Total Synthesis of Polycavernoside A

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Abstract: The first total synthesis of polycavernoside A (1), which was isolated from the red alga *Polycavernosa tsudai* as a causative toxin of fatal human intoxication in Guam in 1991, is described. The synthetic key steps involve the connection of the acyl anion equivalent (9) derived from 3 with aldehyde (8), the stereoselective formation of 6-membered cyclic methyl acetal (7) by lactonization from the requisite secoic acid (22), the stereoselective hydrolytic reconstruction of the acetal moiety of 7 leading to 5-membered cyclic hemiacetal (6), the glycosylation of 6 with 4 derived from L-fucose and D-xylose, and the final triene formation using cross-coupling reaction.

1. Introduction

Yasumoto *et al.* reported the isolation of polycavernoside A in 1992 as a responsible toxin for the fatal human intoxication that occurred in Guam in late April 1991, due to ingestion of the red alga *Polycavernosa tsudai* (refs. 1, 2). They proposed its planar structure, which is a novel 13-membered macrolide disaccharide possessing a triene moiety, on the basis of ^1H and ^{13}C NMR spectra. However, although the respective relative configurations of the tetrahydrofuran ring, the tetrahydropyran ring, and the respective sugar moieties had been clarified, the absolute configuration of the whole molecule had not been established yet. Later, they reported further the isolation and structural determination of four new analogs, polycavernoside A2, A3, B, and B2, from *P. tsudai* (ref. 3).

We started the total synthesis of polycavernoside A (1), because of its unusual molecular structure, the significant toxic activity, and the lack of a satisfactory natural source (ref. 1). Before planning the synthesis, we deduced the whole molecular structure of 1 to have the relative configuration proposed in Scheme 1, based on the following points: (1) *anti* conformational relationship between H7 and H8b suggested by the large $^3J_{\text{H7/H8b}}$ value (9 Hz) and no observation of NOE between H7 and H8b (ref. 1); (2) same-side placement of H8b and H11 on the macrolactone ring suggested by the presence of NOE between H8b and H11 and the absence between H8a and H11 (ref. 1); (3) natural majority of

D-xylose and L-fucose in marine biota. Accordingly, we initially synthesized the tetrahydrofuran (**2**) (ref. 4) and tetrahydropyran parts (**3**) (ref. 5) in both enantiomeric forms, and the disaccharide (**4**) corresponding to the possible sugar moiety of **1** (ref. 6). Concerning the sugar part, we concluded that the moiety might consist of a combination of D-xylose and L-fucose or their enantiomers (ref. 7). How to combine these three components in order to construct the macrolactone disaccharide as well as how to introduce the (*E,E,E*)-triene group were the problems, which we faced, and these have been successfully solved leading to completion of the first total synthesis of **1** (ref. 8). We describe herein the details of our synthetic results.

2. Synthetic Strategy

We planned our synthetic pathway as shown in Scheme 1. Introduction of the triene, considering its potential lability, was scheduled in the final step after the glycosylation of lactone (**6**) with **4** (refs. 7a, 9) derived from L-fucose and D-xylose. Hydrolytic reconstruction of the acetal moiety of **7** within the framework of the lactone was expected to set up the stereochemistry at anomeric C10 of **6** in natural form. The population ratio of the presumable cyclic methylacetals (**10** and **11**) corresponding to **6** and **7** at 300 °K by the semi-empirical calculation (MM2*) was estimated to be 93:7 (Scheme 2) (ref. 10). Further, this synthetic strategy would also rely on the successful lactonization to **7** from the requisite secoic acid, the stereoselective formation of 6-membered cyclic methyl acetal, and the connection of the acyl anion equivalent (ref. 11) derived from **9** with aldehyde (**8**) at the C9-C10 bond.

Scheme 1

Scheme 2

For the preparation of **8** and **9**, alcohols (**2** and **3**) would be available, respectively. First of all, we attempted glycosylation with the enantioisomeric tetrahydropyrans (**12** and **14**) to establish the relative configuration of the sugar component and the bottom (C1-C8)-half of the macrolactone part in **1** (Scheme 3).

3. The Relative Configuration of the Sugar and Tetrahydropyran Parts

Both enantiomers of the tetrahydropyran rings (**12** and **14**) were prepared from the corresponding alcohols (**3** and *ent*-**3**) by acetylation and debenzoylation, respectively (ref. 7a). Glycosidation reactions using **12** or **14** were carried out according to Nicolaou's procedure (ref. 12). The reaction of **12**, **4**, and MS4A in MeCN with NBS at -40 °C for 8 min gave the diastereomeric β - and α -glycosides in 74% and 26% yields, respectively. The corresponding reaction of the enantiomer (**14**) and **4** under similar conditions at -40 °C~-45 °C for 1 min provided β - and α -glycosides in 66% and 34% yields, respectively. The respective β -glycosides were converted on hydrogenolysis with Pd-C in MeOH into the debenzyl derivatives (**13** and **15**) in 80% and 82% yields, respectively. The differences in the chemical shifts of the protons of the tetrahydropyran parts on the ^1H -NMR spectra in CD_3CN (400 MHz) of **13** and **15** with those of natural polycavernoside **1** revealed apparent deviations, because of the presence of acetoxyl and methoxycarbonyl groups being different from **1** (Figure 1). However, when the chemical shifts of the protons at C5 and C9 are compared, both the differences from **1** are smaller in **13**. Furthermore, all the chemical shifts at the proton at C1' and the protons of the OCH_3 groups at C2',

Scheme 3

Figure 1. Differences in Proton Chemical Shifts between **1** and **13** or **15**.

C4', C2'', and C3'' were much more coincident in **13** with those of **1**. In the chemical shifts and the splitting patterns of the residual protons in the disaccharide moiety, less deviation was observed in **13** than in **15**. Accordingly, combining with the NOE experiments between H8b and H11 in **1** (ref. 1) as well as the coupling constants between H7 and H8a (0 Hz) or H7 and H8b (9 Hz) (ref. 1), the relative configuration of the whole molecule of polycavernoside A could be concluded as indicated in **1** (ref. 7), which is different from that tentatively proposed by Yasumoto (ref. 1). It has been well known that the xylose has always been detected as the D-form from marine sources. Thus, we proposed further the absolute configuration of polycavernoside A as **1** without any chemical evidence (ref. 7).

4. Formation and Reconstruction of the Macrolactone Acetal

In order to construct the macrolactone acetal (**6**), we intended to connect the acyl anion equivalent (ref. 11) derived from **9** with aldehyde (**8**) at the C9-C10 bond. The diethyldithioacetal mono-*S*-oxide (**9**) was readily obtained in 7 steps from alcohol (**3**) (Scheme 4). Swern oxidation (ref. 13) and subsequent Wittig reaction provided a methyl vinyl ether (**16**) in 90% yield, which was hydrolyzed under acidic condition to give aldehyde (**17**) (92%). Then, Evans' thioacetalization (ref. 14), reduction of the methyl ester, protection of the resultant alcohol with TBS, and selective oxidation of the thioacetal moiety afforded mono-sulfoxide (**9**) in 92% overall yield.

Deprotonation of **9** with LDA (1 eq) in THF at -78 °C followed by addition of aldehyde (**8**) (0.5 eq), derived from **2** by Swern oxidation (ref. 13), provided acid-sensitive dithioacetal (**19**) (a mixture of diastereomers, 46% based on **8**) (ref. 15) and vinyl sulfide (**20**) (a single diastereomer, 33% based on **8**) (refs. 15, 16) together with recovered **9** (57%) and **8** (17%). When the adduct (**19**) was treated with *p*-toluenesulfonic acid in MeOH-(MeO)₃CH (10:1), removal of the ethylthio and ethylsulfenyl groups, desilylation, and cyclic methyl acetal formation occurred in one-pot to produce the desired bicyclic compound (**21**) (ref. 17) in 50% yield along with its C10-epimer (ref. 17) in 18% yield. Under the same conditions, vinyl sulfide (**20**) was transformed into **21** in 65% yield. Swern oxidation (ref. 13) of diol (**21**) and the following removal of PMB (ref. 18) provided keto-aldehyde in 81% yield. Secoic acid (**22**), obtained quantitatively after NaClO₂ oxidation (ref. 19) of the keto-aldehyde, was lactonized smoothly by modified Yamaguchi's method (ref. 20) to give 12-membered lactone (**7**) in 79% yield.

Scheme 4

Scheme 5

Figure 2. Differences in Proton Chemical Shifts between **1** and **23**.

Based on the calculated population ratio of the model compounds (**10** and **11**) shown in Scheme 2, tetrahydropyran acetal (**7**) was treated with a 5:5:2 mixture of THF-H₂O-TFA at 20 °C for 6 h (Scheme 5). Our expected hydrolytic reconstruction occurred exclusively to afford tetrahydrofuran hemiacetal (**23**) in 81% isolated yield. The structure of **23** was determined judging from the appearance of NOE between the protons at H8b and H11 as well as the vicinal coupling constants of H7-H8a (0 Hz) and H7-H8b (9 Hz). These results were similar to those of natural compound (**1**) (ref. 1). Figure 2 shows differences in proton chemical shifts between **1** and **23**. As another possibility of such reconstruction, we attempted to react an open-chained tetrahydropyran acetal (**25**), which was obtained from **21** via **24** in a 3-step process, under the same conditions as above. The reaction necessitated longer reaction time and led to a quantitative formation of a 1:4 mixture of 6-membered hemiacetal (**26**) and the desired reconstructed tetrahydrofuran hemiacetal (**27**). However, the results using **25** revealed that there might be an equilibrium in the products (**26** and **27**) and the product might always include the tetrahydropyran hemiacetal (**26**). We intended to use the former route to **23** for further reaction development.

5. Total Synthesis of (-)-Polycavernoside A via Glycosylation and Triene Construction

Toward the final construction of the triene part, introduction of the *trans*-iodovinyl group was necessitated at this stage. Dihydroxylation of the vinyl moiety of **7** followed by oxidative cleavage

Scheme 6

and replacement of benzyl to TBS led to aldehyde (29) in 76% overall yield (Scheme 6). Chemo- and stereoselective iodovinylolation of the aldehyde was achieved to produce 30 under Takai's conditions (ref. 21, 22). The 6-membered cyclic methyl acetal (30) was converted to the desired 5-membered cyclic hemiacetal (6) quantitatively under mild acidic conditions. Stereochemistry at C10 of 6 was confirmed by the existence of NOE between H8b and H11 which showed large $^3J_{H7/H8b}$ value (9.2 Hz) as seen in natural 1. In Figure 3 is emphasized the similarity in the proton chemical shifts of 6 and natural 1 except those at C15, C16, and C17 arisen from the presence of the iodovinyl group.

Figure 3. Differences in Proton Chemical Shifts between 1 and 6.

Figure 4. Differences in Proton Chemical Shifts between 1 and 32.

Glycosylation of **6** with fucosylxylose derivative (**4**) (ref. 7a) was carried out according to Nicolaou's procedure (ref. 12) to give the desired β -glycoside (**31**) in 55% yield, in which the benzyl group was removed by DDQ to afford **32**. Only a smaller difference in the respective chemical shifts between **32** and **1** was fortunately observed, except in the protons near the vinyl group (Figure 4).

Scheme 7

Figure 5. CD Spectra of Natural (a) and Synthetic (b) Polycavernoside A.

As the final critical stage, we turned our attention to the construction of the (*E,E,E*)-triene system starting from the (*E*)-vinyl iodide (**32**). While there had been known many reports concerning the (*E,E,E*)-triene synthesis by Pd-catalyzed cross-coupling reaction of a dienylmetal compound with alkenyl halide (ref. 23), we intended to use the less nucleophilic dienyl mercury (**35**) as a diene segment in the cross-coupling reaction (ref. 24) with **32** to avoid any side reactions toward the oxygen-functional groups (Scheme 7). A model experiment on iodovinyl compound (**36**) to (*E,E,E*)-triene (**37**) indicated that the use of excess reagent could complete the cross-coupling reaction, though a homo-coupling reaction proceeded as a side reaction in this system (ref. 24). Thus, excess **35**, which was prepared from known enyne **33** (ref. 25) through a one-pot hydrozirconation-iodination sequence via iodide (**34**) (ref. 26) and sequential lithiation-transmetalation process, was treated with vinyl iodide (**32**) and a Pd-catalyst to produce **1** in good yield.

The synthetic material displayed physical and spectral properties including ^1H and ^{13}C NMR, IR, UV, and FABMS, as well as toxicological property to mice (refs. 1, 27), identical to the natural product. The CD spectrum of natural polycavernoside A was identical with that of synthetic **1** in pattern, sign, and wavelength of each extreme point (ref. 28, Figure 5). Consequently, we have achieved determination of the absolute configuration of polycavernoside A to be **1**, shown in Scheme 1, as proposed (ref. 7). Very recently, Paquette's group has succeeded in the second total synthesis of (-)-**1** (ref. 29). Furthermore, a study on the structure-biological activities of **1** and its synthetic analogues has been started and developed in cooperation with the groups of Prof. L. A. Paquette, The Ohio State University, and Prof. M. Yotsu-Yamashita, Tohoku University (ref. 30).

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References

- (1) Y.-Yamashita, M.; Yasumoto, T.; Haddock, R. L. *34th Symposium on the Chemistry of Natural Products (Tokyo)*, Symposium Abstracts, **1992**, 612-619.
- (2) Y.-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147-1148.
- (3) Y.-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563-5566.
- (4) Hayashi, N.; Mine, T.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1994**, 2143-2146.
- (5) Fujiwara, K.; Amano, S.; Oka, T.; Murai, A. *Chem. Lett.* **1994**, 2147-2150.
- (6) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 191-192.
- (7) a) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 855-856. For the review on these three fragments, see: b) Fujiwara, K.; Hayashi, N.; Amano, S.; Mine, T.; Murai, A. *Proceedings of the International Symposium on Ciguatera and Marine Natural Products*, Hokama, Y.; Scheuer, P. J.; Yasumoto, T., Eds.; South Kohala, Hawaii, 1994; pp 239-250.
- (8) Fujiwara, K.; Murai, A.; Y.-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770-10771.
- (9) For another synthesis of the sugar part of polycavernoside A: Johnston, J. N.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 4341-4344.
- (10) Y. Fukazawa, private communication (Jan. 9, 1997). He kindly calculated the population ratio.
- (11) Herrmann, J. L.; Richman, P. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 4707-4710. Also see: Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1972**, 2681-2684.
- (12) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430-2434.

- (13) a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660. b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480-2482. c) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165-185.
- (14) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009-5017.
- (15) Dithioacetal (**19**) and vinyl sulfide (**20**) were purified by chromatography using silica gel doped with 4% Et₃N.
- (16) Vinyl sulfide (**20**) was gradually produced from some of the diastereomers of **19** under the reaction conditions (checked by TLC analysis). The other diastereomers of **19** were unchanged for prolonged periods under the same conditions.
- (17) The axial orientation of each methoxy group at C9 of **21** and its C10-epimeric alcohol was confirmed by the existence of NOE between H13 and CH₃O at C9 in the derivative of **21** and the intact epimer, respectively.
- (18) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885-888.
- (19) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175-1176.
- (20) a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993. For the efficiency of excess DMAP in the method: b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9. c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613-4628.
- (21) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.
- (22) The use of large excess reagents accelerated the reaction rate to prevent the epimerization at C15.
- (23) For construction of all *E*-polyenes by Pd-catalyzed cross coupling of an alkenylzinc with an alkenyl iodide, see: a) Negishi, E.-i.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683-6686. b) Lipshutz, B. H.; Lindsley, C. J. *Am. Chem. Soc.* **1997**, *119*, 4555-4556 and references cited therein. For the review on Pd-catalyzed cross-coupling reactions of organoboron compounds, see: c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
- (24) The cross-coupling reaction between alkadienylmercury and alkenyl halide for triene-synthesis has not been reported. For cross-coupling reactions using alkenylmercury and arylmercury reagents, see: a) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393-2401. b) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551-564 and references cited therein.
- (25) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223-8228.
- (26) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257-7260.
- (27) LD₅₀ in mice (ip) of synthetic **1** was 240-360 µg/kg, while that of natural **1** was 200-400 µg/kg.
- (28) CD spectral data of **1**: natural, CD (CH₃CN, 22 °C) λ_{ext} 210.2 nm (Δε 0.71), 227.8 (-0.15), 246.0 (0.21), 258.6 (0.03), 260.8 (0.15), 269.6 (-0.63), 280.4 (-0.65), 299.0 (-0.78); synthetic, CD (CH₃CN, 22 °C) λ_{ext} 210.2 nm (Δε 0.32), 228.8 (-0.25), 248.0 (0.19), 260.0 (-0.12), 262.8 (0.15), 268.6 (-0.42), 279.6 (-0.55), 299.8 (-0.73). Optical rotation data of **1**: natural, [α]_D²² -59 (c 0.012, CH₃CN); synthetic, [α]_D²² -66 (c 0.02, CH₃CN).
- (29) Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **1999**, *121*, 4542-4543.
- (30) For our preliminary finding that both the macrocyclic core and the side chain are required for the toxicity to mice, see: Barriault, L.; Boulet, S. L.; Fujiwara, K.; Murai, A.; Paquette, L. A.; Yotsu-Yamashita, M. *Bioorgan. Med. Chem. Lett.* in press.

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