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Total Synthesis of Polycavernoside A, A Lethal Toxin of the Red Alga *Polycavernosa tsudai*

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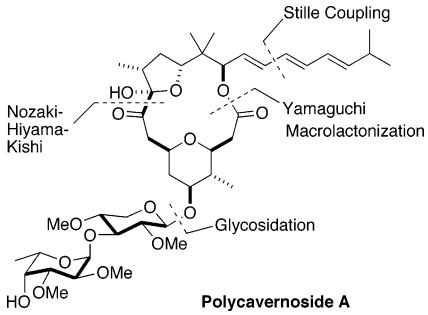

Two approaches to the synthesis of the aglycon **120** of polycavernoside A (**1**) were developed, only one of which was completed. The successful "second-generation" route assembled the aglycon seco acids **102** and **106** via Nozaki−Hiyama−Kishi coupling of aldehyde **70**, prepared from methyl (*S*)-3-hydroxy-2-methylpropionate (**72**) and (*S*)-pantolactone (**73**), with vinyl bromide **71**. The latter was obtained from a sequence which commenced from the silyl ether **24** of 3-hydroxypropionaldehyde and entailed cyclization of (*Z*)-ζ-hydroxy-α,β-unsaturated ester **82**. Regioselective Yamaguchi lactonization of trihydroxycarboxylic acids **102** and **106** and subsequent functional-group adjustments led to macrolactone **120**, to which the fucopyranosylxylopyranoside moiety was attached. Stille coupling of the glycosidated aglycon **128** with dienylstannane **129** furnished polycavernoside A in a synthesis for which the longest linear sequence was 25 steps. The overall yield to lactone **120** was 4.7%.

Introduction

In early 1991, 13 people were unexpectedly poisoned after consuming an edible seaweed purchased from a food market near Tanguisson Beach on the island of Guam.[1] The seaweed responsible for this incident was identified as the red alga *Polycavernosa tsudai* (formerly *Gracilaria edulis*), which is widely consumed in the area. Curiously, no previous reports of toxicity associated with this food source had been recorded. The individuals poisoned by this alga exhibited severe neuropathic symptoms, and three of them died after suffering cardiac arrest. Preliminary examination of the ingested alga revealed the presence of a virulent toxin, and a collection of *P. tsudai* made soon after the outbreak led to the isolation of two substances, polycavernosides A and B, which elicited very similar symptoms in a rodent bioassay to those seen in the human victims of the Tanguisson Beach episode.[2] Skillful structural analysis of the very small quantity of available polycavernoside A (**1**) by Yasumoto and co-workers resulted in determination of its planar structure and enabled a tentative stereochemical assignment to be made.[2,3] A second collection of *P. tsudai* from Tanguisson Beach by Yasumoto in 1992 produced a sufficient quantity of polycavernoside B and three additional congeners to establish that these substances all shared the same aglycon with **1** and differed only in the disaccharide moiety.[4] However, subsequent extractions of *P. tsudai* yielded no polycavernosides at all, and it now appears that production of these metabolites by the seaweed was a transient phenomenon.

(1) Haddock, R. L.; Cruz, O. L. T. *Lancet* **1991**, *338*, 195.

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

(3) Yotsu-Yamashita, M.; Yasumoto, T.; Haddock, R. L. In *34th Symposium on the Chemistry of Natural Products*; Tokyo: 1992; p 612.

(4) Yotsu-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563.

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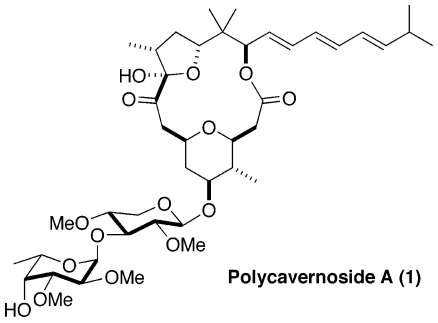


Polycavernoside A (1)

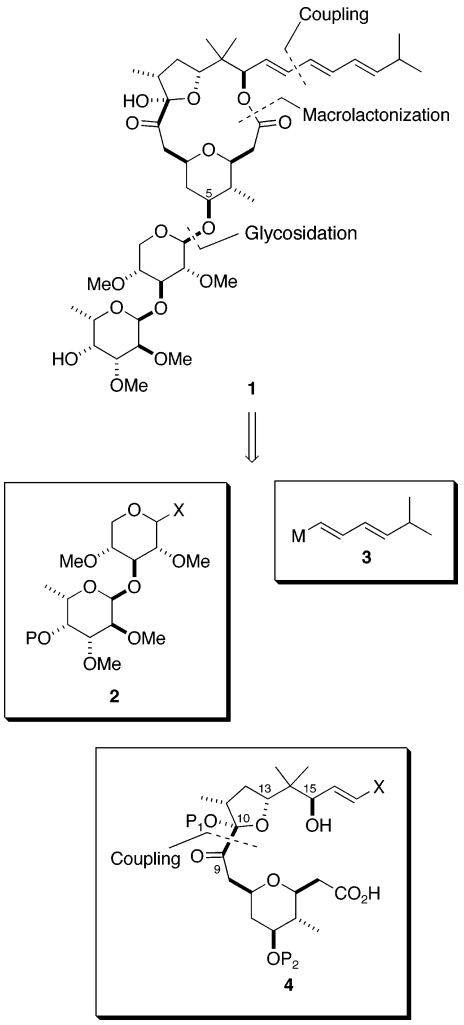
With the natural source of polycavernosides having vanished, toxicological studies of **1** and its congeners remain incomplete, and the precise cause of the human fatalities in Guam is uncertain. This situation presents an irresistible invitation to synthesis, and the challenge has been met by two elegant syntheses of polycavernoside A, the first by Murai[5] and the second by Paquette.[6,7] Our own approach to **1** differs significantly from both of these syntheses and has been disclosed in preliminary form.[8] We now describe details of our approach which led to the successful asymmetric synthesis of polycavernoside A and which confirmed its absolute configuration as represented by **1**.

The synthesis plan for polycavernoside A as initially conceived is shown in Scheme 1, but in the event, this blueprint served only to guide us toward the major subunits, i.e., **2**, **3**, and **4**, and left the critical issue of uniting them to improvisation. Attachment of the disaccharide appendage to the aglycon core of polycavernoside A appeared to be the most straightforward connection and was envisioned by glycosidation at C-5 with an activated form of a suitably protected fucopyranosylxylopyranoside **2**. A late-stage elaboration of the all-trans triene side chain was projected via Stille coupling using a metallodiene **3**, and the aglycon itself would be assembled by macrolactonization of seco acid **4** in a process which we hoped could be carried out with much of the polycavernoside functionality already in place. A key question with **4** was how the bond between C-9 and C-10 would be forged since this was the locus at which we planned to connect northern and southern fragments of the seco acid. Two methods for this bond construction were examined, only one of which was successful.

Results

First-Generation Approach. At the outset of this study, the absolute configuration of the aglycon of polycavernoside A was not known and even the configuration of the disaccharide portion was not settled with certainty. An early attempt to correlate the configuration of the sugar with that of the aglycon through an NMR experiment was less than conclusive and forced us to make an arbitrary selection of aglycon absolute configuration for the purpose of synthesis. In consequence, our first attack

SCHEME 1

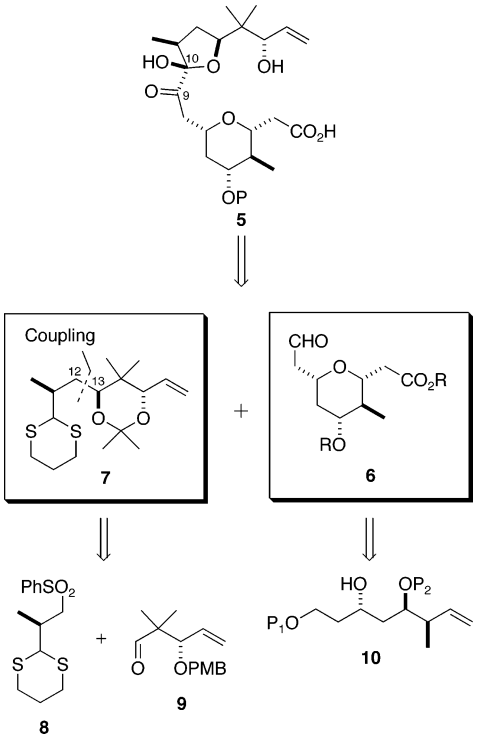


on the aglycon of polycavernoside A became focused on the enantiomeric version of the structure now known to be correct (Scheme 2). The two subunits initially programmed for assembling seco acid **5** were tetrahydropyran **6** and dithiane **7**, the key C-9,10 bond formation being performed via nucleophilic attack at the aldehyde of **6** by the α-thianyl anion of **7**. The latter was foreseen as the product of two primary subunits, sulfone **8** and aldehyde **9**.

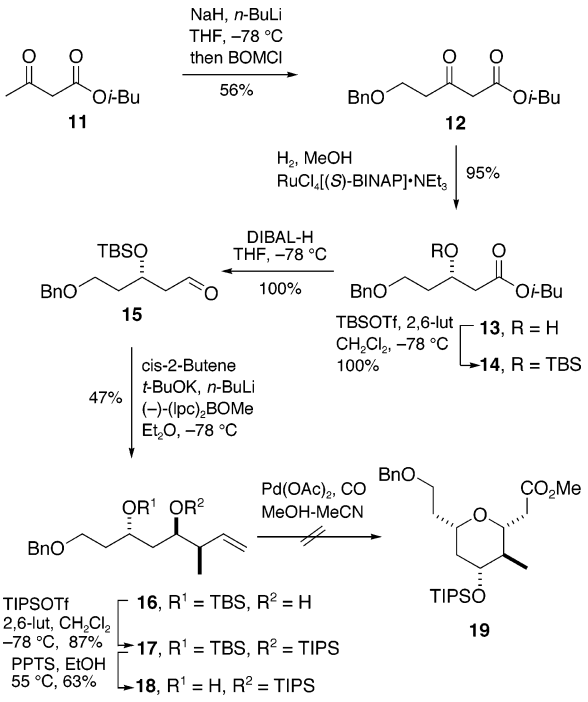
The Southern Subunit. Our first plan for creating the tetrahydropyran of **6** was based on a reaction, the intramolecular Pd(II)-mediated alkoxycarbonylation of a 6-hydroxy alkene,[9] which had resulted in a favorable outcome for us in another context[10] and for this we needed to prepare a protected 4,6,8-trihydroxy-3-methyloctene such as **10**. The starting point for this objective was isobutyl acetoacetate (**11**). Alkylation of the dianion of **11** with chloromethyl benzyl ether afforded **12**, which was hydrogenated with Noyori's Ru(II)−(*S*)-BINAP catalyst[11,12] to give (*S*)-hydroxy ester **13** in excellent yield and very high enantiomeric excess (Scheme 3).After silylation

(5) Fujiwara, K.; Murai, A.; Yotsu-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770.
(6) Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619.
(7) Paquette, L. A. *Chemtracts* **2002**, *15*, 345.
(8) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593.
(9) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035.
(10) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003.
(11) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

SCHEME 2

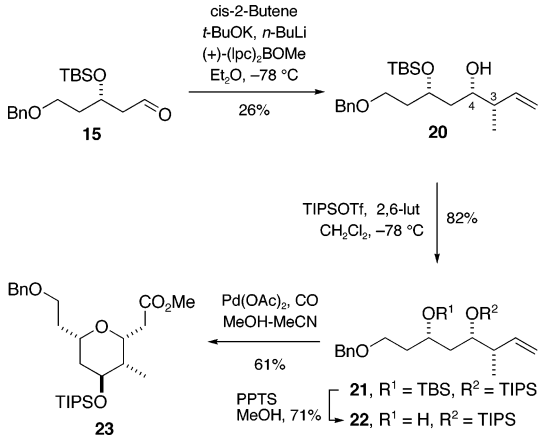


SCHEME 3



of alcohol **13**, the ester of **14** was reduced to aldehyde **15**, which was subjected to Brown asymmetric crotylation[13] to furnish homoallylic alcohol **16** as the predominant diastereomer. Protection of this alcohol as its triisopropylsilyl (TIPS) ether **17** was followed by selective removal of the *tert*-butyldimethylsilyl (TBS) ether to produce the 1-octene derivative **18**. Unfortunately, all

SCHEME 4



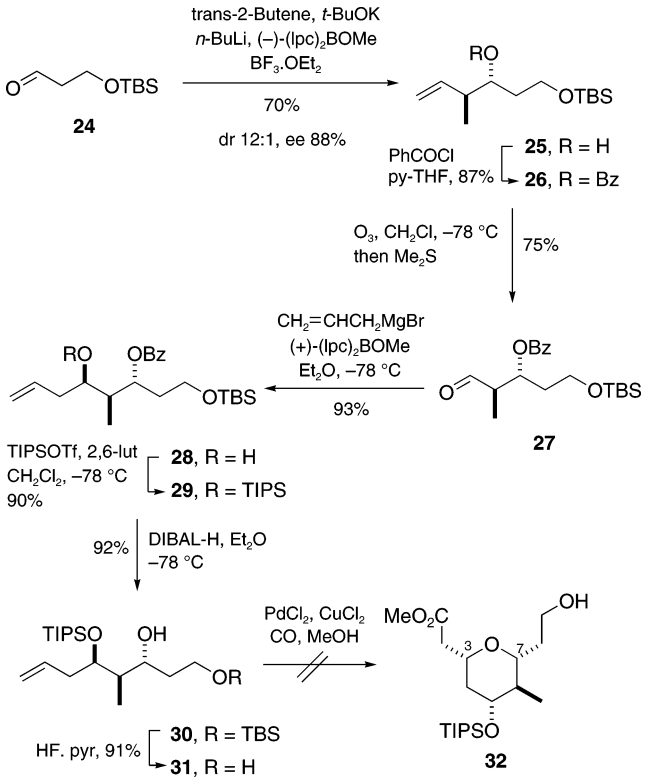
attempts to effect intramolecular alkoxycarbonylation of **18** were unsuccessful, and no tetrahydropyran resembling **19** could be detected in the complex mixture of products.

This result was puzzling in view of the fact that the substituents in **18** were aligned in a manner which would have resulted in an all-equatorial arrangement of the four substituents in tetrahydropyran **19**. Suspicious that there was opposition to the cyclization of **18** due to the configuration of its substituents, we prepared its diastereomer **22** in which the substituents at C-3 and C-4 were reversed in configuration from **18** (Scheme 4). The hydroxy alkene **22** obtained from **15** via **20** and **21** underwent smooth intramolecular alkoxy carbonylation mediated by palladium acetate in methanol−acetonitrile to afford tetrahydropyran **23**, in which two of the tetrahydropyran substituents must be axial. Although the contrasting results with **18** and **22** appear counterintuitive, a possible explanation for the failure of **18** to undergo cyclization may lie in an unfavorable steric interaction in the transition state between the initially formed palladium-complexed alkene and the adjacent methyl substituent.[14] This rationale suggested that relocating the methyl group to a site more remote from the alkene would remove the encumbrance associated with alkoxy carbonylation of **18**. To test this hypothesis, the preparation of a new substrate which reversed the direction of cyclization was carried out. This is shown in Scheme 5.

The known aldehyde **24**[15] was reacted with Brown's (*E*)-crotyldiisopinocampheylborane,[13] and the resulting alcohol **25** was esterified with benzoyl chloride to give anti benzoate **26** in high diastereomeric excess and enantiomeric purity. After ozonolysis of **26**, the aldehyde **27** was subjected to asymmetric allylation and the homoallylic hydroxyl group of **28** was protected as its silyl ether **29**. Reductive cleavage of the benzoate from **29** afforded a hydroxy alkene **30**, which we had hoped would be a suitable substrate for alkoxy carbonylative cyclization. However, exposure of this substance to $PdCl_2$, CO, and MeOH gave a complex mixture in which the silyl groups appeared to have migrated and/or were lost. An attempted cyclization of the diol **31** from **30** in which both

(12) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549.
(13) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(14) White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463.
(15) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301.

SCHEME 5

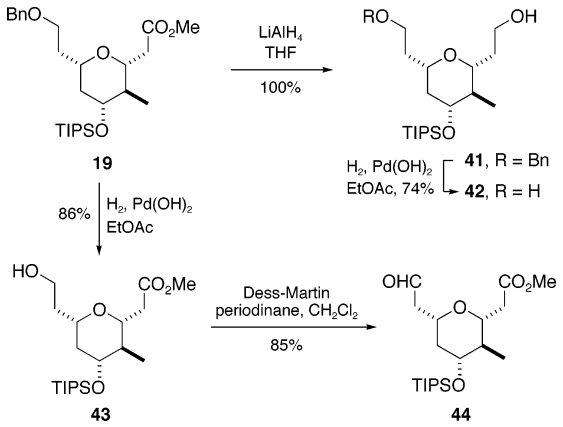


the benzoate and TBS group had been removed also failed to yield tetrahydropyran **32**.

The difficulty associated with preparing a tetrahydropyran subunit corresponding to **6** bearing four correctly placed substituents in the desired relative configuration for polycavernoside A was exacerbated by the fact that, even if **32** could be acquired, oxidation states of side chains at C-3 and C-7 would need to be reversed in order to reach **6**. These shortcomings persuaded us to explore a different strategy to the southern portion of polycavernoside A, which relied upon a more conventional cyclization of a ζ-hydroxy-α,β-unsaturated ester for constructing the tetrahydropyran nucleus. This sequence is shown in Scheme 6.

An Evans aldol coupling between the previously prepared aldehyde **15** (Scheme 3) and the enol borinate of

SCHEME 7

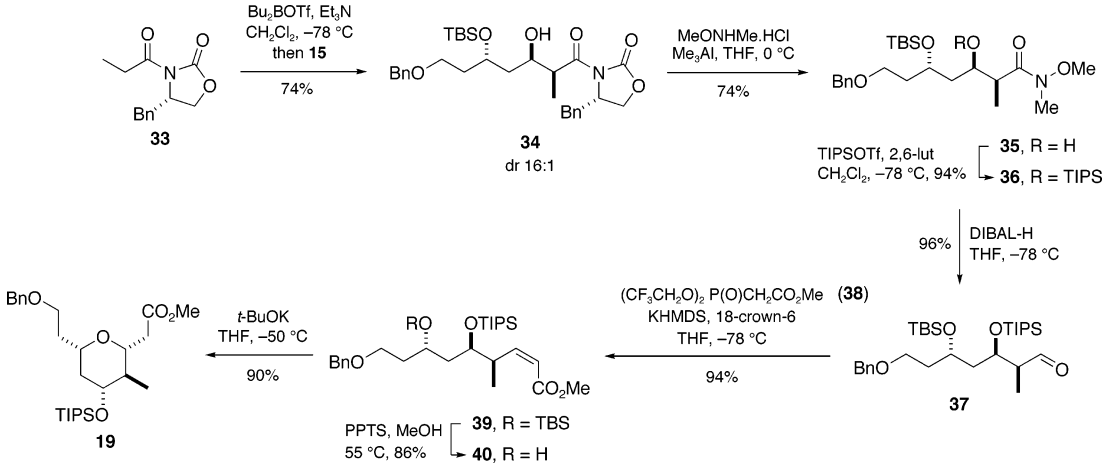


(*S*)-3-propionyl-4-benzyloxazolidin-2-one (**33**)[16] gave **34**, which was converted to Weinreb amide **35**.[17] Silylation of the secondary alcohol yielded **36**, and reduction of the amide afforded aldehyde **37**, which was subjected to condensation with the Still-Gennari phosphonate **38**[18] to give (*Z*)-α,β-unsaturated ester **39** in excellent yield. Selective cleavage of the TBS ether from **39** furnished cyclization substrate **40**, and when this hydroxy ester was exposed to potassium *tert*-butoxide in THF at low temperature it underwent exceptionally clean cyclization to produce tetrahydropyran **19** as the sole detectable stereoisomer. Cyclization of the (*E*)-α,β-unsaturated ester isomeric with **40** was much less satisfactory in terms of yield and stereoselectivity, an observation in concert with a result we have noted previously.[19]

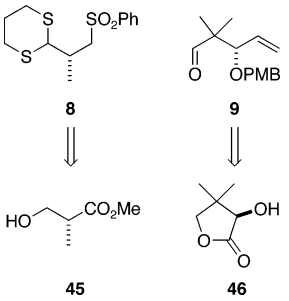
A proof of structure of tetrahydropyran **19** was initially sought through its conversion to alcohol **41**, obtained by hydride reduction of the ester appendage (Scheme 7). However, neither **41** nor diol **42**, prepared by hydrogenolysis of the benzyl ether **41**, afforded crystals suitable for X-ray analysis. Fortunately, when benzyl ether **19** was subjected to hydrogenolysis and alcohol **43** was oxidized,[20] it produced the crystalline aldehyde **44**. X-ray crystallographic analysis fully confirmed the stereostructure of **44**, which now became the de facto subunit representing the southern portion of polycavernoside A.

The Northern Subunit. Our strategy for constructing the northern segment of polycavernoside A aglycon

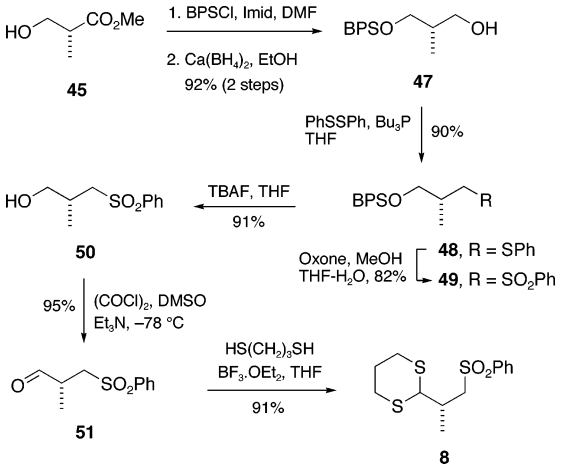
SCHEME 6



SCHEME 8



SCHEME 9

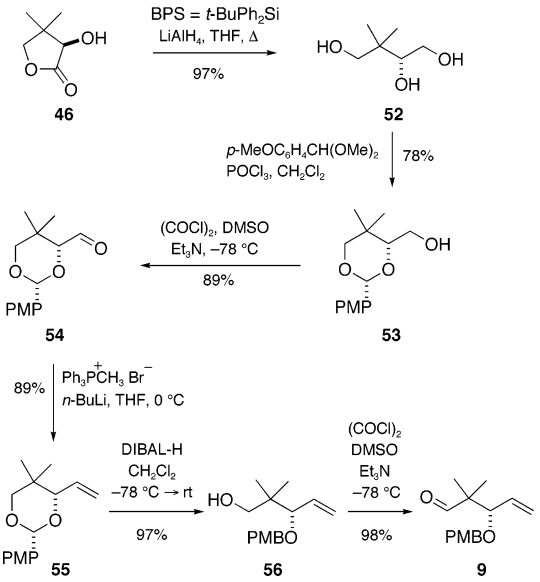


hinged upon coupling of sulfone **8** with aldehyde **9** and is shown in Scheme 2. An attractive feature of this plan is that **8** can be envisioned as a "double-headed" nucleophile, first as a sulfonyl anion for linkage with **9** to form the C12−C13 bond and then as a dithianyl anion for connection of the northern subunit **7** to aldehyde **6**. A direct route to **8** was foreseen from methyl (*R*)-3-hydroxy-2-methylpropionate (**45**), and access to **9** appeared to be feasible from (*R*)-(−)-pantolactone (**46**) (Scheme 8).

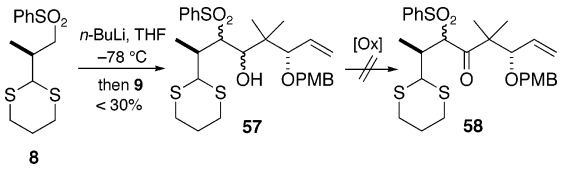
The synthesis of **8** commenced with protection of **45** as its *tert*-butyldiphenylsilyl (BPS) ether, after which the ester was reduced with calcium borohydride[21] to yield alcohol **47** (Scheme 9). Replacement of the hydroxyl function by a phenylthio group and then treatment of sulfide 48 with oxone gave sulfone **49**.[22] Cleavage of the silyl ether from **49** followed by Swern oxidation[23] of alcohol **50** afforded aldehyde **51**, which was advanced to dithiane **8** by reaction with 1,3-propanedithiol in the presence of boron trifluoride etherate.

Aldehyde **9** was prepared in six steps from (−)-pantolactone (**46**) as shown in Scheme 10. The triol **52**,

SCHEME 10



SCHEME 11

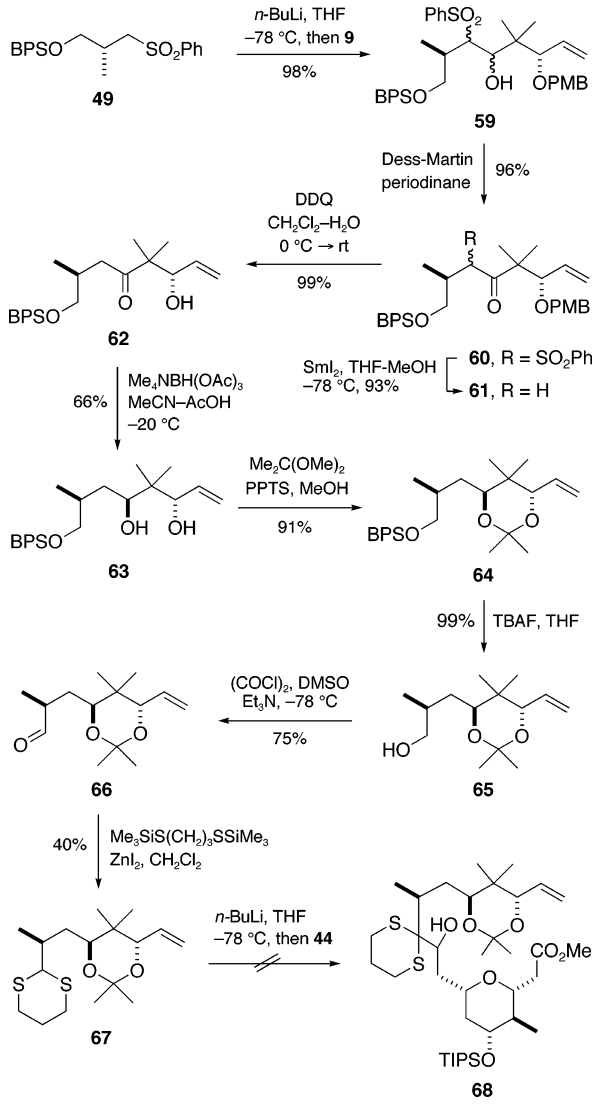


obtained by reduction of **46**, condensed with *p*-methoxybenzaldehyde dimethyl acetal to give the six-membered cyclic acetal **53** exclusively.[24] The latter underwent Swern oxidation[23] to aldehyde **54**, and subsequent Wittig methylenation afforded alkene **55**. Reductive cleavage of acetal **55** with diisobutylaluminum hydride occurred with complete regioselectivity[25] to deliver primary alcohol **56**, which was oxidized to aldehyde **9** under Swern conditions.

Addition of the lithio anion from **8** to aldehyde **9** produced hydroxy sulfone **57** as a mixture of four diastereomers in disappointingly low yield (Scheme 11), and our intended advance from this intermediate, already complicated by inefficiency, met with another obstacle resulting from the fact we could find no way to oxidize the sterically encumbered alcohol **57** to keto sulfone **58** without causing oxidation at sulfur. The problem was overcome by returning to sulfone **49**, the anion of which coupled smoothly with **9** to give **59**, again as a mixture of all stereoisomers (Scheme 12). In this case, oxidation of **59** to keto sulfone **60** was straightforward, as was subsequent reductive cleavage of the sulfonyl group with samarium diiodide,[26] which yielded ketone **61**. Cleavage of the *p*-methoxybenzyl ether followed by directed reduction of the resulting *β*-hydroxy ketone **62** with tetramethylammonium triacetoxyborohydride[27] furnished antidiol **63**, which was subsequently protected as its acetonide **64**. The silyl ether was cleaved from **64**, and

(16) Gage, J. R.; Evans, D. A. In *Organic Syntheses*; John Wiley & Sons: New York, 1993; Collect. Vol. 8, p 339.
(17) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(18) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(19) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750−7760.
(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(21) Brown, H. C.; Narasimha, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.
(22) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(24) Lavall_e, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679.
(25) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Vehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
(26) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(27) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

SCHEME 12



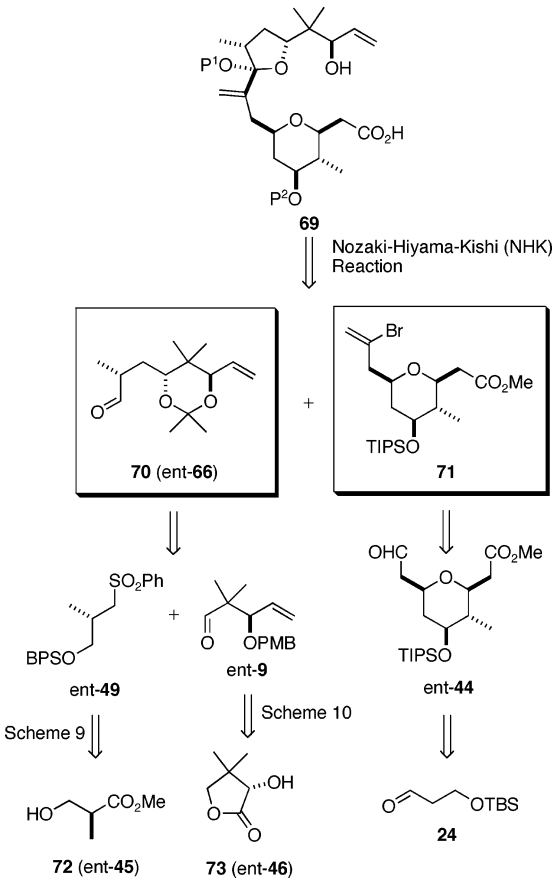
the resulting primary alcohol **65** was oxidized to aldehyde **66**. The latter was reacted with the bistrimethylsilyl thioether of 1,3-propanedithiol in the presence of zinc iodide to afford dithiane **67**.[28]

Here, unfortunately, our first approach to polycavernoside A met its demise; for although dithiane **67** could be deprotonated, the lithio derivative proved to be surprisingly unreactive. In particular, no coupling product **68** could be coaxed from a mixture containing the anion of **67** and aldehyde **44**. A speculative rationale for the unreactive nature of the lithio anion of **67** is that an exceptionally stable six-membered chelate is formed between the metal and the proximal ketal oxygen atom in this structure. In any event, we were now confronted with an impasse, which necessitated a major revision of our original strategy for connecting the northern and southern portions of polycavernoside A.

Second-Generation Approach. In 1995, the uncertainty surrounding the absolute configuration of polycavernoside A began to clear, thanks to seminal studies by Murai and co-workers. First, it was shown that only

(28) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

SCHEME 13

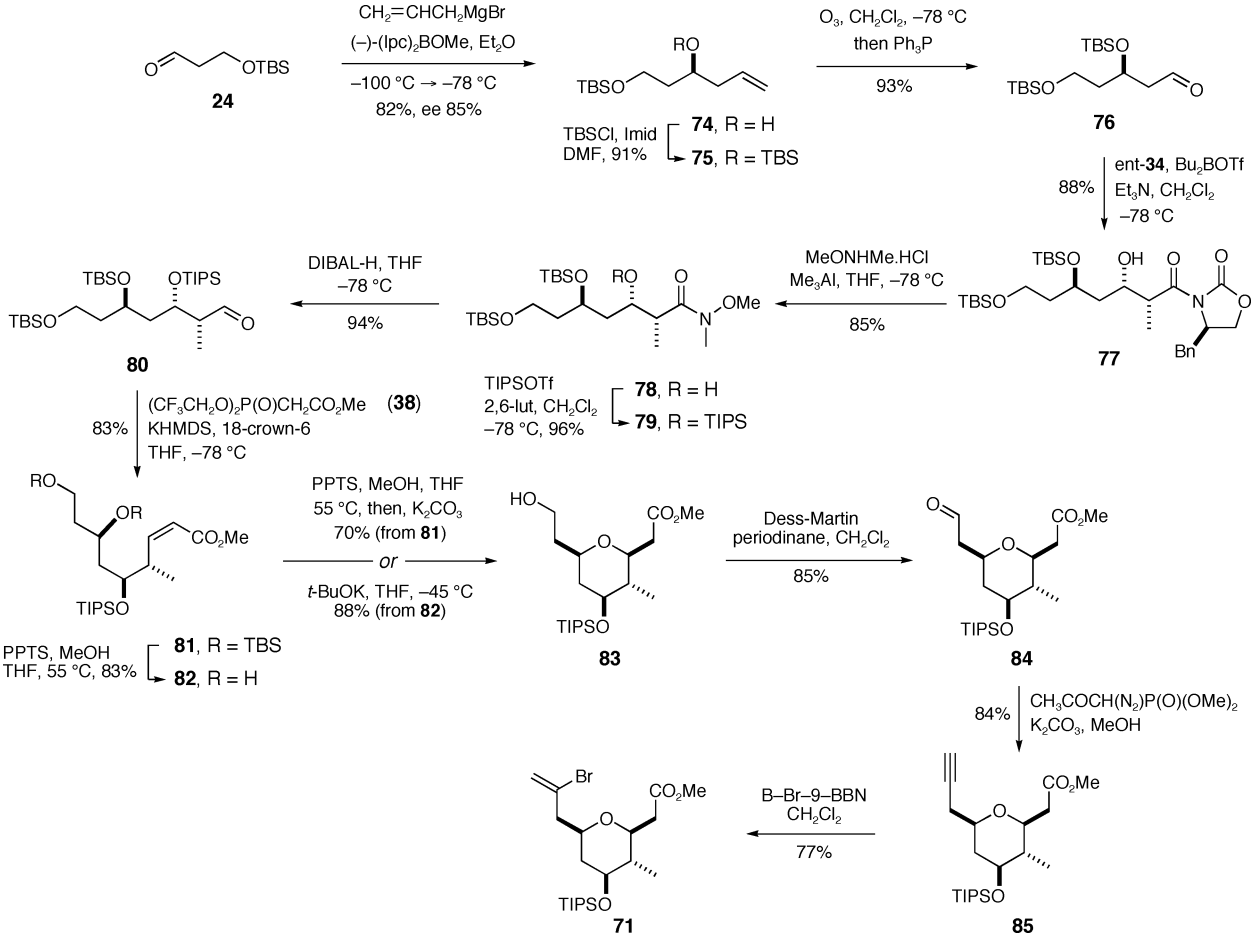


the disaccharide derived from L-fucose and D-xylose matched well in a comparison of its ^{1}H NMR spectrum with the corresponding spectral region of the natural material.[29] Enantiomers of a truncated C1−C9 segment of polycavernoside A aglycon[30] were then separately glycosidated with L-fucosyl-D-xylopyranoside, and of the two diastereomeric products, the NMR spectrum of one was found to closely resemble the spectrum of the glycosidated macrolide.[31] Finally, the spatial relationship between the tetrahydrofuran moiety of the northern portion and the tetrahydropyran segment in the southern subunit was established by a nOe experiment, which linked the methine proton at C11 with one of the diastereotopic protons at C8. These results led Murai to propose the absolute configuration shown in **1** for polycavernoside A, a postulate he later proved correct by synthesis.[5]

Revision of our original plan for the synthesis of polycavernoside A now required not only a new tactic for uniting the northern and southern portions of the aglycon but also demanded construction of these two segments in their antipodal form. The latter stipulation could be accommodated without difficulty since we had adopted an approach from the outset in which starting materials and stereocontrolling reagents were available in both enantiomeric forms. A new plan also gave us an opportunity to solve the north−south unification problem

(29) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 191.
(30) Fujiwara, K.; Amano, S.; Oka, T.; Murai, A. *Chem. Lett.* **1994**, 2147.
(31) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 855.

SCHEME 14



that had defeated the initial design outlined in Scheme 2. Specifically, we decided to reverse the roles of electrophile and nucleophile in the connection of the northern and southern subunits of the putative aglycon precursor **69**. As outlined in Scheme 13, our second generation strategy takes aldehyde **70**, the enantiomer of previously synthesized **66**, as the northern partner for coupling with bromo alkene **71** in a putative Nozaki–Hiyama–Kishi (NHK) reaction.[32,33]

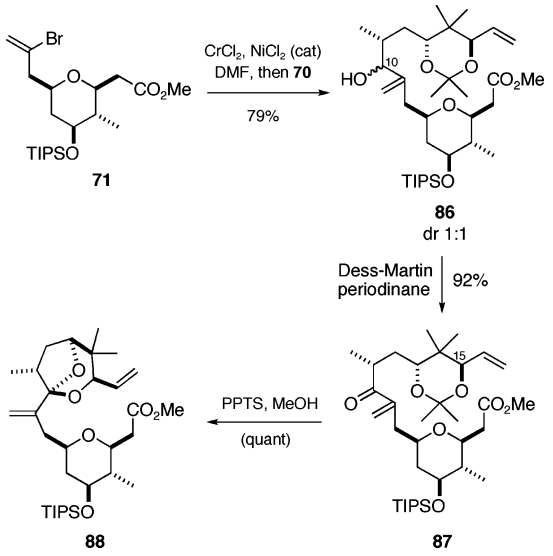
Aldehyde **70** was obtained from methyl (*S*)-3-hydroxy-2-methylpropionate (**72**) and (*S*)-(+)-pantolactone (**73**) exactly as shown in Schemes 9, 10, and 12 but in the antipodal sequence. For the tetrahydropyran **71**, however, we were able to devise a more efficient route to its direct precursor, the enantiomer of **44**, than that used previously and shown in Schemes 3, 6, and 7. In particular, we wanted to avoid steps **11** → **12** → **13** at the beginning of the sequence which we found difficult to scale up, and we therefore elected to commence from aldehyde **24**.

Asymmetric allylation of **24** afforded homoallylic alcohol **74**, which was first silylated to give **75** and then ozonized to produce aldehyde **76** (Scheme 14). A sequence similar to that used previously (Scheme 6) led to *N*-acyloxazolidinone **77** and then to Weinreb amide **78**. Silylation of **78** gave **79**, which was reduced to aldehyde **80**, and olefination of the latter with the phosphonate **38**[18] furnished α,β-unsaturated ester **81**. Cleavage of both TBS ethers of **81** was accomplished as before, leaving the TIPS ether intact, and exposure of the resulting diol **82** to potassium *tert*-butoxide at −45 °C in THF furnished tetrahydropyran **83** in 73% yield for the two steps from **81**. Alternatively, **83** could be obtained directly from **81** in 70% yield by adding solid potassium carbonate to the reaction vessel following acid-catalyzed desilylation. This one-pot process obviated oligomerization of hydroxy ester **83**, a problem which sometimes plagued the potassium tert-butoxide mediated cyclization. Oxidation of the primary alcohol of **83** and reaction of the derived aldehyde **84** with the Ohira–Bestmann reagent[34] in the presence of base yielded terminal alkyne **85**, which was treated with *B*-bromo-9-borabicyclo[3.3.1]nonane[35] to furnish **71** in an overall yield of 13% from **24**.

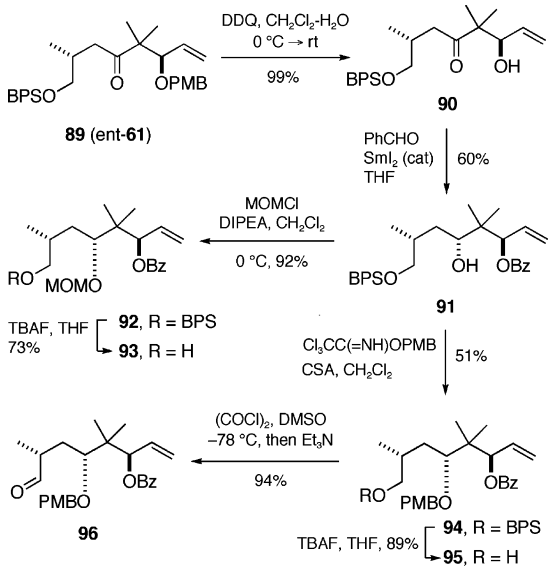
Assembly of Subunits. The critical union of bromoalkene **71** and aldehyde **70** proceeded smoothly under NHK conditions[32,33] if a large excess of $CrCl_2$ and a substoichiometric quantity of $NiCl_2$ was employed (Scheme 15). The resulting 1:1 mixture of C-10 allylic alcohols **86** was oxidized to a single ketone **87**, which we had expected to yield a diol upon acid-catalyzed methanolysis of the acetonide. Instead, the internal ketal **88** was

(32) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
(33) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
(34) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(35) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

SCHEME 15



SCHEME 16

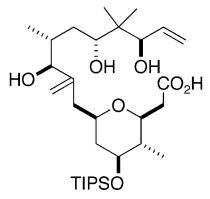
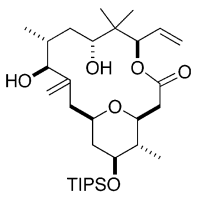
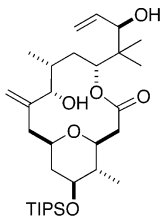
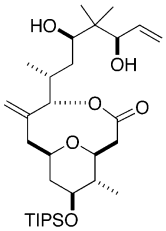
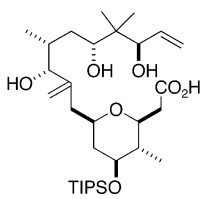
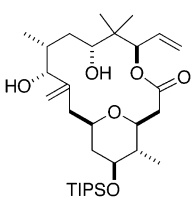
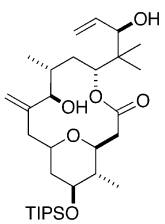
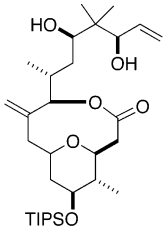


produced, leading us into a cul-de-sac from which we were unable to find an exit.

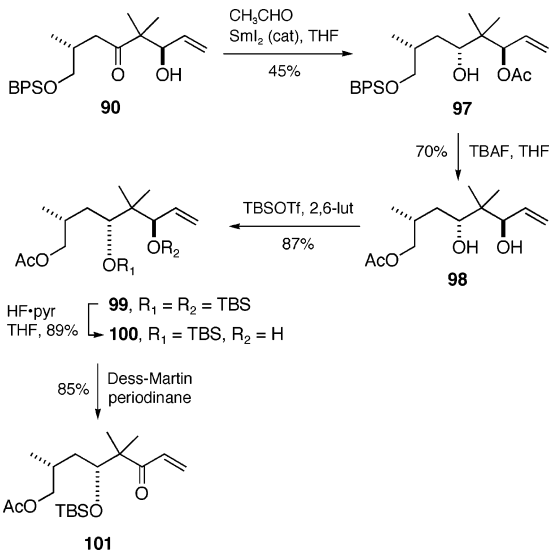
Our failure to unmask acetonide **87** in a manner which would release the C15 hydroxyl function for future macrolactonization persuaded us to return to a precursor of the northern segment which would permit differentiated protection of the C-13 and C-15 hydroxyl groups. Our starting point for this purpose was ketone **89**, the enantiomer of **61**, which was obtained by a sequence antipodal to that described in Scheme 12 from the enantiomers of **9** and **49**. Cleavage of the *p*-methoxybenzyl ether from **89** gave *β*-hydroxy ketone **90**, which now became the focus of studies designed to furnish a selectively protected 1,3-anti diol (Scheme 16). The Evans–Tishchenko reaction[36] seemed well suited to this purpose, and treatment of **90** with benzaldehyde yielded the expected hydroxy ester **91**. Benzoate **91** was advanced to a prospective coupling partner for **71** by protection of the secondary alcohol as its methoxymethyl (MOM) ether **92** followed by cleavage of the silyl ether to yield primary alcohol **93**. However, oxidation of this alcohol was complicated by loss of the MOM group and subsequent oxidation of the liberated secondary alcohol. A second option with **91** was protection of the secondary alcohol as its *p*-methoxybenzyl ether **94**, and this was followed by cleavage of the primary silyl ether to yield **95**.

Swern oxidation[23] of **95** gave aldehyde **96** in excellent yield, but this aldehyde performed poorly in the NHK reaction with **71**, affording no more than 30% of the

TABLE 1. Calculated Energies (Δ*E*) of Prelactonization Complexes and Results of Lactonization of 102 and 106 under Yamaguchi Conditions

Seco Acid		Product		
	2,4,6-$Cl_3C_6H_2COCl$, tol, DMAP, Δ			
102		**103**	**104**	**105**
ΔE (Kcal mol^{-1})		0.0	9.1	8.8
Yield (%)		75	0	0
	2,4,6-$Cl_2C_6H_2COCl$, tol, DMAP, Δ			
106		**107**	**108**	**109**
ΔE (Kcal mol^{-1})		0.0	12.1	8.6
Yield (%)		46	16	0

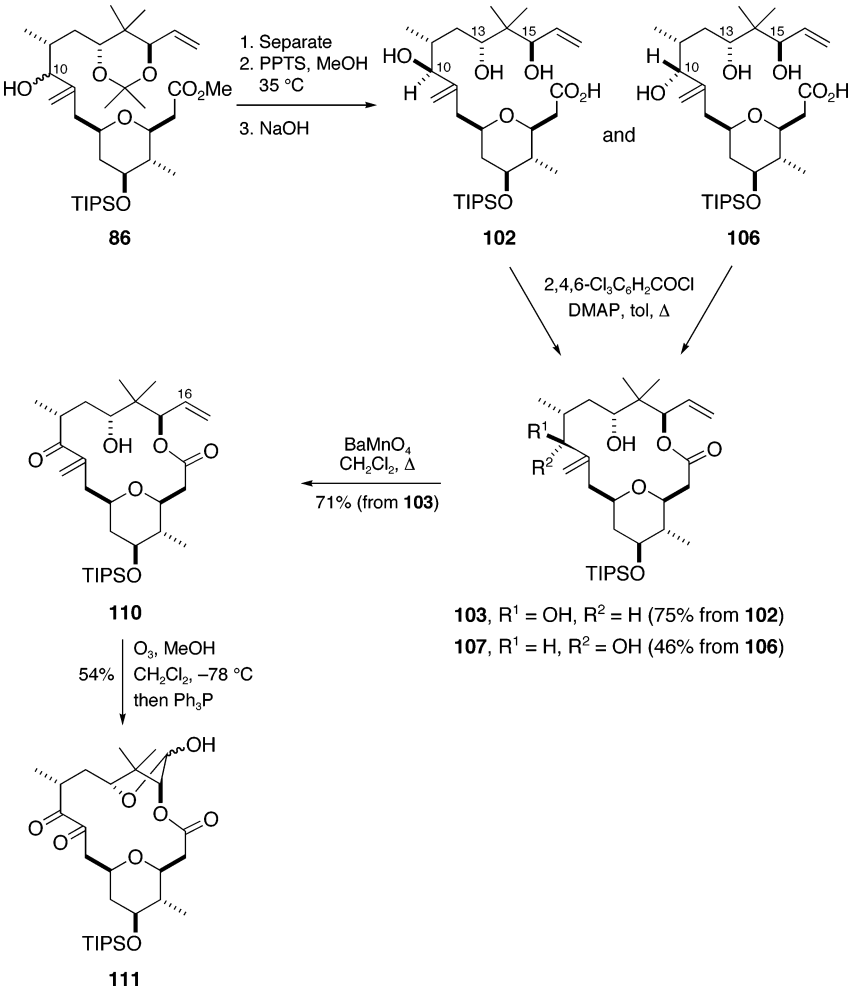
SCHEME 17



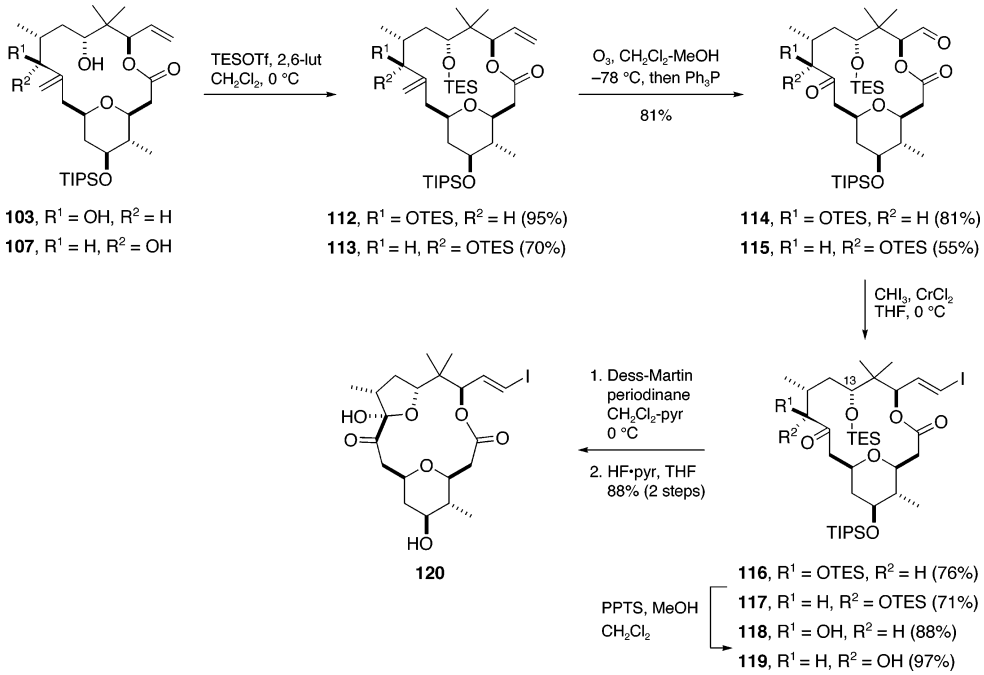
coupled product. The source of the problem was traced to the allylic benzoate of **96**, which appeared to have been reduced by excess Cr(II) present in the NHK medium. We hoped that hydroxy acetate **97**, prepared by an Evans–Tishchenko reaction[36] of **90** with acetaldehyde in the presence of samarium diiodide, would be a more compliant substrate for NHK coupling and to that end we first removed the silyl group from **97** with a fluoride source expecting to obtain a primary alcohol (Scheme 17). Instead, diol **98** bearing two secondary alcohols was produced, evidently the result of a base-catalyzed acetate migration driven by the sterically hindered environment of the secondary neopentyl-type ester. Confirmation that this rearrangement had occurred was obtained when **98** was converted to bis-silyl ether **99**, then selectively deprotected to allylic alcohol **100**, which yielded vinyl ketone **101** upon oxidation.

At this juncture, the more obvious methods for differentiating the hydroxyl groups at C-13 and C-15 appeared to have been exhausted, leaving only the easiest but riskiest option of completely eschewing the use of protecting groups in the pivotal macrolactonization step. The risk was compounded in the present case by the fact that, if hydroxyl groups at C-13 and C-15 were left unprotected, the formation of **88** from **87** had already demonstrated that functionality at C-10 must remain at the hydroxyl oxidation level in order to avoid formation of an internal ketal. In this fully exposed scenario, there would therefore be three hydroxyl groups in the seco acid with which the carboxyl could potentially form a lactone. It seemed improbable that the three contending lactones would be equally favored, but hoping to put intuition on a firmer footing, a computational study was carried out

SCHEME 18



SCHEME 19



in order to obtain an estimate of the energetics associated with each of the three lactonization pathways.

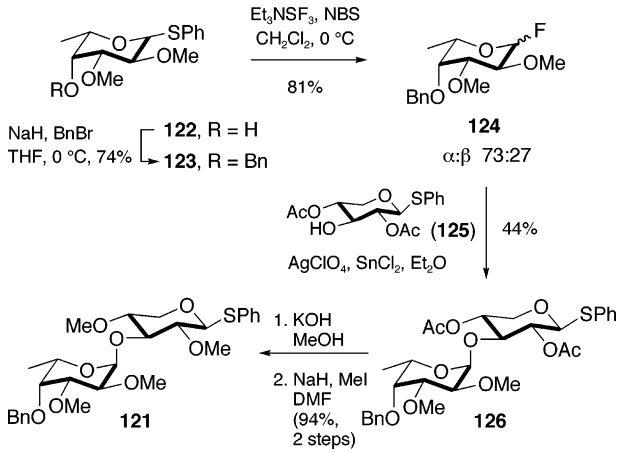
Computational Results and Macrolactonization of a Trihydroxy Carboxylic Acid. A consequence of **86** being obtained as a 1:1 mixture of C10 epimeric alcohols from the NHK coupling of **70** and **71** was that both stereoisomers would need to be considered in a macrolactonization event even though the configuration at C10 becomes inconsequential when this center evolves as the hemiketal carbon of **1**. In practice, the two epimers of **86** were easily separable by chromatography, so that a modeling exercise with each stereoisomer became meaningful. The model chosen for this purpose was the acyl DMAP adduct considered to be the active species in the Yamaguchi lactonization protocol,[37] and three prelactonization conformations were examined corresponding to ring closure at C-10, C-13, and C-15 hydroxyl groups. These conformations assumed that attack by each of the three hydroxyl groups on the acyl-DMAP complex would occur along a Bürgi−Dunitz trajectory.[38] The relative energies of the three conformations were calculated at the PM3 level, and the results are shown in Table 1 for both C-10 epimers of trihydroxy acid **86**. On the assumption that the relative energies of the prelactonization conformations provide an approximate guide to the value of $\Delta\Delta G^{\dagger}$ between the three lactonization pathways available to **102** and **106**, our calculation suggested there should be a preference for the formation of a 16-membered lactone, i.e., **103** from **102** and **107** from **106**, over 14-membered lactones **104** and **108**. Although formation of 11-membered lactone **105** was not expected and, indeed, was not observed, lactone **109** appeared to be a viable candidate from lactonization of seco acid **106**. However, we found no evidence for the formation of **109**.

With this encouraging portent, the separated epimers of **86** were each advanced to the corresponding seco acids **102** and **106**, as shown in Scheme 18, and each of these acids was subjected to lactonization with 2,4,6-trichlorobenzoyl chloride and DMAP in toluene at high dilution. The lactonization yields are shown in Table 1. The (10*S*)-trihydroxy acid **102** gave a crystalline macrolactone in good yield whose structure was established by X-ray analysis as **103**. The crystal structure of **103** shows good correspondence with the conformation of the energy-minimized prelactonization complex, suggesting relatively little atomic displacement is required to close **102** to lactone **103**. No other lactones could be detected in the reaction mixture. Lactonization of the (10*R*) alcohol **106** was less clean, the 16-membered lactone **107** being formed in modest yield accompanied by a significant quantity of the 14-membered lactone **108**. Again, none of the 11-membered lactone was found in the mixture.

With lactone **103** in hand, the steps to polycavernoside A aglycon now appeared straightforward, and to this end, **103** was oxidized with barium manganate[39] to give hydroxy ketone **110**. We had expected to see this product in the form of a cyclic hemiketal, as it appears in polycavernoside A itself, but conjugation apparently stabilizes the ketone sufficiently to prevent cyclization. Since we intended to cleave both alkenes of **110** simultaneously to generate an α-diketo aldehyde in which we believed the formation of a cyclic five-membered hemiketal with the proximal ketone would now be favored, a reductive ozonolysis of this diene was carried out. An unexpected result confounded us again, and only an unstable hemiacetal believed to be **111** could be isolated from this reaction. This diversion foiled our plan for elaborating functionality at C16 of **110** for attachment of the metallodiene **3**, and once more we were forced to revise our end-game strategy.

(36) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
(37) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(38) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.
(39) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.

SCHEME 20



The problem was solved by returning to diol **103**, converting both hydroxyl groups to TES ethers, and carrying out ozonolysis on the protected diene **112**. Keto aldehyde **114** was produced in excellent yield by this process, enabling a Takai reaction[40] with iodoform and chromous chloride to transform the aldehyde function into trans iodoalkene **116**. Selective silyl ether cleavage of **116** yielded α-hydroxy ketone **118**, which was oxidized to an α-diketone with Dess−Martin periodinane.[20] Exposure of this diketone to fluoride ion cleaved both of the remaining silyl ethers, and the liberated C13 alcohol then spontaneously hemiketalized with the C10 ketone to produce **120**. The same six-step sequence from **107** also led to **120** via **113**, **115**, **117**, and **119** in a similar 45% overall yield, thus enabling the synthesis to make use of both stereoisomers of **86** produced in the NHK coupling. It happens that **120** was a key compound in both the Murai[5] and Paquette[6] routes to polycavernoside A, and we were able to show through comparison of IR and NMR spectral data that our **120** was identical to their lactone. Our optical rotation, $[\alpha]_D^{22}$ −36 (c 0.09, $CHCl_3$), also matched well with the value reported by Murai,[5] $[\alpha]_D^{22}$ −38 (c 0.12, $CHCl_3$), for **120**. This correspondence, together with the fact that the structure of **103** had been secured by X-ray crystallographic analysis, lent assurance to Murai's assignment of absolute configuration to the aglycon which had relied on nOe data.

The final stages of our synthesis of **1** from **120** adhered closely to the pathway laid down by Murai[5] and Paquette[6] and employed the known protected fucopyranosylxylopyranoside **121**,[30] prepared as shown in Scheme 20, for glycosidation of **120**. Thus, the C4 hydroxyl group of the fucopyranose derivative **122** was benzylated, and benzyl ether **123** was converted to an anomeric mixture of fluorides **124** as carried out by Murai.[31] This mixture was coupled to the known xylopyranoside **125**[41] to give disaccharide **126** as the major anomer (α:β 4:1). Saponification of the two acetates of **126** and subsequent O-methylation was followed by chromatographic purification to furnish Murai's α anomer **121** in good yield.

Glycosidation of **120** with **121** was carried out with NBS in acetonitrile and gave **127**, albeit in low yield (Scheme 21). The benzyl ether of **127** was cleaved with DDQ, and the iodo alkene **128** was subjected to Stille coupling with the known dienylstannane **129**[6] to furnish polycavernoside A (**1**). Confirmation that our synthesized material was identical with natural polycavernoside A was obtained by comparison of their proton NMR spectra.

SCHEME 21

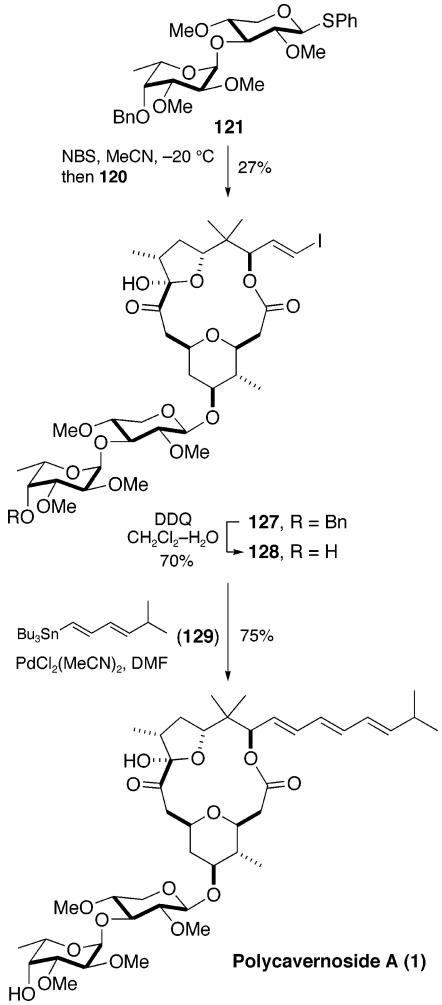


TABLE 2. Comparison of Synthetic Routes to 120

	Murai	Paquette	this work
no. steps to C1−C9 subunit	21	16	14
no. steps to C10−C16 subunit	21	18	14
longest linear sequence (steps)	32	29	22
overall yield (%)	2.6	1.5	4.7

In summary, we have completed a total synthesis of the algal toxin polycavernoside A (**1**) via the aglycon precursor **120**. The latter was obtained using a convergent pathway in which the longest linear sequence was 22 steps, and the overall yield was 4.7%. This compares favorably with other routes to this compound (see Table 2).

Acknowledgment. We are grateful to Professor Alex Yokochi, Department of Chemical Engineering, Oregon State University, for the X-ray crystal structures of **44** and **103**. Financial support was provided by the National Institute of General Medical Sciences (GM50574).

(40) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(41) Johnston, J. N.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 4341.

Supporting Information Available: General experimental techniques, experimental procedures and characterization data for new compounds, crystallographic data and ORTEP plots for **44** and **103**, molecular modeling data for lactonization of **102** and **106**, and copies of ^{1}H and ^{13}C NMR spectra of new purified compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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