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The First Construction of the B,C,D-ring Fragment of Pinnatoxins *via* Highly Stereocontrolled Acetallization

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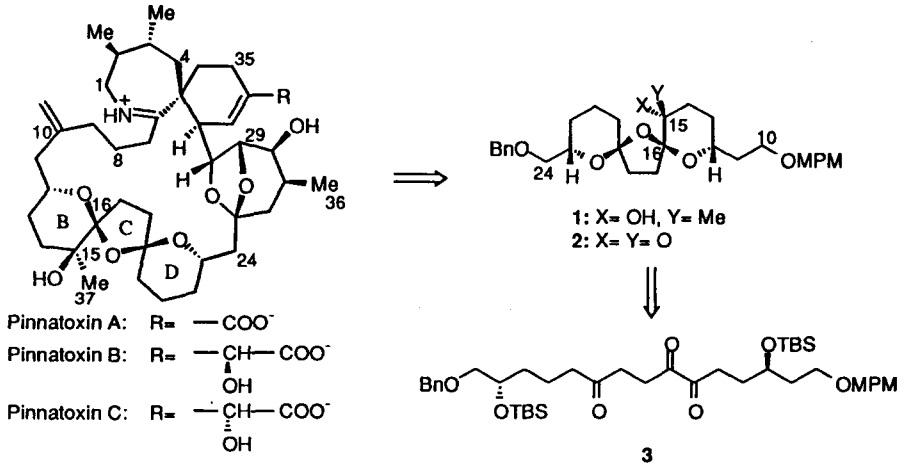
Abstract: The synthesis of the B,C,D-ring fragment of pinnatoxins is described. The highly stereocontrolled construction of the 6,5,6-tris-spiroacetal core was achieved on treatment of compound **3** with aqueous HF in CH_3CN. The anomeric effect at C_{16} enhanced by neighboring carbonyl group led to form the tris-spiroacetal having the natural configuration. © 1997 Elsevier Science Ltd.

Shellfish of the genus *Pinna* lives mainly in shallow areas of the temperate and tropical zones of the Indian and Pacific Oceans.[1] The adductor muscle of this bivalve is eaten in Japan and China, and food poisoning resulting from its ingestion occurs frequently.[2] Chinese investigators had reported that the toxic extract from *Pinna attenuata*, referred as pinnatoxin, activates Ca^{2+} channel.[3]

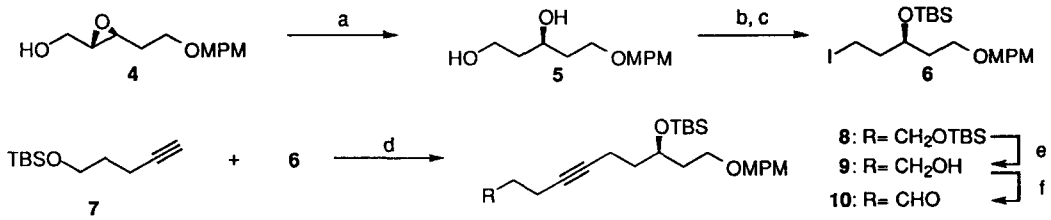
The isolation and determination of the relative structures of pinnatoxins A, B, C, and D were reported by Uemura *et al.*[4] These unique structures, which include 6,7-azaspiro and 6,5,6-tris-spiroacetal rings, and their biological activities (LD_{99} 22 mg/kg, pinnatoxin B) attract attention of scientists. The absolute configurations



Scheme 1

of these compounds have not yet been determined. We describe here the first construction of one of the possible enantiomers of the C_{10}-C_{24} fragment **1**, which is included as the common structure in pinnatoxins A, B, and C.

Our synthetic strategy is shown in Scheme 1. The chiral center at C_{15} could be introduced after acetallization. In our case, the spiroacetallization reaction could probably afford both the 6,5,6- and 6,6,5-tris-spiroacetal ring systems. However, the former ring system should be thermodynamically more favored than the latter ring system because of the existence of sever steric repulsion in the latter. Additionally, the anomeric effect at C_{16} enhanced by the neighboring carbonyl group[5] would lead to form the corresponding tris-spiroacetal having the natural configuration. Furthermore, based on molecular orbital calculations by MOPAC 6.1 (AM1), **2** was predicted to be the most stable structure among the other possible isomers.

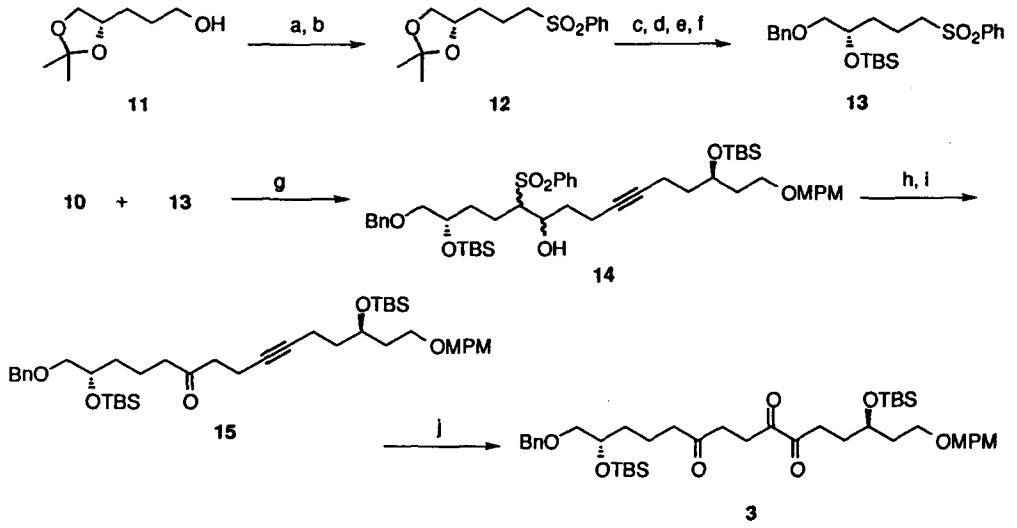


Scheme 2. *Reagents and conditions*: a) Red-Al, THF, 23 °C, 2.5 h, quant.; b) I_2, PPh_3, imidazole, THF, 0 °C, 90%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0° C, 20 min, 98%; d) BuLi, THF, 0 °C, 30 min, then **7**, THF-HMPA (1:1), 0 °C, 20 min, 91% based on **6**; e) TBAF, THF, -20 °C, 32 h, 83%; f) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1 h, then Et_3N.

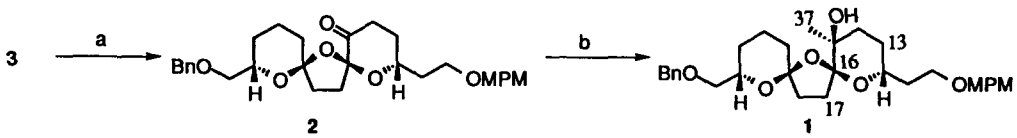
Epoxide **4**[6] was prepared from commercially available 1,3-propanediol in >95% ee (Scheme 2). Reduction of **4** by Red-Al® underwent regioselectively to afford the 1,3-diol **5** in quantitative yield. Iodination of the primary alcohol, followed by protection of the secondary alcohol, gave **6**. On the other hand, **7** was prepared from 4-pentyn-1-ol (TBSCl, imidazole, CH_2Cl_2, 0 °C- 22 °C, 20 h, 94%). The coupling reaction of **6** and **7** proceeded at 0 °C in THF-HMPA (1:1) to afford **8** in 91% yield. Selective detachment of the primary TBS group with TBAF provided alcohol **9** in 83% yield, which was oxidized to the aldehyde **10**. The aldehyde was used in the following coupling reaction without purification.

Next, compound **13** was prepared from the known compound **11**[7] (Scheme 3). The alcohol **11** was converted to phenyl sulphide, and the subsequent oxidation afforded sulphone **12**. The acetonide group of **12** was removed and the resulting primary alcohol was transformed into the benzyl ether *via* the cyclic stannylene acetal. The remaining secondary hydroxyl group was then protected as the TBS ether. The Julia coupling of **10** and **13**, followed by oxidation of the resulting alcohol and desulphonation, presented compound **15**. The oxidation of the triplebond in **15** was succeeded with RuO_4 under the conditions reported by Sharpless[8] leading to trione **3**.

We explored the key spiroacetallization reaction (Scheme 4). When compound **3** was exposed to aqueous HF in acetonitrile, two TBS groups were removed within 20 minutes, judged from TLC, and the additional acetallization was in equilibrium in 2 h. The mixture of the products was easily separated by SiO_2 column chromatography to afford compound **2** as a major product in 76% yield. Treated under the same conditions, the other isomers were converted to **2** in 38% yield. Eventually, **2** was yielded in 86% combined yield from **3**. The stereoselective methylation of **2** was achieved by MeLi in THF to afford **1**[9] in 82% yield. The structure of **1** was confirmed by NOE experiment (Figure 1). When C_{37} methyl signal (δ1.21, 3H, s) was



Scheme 3. *Reagents and conditions*: a) PhSSPh, Bu_3P, CH_2Cl_2, 22 °C, 21 h, 85%; b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 22 °C, 4 h, 91%; c) *conc.* HCl, MeOH, reflux, 2 days; d) Bu_2SnO, PhH-MeOH (10:1), reflux, 5 h; e) BnBr, TBAI, toluene, reflux, 2 h; f) TBSCl, imidazole, DMF, 25 °C, 3 h, 82% from 12; g) BuLi, THF, -78 °C, 10 min, then 10, THF, -78 °C, 1 h, 83% from 9; h) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 2 h, then Et_3N; i) Al(Hg), THF-H_2O (10:1), 25 °C, 23 h, 86% from 14; j) $RuO_2 \cdot H_2O$, $NaIO_4$, CCl_4-CH_3CN-H_2O (1:1:1.5), 25 °C, 40 min, 72%.



Scheme 4. *Reagents and conditions*: a) 46% aqueous HF, CH_3CN, 25 °C, 2 h, 86% after one recycle; b) MeLi, THF, -78 °C, 20 min, 82%.

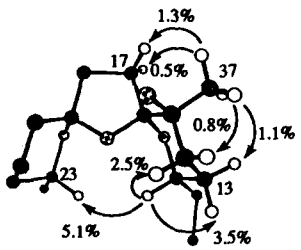


Figure 1. NOE's correlations of 1.

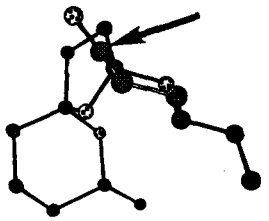


Figure 2. Methylation agent approaches from the direction shown by the arrow. Another face of the carbonyl group is hindered by another 6-membered ring skeleton.

irradiated, 1.1% enhancement of NOE was detected at the axial proton of C_{13} (δ 1.45, 1H, dq, J= 3.9, 12.2 Hz). The other correlations of NOEs are shown in Figure 1. The stereoselectivity of methylation was attributed to the steric hindrance of the β-face of the carbonyl group in **2** (Figure 2).

Interestingly, compound **1** was unstable when allowed to stand in $CDCl_3$ including a trace amount of

HCl at 25 °C, being converted to the other isomers in >30% in 12 h, while compound **2** was stable under the same conditions for 3 days. Presumably, this observation in **1** is rationalized by 1) decrease of the anomeric effect at C_{16} by losing the adjacent carbonyl group, 2) generation of steric repulsion in C_{37} methyl group, C_{17} methylene group, and the axial hydrogen atom at C_{13} (see Figure 1).

In conclusion, we have completed the first synthesis of the common intermediate **1** corresponding to the B, C, and D ring fragment of pinnatoxins. Further efforts toward the total synthesis of pinnatoxins are underway in our laboratory.

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9. **1**: ^{1}H NMR (400 MHz, CD_3OD), δ 1.21 (3H, s, H-37), 1.34 (1H, brdq, J= 2.0, 12.0 Hz, H-22ax), 1.45 (1H, dq, J= 3.9, 12.2 Hz, H-13ax), 1.51 (1H, m, H-20ax), 1.56 (1H, m, H-14eq), 1.61 (1H, m, H-22eq), 1.63 (1H, m, H-13eq), 1.64 (1H, m, H-11a), 1.66 (1H, m, H-21eq), 1.72 (1H, m, H-11b), 1.80 (1H, m, H-17a), 1.81 (1H, m, H-20eq), 1.82 (1H, m, H-18a), 1.96 (1H, tq, J= 3.8, 13.1 Hz, H-21ax), 2.02 (1H, m, H-14ax), 2.09 (1H, m, H-18b), 2.15 (1H, m, H-17b), 3.37 (2H, d, J= 4.5 Hz, H-24), 3.42-3.53 (2H, m, H-10), 3.74 (3H, s, MPM), 3.91-3.98 (1H, m, H-12), 4.04 (1H, ddt, J= 2.3, 12.0, 4.5 Hz, H-23), 4.28 (2H, s, MPM), 4.44 (1H, d, J= 12.2 Hz, Bn), 4.47 (1H, d, J= 12.2 Hz, Bn), 6.83 (2H, d, J= 8.5 Hz, MPM), 7.17 (2H, d, J= 8.5 Hz, MPM), and 7.21-7.32 (5H, m, Bn); ^{13}C NMR (100 MHz, CD_3OD), δ 20.60 (C21), 22.69 (C37), 28.62 (C22), 31.23 (C13), 31.87 (C17), 35.38 (C20), 35.85 (C14), 36.81 (C11), 38.65 (C18), 55.68 (MPM), 68.39 (C10), 69.77 (C12), 71.24 (C15), 73.08 (C23), 73.41 (MPM), 74.31 (Bn), 74.79 (C24), 109.55 (C19), 112.18 (C16), 114.73 (MPM), 128.56 (Bn), 128.79 (Bn), 129.32 (Bn), 130.37 (MPM), 131.84 (MPM), 139.84 (Bn), and 160.72 (MPM); IR (neat), 3580, 3512, 3064, 3032, 2940, 2864, 1614, 1588, 1514, 1456, 1364, 1248, 1100, 1004, 860, 818, 736, and 698 cm^{-1}.

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