** into **9** could not be satisfactorily realized because saponification of the acetate groups was unavoidably met with migration of the silyl functionality. Three products were formed as a consequence of each possible permutation resulting from translocation about the fucose ring. For lack of a practical solution to this problem, our focus turned instead to the obtention of **13.**

This decision led us to peracetylate L-fucose,[10] expose this intermediate to the combined action of thiophenol and tin(IV) chloride, and subsequently to effect saponification of the thioglyco-

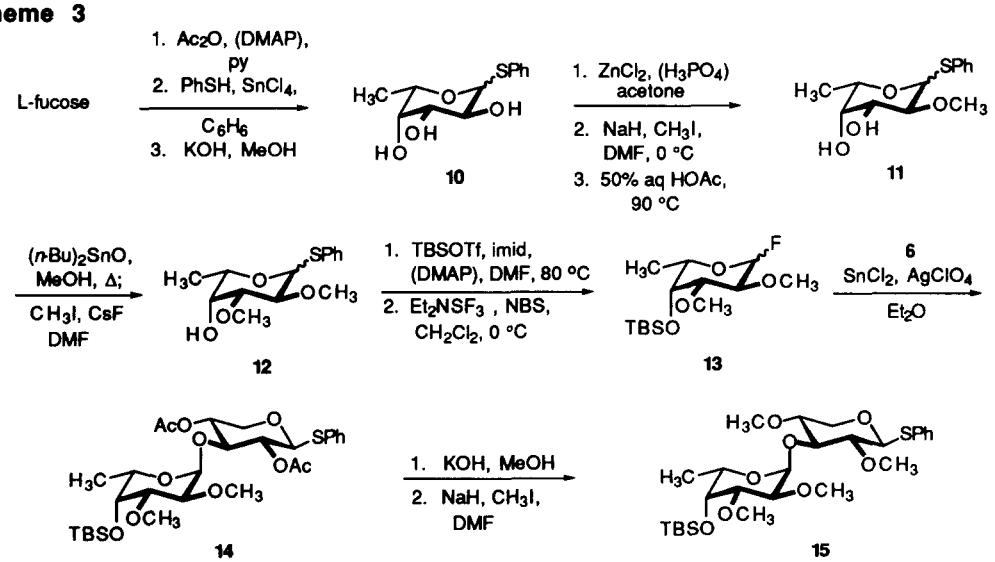
Scheme 2



side[7] so formed to provide **10** (91% for 3 steps, Scheme 3). Formation of the 3,4-acetonide, O-methylation of the C-2 carbinol, and hydrolytic removal of the protecting group[11] furnished diol **11** (83%). At this point, advantage was taken of the high propensity exhibited by O-stannylene acetals for equatorial O-alkylation[12] in order to achieve selective formation of the 3,4-dimethoxy thioglycoside **12** (99%). The substitution pattern and stereochemistry present in **12** was corroborated by semiselective DEPT-45 experiments. Protection of the axial alcohol with a *tert*-butyldimethylsilyl moiety gave the fully protected pyran (77%), which could be transformed into fluoride **13** (88%) with diethylaminosulfur trifluoride and N-bromosuccinimide.[13]

The coupling of **6** with **13** proceeded well under the Mukaiyama conditions[14] to give the desired disaccharide **14** as the only detectable anomer (57%). Ultimate conversion to **15** was uneventful (84% for 2 steps). Three-bond-coupling correlation between the H-2 and H-4 atoms in

Scheme 3



the xylose subunit to the methoxyl-substituted carbons, as determined by semiselective DEPT-45 experiments, verified the methoxyl substitution pattern. H-3 in the xylose ring was similarly correlated to the fucosyl anomeric carbon to confirm further the structural assignment to **15**.

The second-stage coupling of **15** to aglycone building blocks is currently under active investigation.[15]

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