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Total Synthesis of (−)-Polycavernoside A: Suzuki−Miyaura Coupling Approach

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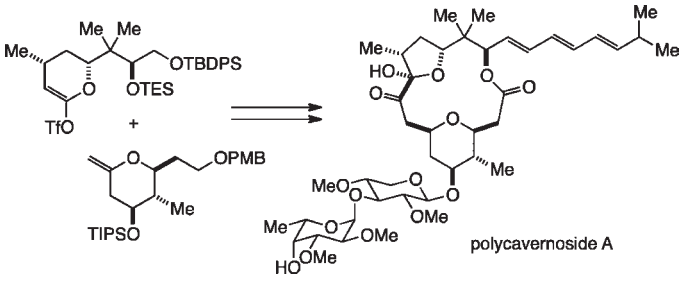
ABSTRACT



A total synthesis of (−)-polycavernoside A, a marine lethal toxin isolated from the edible alga *Gracilaria edulis*, has been achieved via a convergent approach. The synthesis is highlighted by catalytic asymmetric syntheses of the two key fragments and their union through Suzuki−Miyaura coupling and Keck macrolactonization.

Polycavernoside A (**1**, Figure 1) was isolated in 1993 by Yasumoto and co-workers, together with a minor analogue polycavernoside B, as causative toxins for the fatal human poisoning that occurred in Guam in 1991 and in the Philippines in 2002−2003, due to ingestion of the edible red alga *Gracilaria edulis* (*Polycavernosa tsudai*).[1,2] The LD_{99} value of **1** in mice (ip) was estimated to be 200−400 μg/kg. The planar structure of **1** was elucidated on the basis of extensive 2D NMR studies, which showed it to be a novel glycosylated macrolide.[1] The complete stereochemistry, including the absolute configuration, was established by the Murai group with their first total synthesis of (−)-polycavernoside A in 1998.[3] Thereafter, five congeners, polycavernosides A2, A3, B2, C, and C2, were isolated as minute constituents from *G. edulis* and structurally determined by Yotsu-Yamashita et al.[4] The structure of **1** consists

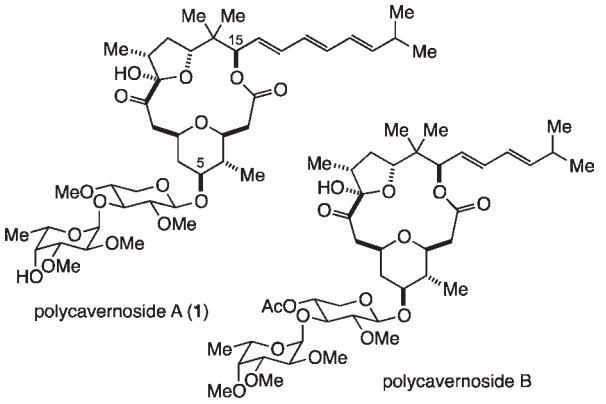


Figure 1. Structures of polycavernosides A and B.

of a 16-membered macrolactone adorned with tetrasubstituted tetrahydropyran and five-membered hemiacetal rings, a conjugated triene side chain appended at C15, and a highly *O*-methylated L-fucosyl-D-xylose unit attached at C5.

The complex molecular architecture of polycavernoside A, coupled with the lethal toxicity and very limited availability from natural sources, makes this natural substance an attractive target molecule for total synthesis. While four

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(2) Yotsu-Yamashita, M.; Yasumoto, T.; Yamada, S.; Bajarias, F. F. A.; Formeloza, M. A.; Romero, M. L.; Fukuyo, Y. *Chem. Res. Toxicol.* **2004**, *17*, 1265–1271.
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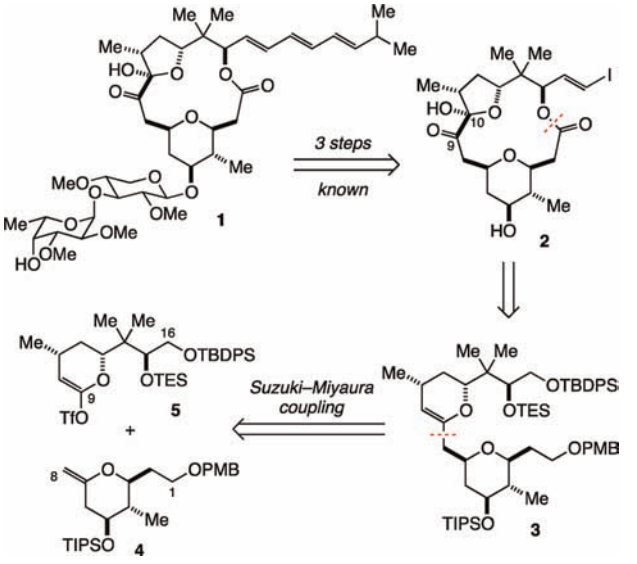
total syntheses[3,5] and several synthetic approaches[6] have been reported to date, its detailed mechanism of action still remains unresolved due to the lack of natural sample.[7] Herein, we report a new convergent total synthesis of polycavernoside A based on a Suzuki–Miyaura coupling strategy.

Our retrosynthetic analysis of polycavernoside A (**1**) is illustrated in Scheme 1. We envisioned that the known intermediate **2**, which was used in all previous total syntheses,[3,5] would be derived from bis-pyran **3** through oxidation of the enol ether moiety to the C9–C10 diketone functionality followed by macrolactone formation. The cyclic enol ether **3**, in turn, could be constructed by Suzuki–Miyaura coupling of an alkylborane generated from the *exo*-olefin **4** and enol triflate **5**.[8,9] These two key fragments **4** and **5**, of comparable complexity, would be constructed through catalytic asymmetric reactions.

Scheme 1. Retrosynthetic Analysis



The synthesis of the C1–C8 *exo*-olefin **4** started with the known enone **6**, which is readily available in three steps from 1,3-propanediol.[10] Catalytic asymmetric hetero-Diels–Alder reaction between silyloxy diene **7**, derived from **6** (TMSTOf, Et_3N, room temperature), and aldehyde **8**[11] was promoted by the Jacobsen tridentate chromium(III) catalyst **9** (3 mol %)[12] and afforded the desired cycloadduct **10** (Scheme 2). Subsequent treatment with K_2CO_3 in MeOH produced a 6:1 mixture of ketone **11a** with the desired stereochemistry at C4 and its isomer **11b**, which was separated by flash column chromatography on silica gel. Isomerization of the undesired **11b** was realized by using DBU (toluene, room temperature) and gave a 10:1 mixture of **11a** and **11b**. After two cycles of isomerization, the desired **11a** was obtained in 60% overall yield from **6**. Luche reduction of **11a** ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −20 °C)[13] delivered alcohol **12** in 94% yield as a single stereoisomer at C5. At this stage, the enantiomeric excess (96% ee) and the absolute configuration of **12** were established by ^1H NMR analysis of its Mosher esters.[14] After protection as a triisopropylsilyl (TIPS) ether, selective deprotection of the TBS group and iodination of the resultant alcohol gave iodide **13** in 86% yield (three steps). Treatment of **13** with *t*-BuOK furnished the *exo*-olefin **4**, which was directly used in the next coupling reaction (see Scheme 4).

The synthesis of the C9–C16 enol triflate **5** commenced with (*R*)-(+)-citronellal (97.2% ee), which was converted into alcohol **14** via a six-step sequence[15] (Scheme 3). Ozonolysis of the double bond gave aldehyde **15** in 92% yield. Catalytic asymmetric allylation of **15** with prenyl bromide was carried out using the chiral sulfonamide ligand **16** and following the procedure of Kishi and coworkers;[16] it provided alcohol **17** (31%) and the corresponding diol (69%) as single stereoisomers, respectively. Reprotection of the primary alcohol of the latter as its TBS ether afforded **17** in 86% yield. Asymmetric dihydroxylation of the terminal alkene using $(DHQ)_2PYR$ as a chiral ligand[17] led to triol **18** in 97% yield. Selective protection of the primary alcohol as its *tert*-butyldiphenylsilyl (TBDPS) ether, removal of the TBS group under acidic conditions

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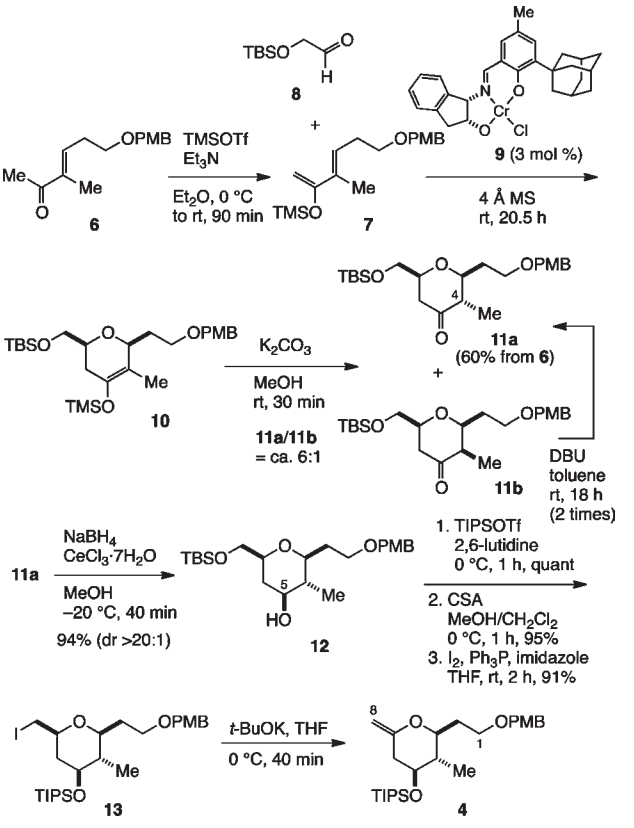
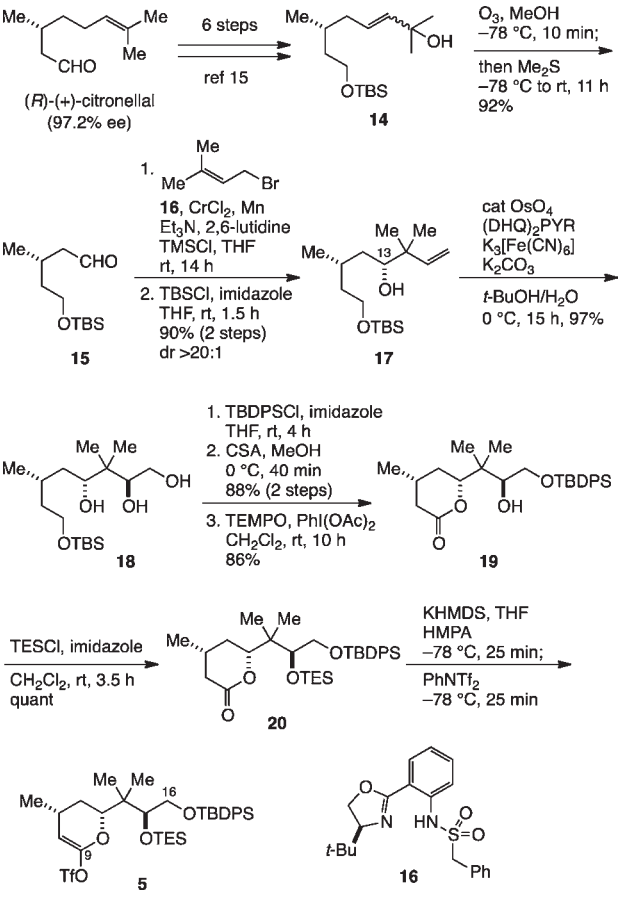
Scheme 2. Synthesis of the C1−C8 *exo*-Olefin **4**



Scheme 3. Synthesis of the C9−C16 Enol Triflate **5**



(CSA, MeOH), and oxidative lactonization of the resultant 1,5-diol with TEMPO and $PhI(OAc)_2$[18] delivered lactone **19** in 76% yield for the three steps. The residual secondary alcohol was then protected as its triethylsilyl (TES) ether to give **20** in quantitative yield which, upon treatment with KHMDS and $PhNTf_2$ (HMPA, THF, −78 °C), furnished the desired enol triflate **5**.

With the requisite fragments in hand, we next turned our attention to their union through Suzuki−Miyaura coupling.[8,9] After extensive experimentation, Suzuki−Miyaura coupling of the alkylborane generated from *exo*-olefin **4** (9-BBN-H, THF, 0 °C to room temperature) with enol triflate **5** was achieved under the conditions which used aqueous Cs_2CO_3 as a base, $PdCl_2(dppf)\cdot CH_2Cl_2$ as a catalyst, and Ph_3As as a coligand in DMF/THF at room temperature, affording the desired coupled product **3** in high yield.[19] The cyclic enol ether moiety of **3** was then oxidized with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2/MeOH to afford an inconsequential epimeric mixture of alcohols **21a** and **21b** in 66 and 25% overall yields from **13**, respectively. These alcohols were individually oxidized to the same ketone **22** in high yields.[20] Selective cleavage of the TES ether and oxidative removal of the PMB group afforded diol **23** in 98% yield for the two steps. The primary alcohol of diol **23** was selectively oxidized with TEMPO/$PhI(OAc)_2$ in CH_2Cl_2/H_2O (10:1)[21] to provide the corresponding carboxylic acid in 97% yield. Subsequent macrolactonization proved to be more difficult than expected. After extensive experimentation, it was finally found that the best result was obtained by using Keck protocol[22] employing DCC, pyridine, and PPTS[23] under reflux to afford macrolactone **24** in quantitative yield.[24] The primary TBDPS ether was selectively cleaved with buffered HF·pyridine, and oxidation of the resulting alcohol with Dess−Martin periodinane[25] followed by

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(19) Suzuki−Miyaura coupling of the phosphate counterpart resulted in a low yield of **3** [$Pd(PPh_3)_4$, $PdCl_2(dppf)\cdot CH_2Cl_2$, or $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$] presumably due to the low reactivity.

(20) 10β-Alcohol **21a** was labile even under mild acidic conditions. For example, Swern oxidation of **21a** caused partial cleavage of the methyl acetal and resulted in a low yield of ketone **22** (37%).

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(24) Fujiwara et al. reported that Yamaguchi lactonization of a substrate closely related to **23** proceeded smoothly to give the corresponding 16-membered macrolactone in good yield. However, macrolactonization of a hydroxy acid derived from **23** under Yamaguchi or Shiina conditions resulted in only a low yield of **24**.

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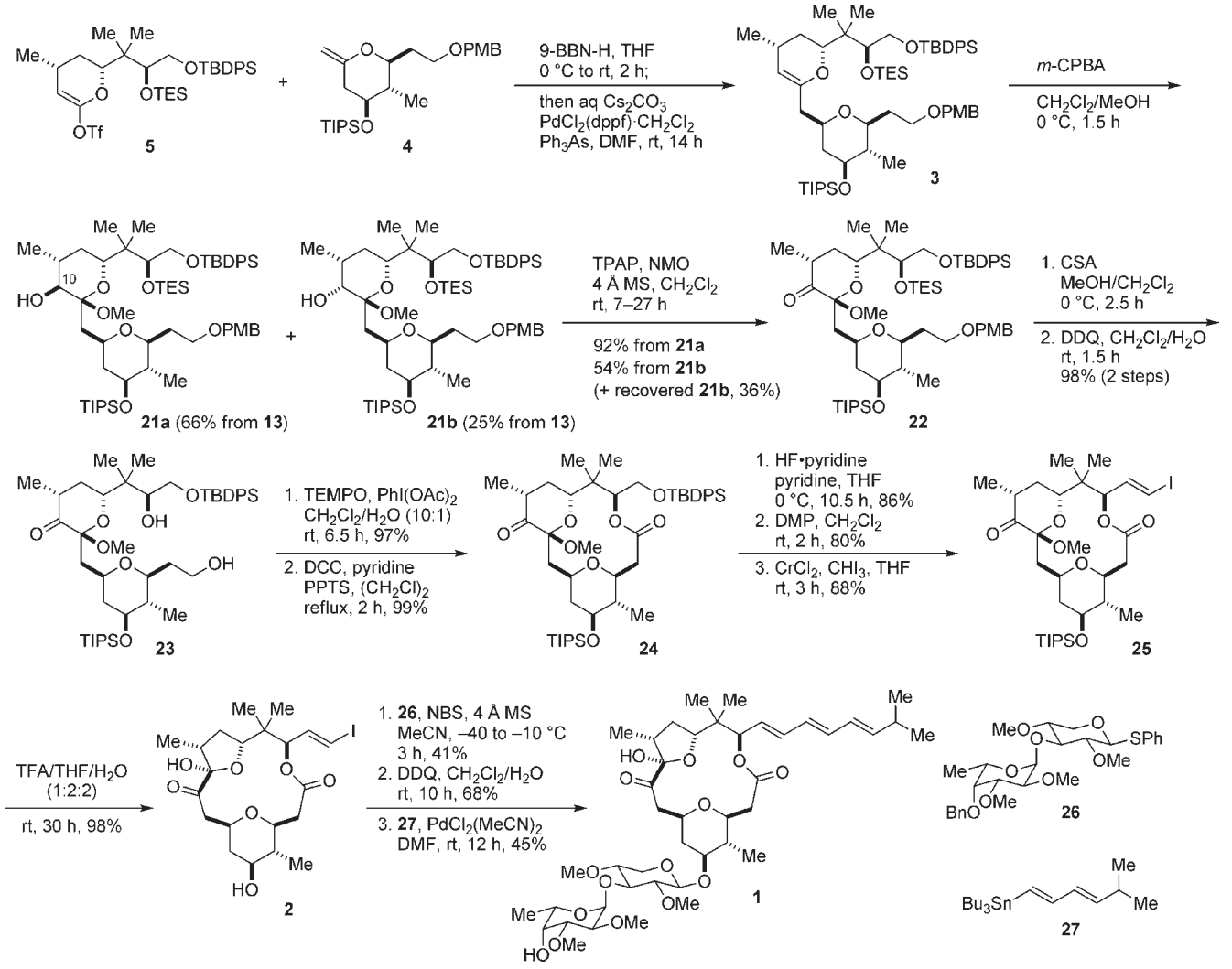
Scheme 4. Fragment Coupling and Completion of the Synthesis of Polycavernoside A



Takai reaction (CHI_3, $CrCl_2$)[26] led to (*E*)-vinyliodide **25** in 61% yield (three steps). Treatment of **25** with TFA/THF/H_2O (1:2:2)[3] effected deprotection of the TIPS ether and methyl acetal with concomitant reconstruction of the five-membered hemiacetal to afford alcohol **2** in 98% yield.

Finally, glycosylation of **2** with thioglycoside **26**[5c,d] under the influence of NBS[27] (41%), oxidative cleavage of the benzyl ether with DDQ (68%), and Stille coupling with the known dienylstannane **27**[5a,b] (45%) completed the synthesis of (−)-polycavernoside A (**1**).

In summary, an efficient total synthesis of polycavernoside A has been accomplished via a convergent approach (a longest linear sequence of 29 steps and 2.4% overall yield from commercially available (*R*)-(+)-citoronellal). The synthesis features catalytic asymmetric syntheses of the C1−C8 and C9−C16 fragments and their assembly through Suzuki−Miyaura coupling and Keck macrolactonization to form the macrolactone core. Our convergent fragment coupling strategy allows for the preparation of sufficient quantities of polycavernoside A itself and its analogues for detailed biological studies. Further studies along this line are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.