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One-step assembling reaction to the pentacyclic acetal of pinnatoxins

Jun Ishihara, Shingo Tojo, Akio Kamikawa and Akio Murai*

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan. E-mail: amurai@sci.hokudai.ac.jp; Fax: +81-11-706-2714; Tel: +81-11-706-2714

Received (in Cambridge, UK) 9th May 2001, Accepted 13th June 2001
First published as an Advance Article on the web 11th July 2001

Treatment of acyclic tetraketone 8 with HF·py in MeCN afforded the pentacyclic system 1 in pinnatoxins with a high selectivity in good yield.

The intramolecular acetal functionalities widely appear as subunits of many biologically active natural products, including polyether ionophores, and the construction of these acetal systems represents a synthetic challenge.[1,2] The favored conformation of the spiroacetal is predictable on the basis of stabilizing anomeric and *exo*-anomeric effects that direct C–O bonds to axial positions on the respective rings.[3] Pinnatoxins, which were isolated from *Pinna muricata* by Uemura, included the unique dispiroacetal and bicycloacetal moieties in their skeletons.[4] Recently, Kishi and co-workers accomplished the total synthesis of pinnatoxin A, and the absolute stereochemistry was determined at the same time.[5,6] Independently, we reported an efficient formation of the trioxadispiroacetal moieties,[7] and also the construction of the BCDEF ring system of pinnatoxins, however acetal formation of the BCDEF ring system was rather problematic as an undesired acetal was generated as a major product.[8] On our way to the syntheses, it was found that both of the BCD-fragment and the EF-fragment could be constructed under the same conditions. These results suggested the possibility of a one-step formation of two intramolecular acetals, which would allow fewer steps and seemed to be more attractive. Herein, we describe a one-step assembling reaction to the pentacyclic system of pinnatoxin A, **1**† (Fig. 1).

In our initial efforts, tetra-TBS‡ compound **2** was selected as a precursor for the cyclization in the unnatural enantiomeric form (Scheme 1). Various conditions were examined, however, none of the acidic conditions provided compound ***ent*-1**. Upon terminating the reaction after 1 hour, it seemed that the TBS groups at C-29 and 30 positions still remained intact, while the BCD-ring moiety might be gradually formed. At longer reaction time, the cyclic products were overreacted to afford a complex mixture, including β-eliminated and retro-aldol compounds. These results suggested that the formation of the EF-ring should precede the cyclization of the BCD-ring, which implied the faster hydrolysis of the protective groups at C-29 and 30 than the others. Therefore, 29,30-di-TES compound, which would be more detachable than di-TBS, was directed at the next stage.

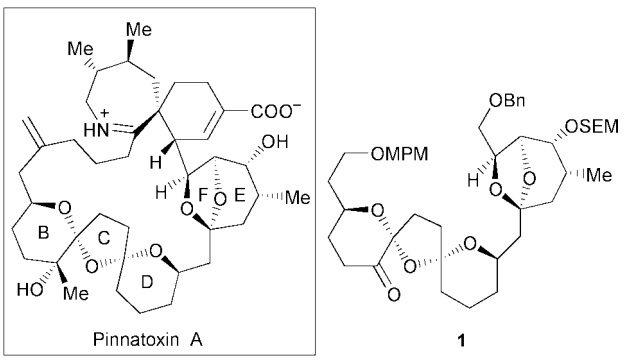
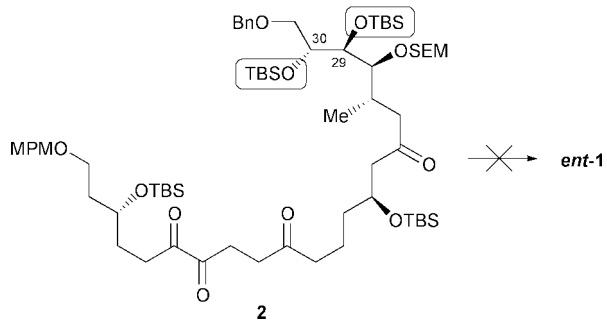


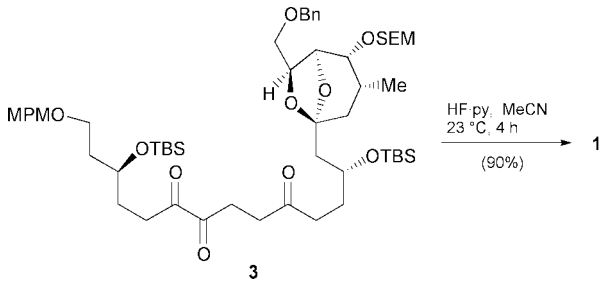
Fig. 1



Scheme 1

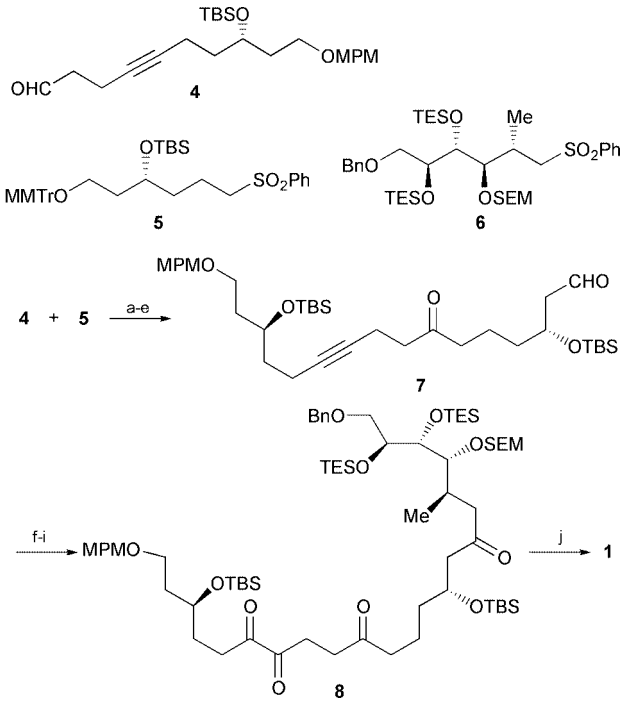
Prior to one-step assembling reaction, stepwise acetalization was elucidated, which involves the construction of the BCD-ring after formation of diacetal moiety (Scheme 2). The acetalization reaction of **3**[9] was performed with HF·py in MeCN at 23 °C for 4 h to afford the desired compound **1** in 90% yield as a sole component of the pentacyclic compounds in spite of the possibility of eight products.[10] According to our previous results, the acetal formation of BCD-ring would be controlled by the thermodynamic effect,[11] which is based on the anomeric effect enhanced by the presence of an α-ketone.[12]

Since formation of the BCD-ring acetal proceeded independently of the EF-ring, the one-step assembling reaction to the pentacyclic system seemed to be realized. Reaction of **4** and **5**, followed by oxidation and desulfurization,[13] gave a coupled ketone in 84% yield in 4 steps (Scheme 3). The MMTr‡ group was detached with PPTS in MeOH and CH_2Cl_2 to the alcohol in 86% yield,[14] which was subsequently oxidized to aldehyde **7** in 99% yield. Analogous reaction of the sulfone **6** and **7** proceeded moderately to furnish another coupled ketone in 60% yield in 3 steps, which was converted to tetraketone **8** by ruthenium oxidation in 77%. Now the precursor for cyclization was obtained in our hands. When **8** was exposed to HF·py in MeCN at 24 °C for 7.5 h, the desired pentacyclic acetal compound **1** was produced as a single pentacyclic isomer in 71% yield, which was accompanied by a mixture of by-products lacking the pentacyclic system. The incompletely cyclized by-products were convertible to **1** under the same conditions. Eventually, the desired **1** was provided in an 83% combined yield from **8**. On the other hand, in the case of THF as a solvent, the reaction afforded the pentacyclic compound as a mixture of three isomers (**9**:**10**:**1** = 2:1:1) in 83% yield (Scheme 4). When this

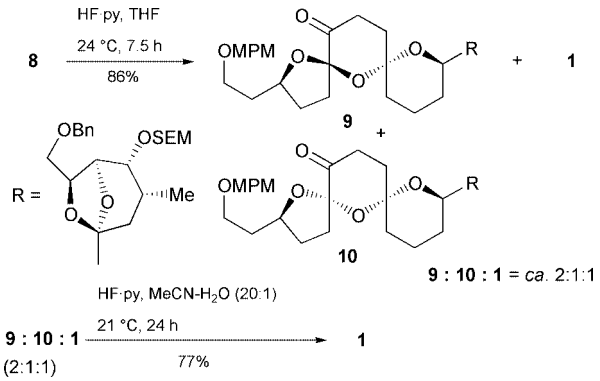


Scheme 2

 DOI: 10.1039/b104200a



Scheme 3 (a) **5**, BuLi, THF, −78 °C, 30 min, then **4**, −78 °C, 30 min; (b) Swern oxidation; (c) (i) SmI_2, MeOH, THF, 0 °C, 30 min, (ii) Al(Hg), THF–H_2O (10:1), 23 °C, 16 h (84% in 4 steps); (d) PPTS (cat.), MeOH–CH_2Cl_2 (1:50), 21 °C, 10.5 h (88%); (e) DMPI,‡ $NaHCO_3$, CH_2Cl_2, 23 °C, 20 h (99%); (f) **6**, BuLi, Et_2O, −78 °C, 30 min, then **7**, −78 °C, 15 min; (g) DMPI, $NaHCO_3$, CH_2Cl_2, 23 °C, 11.5 h; (h) SmI_2, MeOH, THF, 0 °C, 30 min (60% in 3 steps); (i) $RuO_2{\cdot}H_2O$, $NaIO_4$, CCl_4–MeCN–pH 7 buffer (1:1:1.5), 23 °C, 195 min (77%); (j) HF·py, MeCN, 24 °C, 7.5 h (83% after one recycle).



Scheme 4

mixture of **9**, **10**, and **1** was treated with HF·py in MeCN–H_2O (20:1) at 21 °C for 24 h, **1** was generated in 77% yield. The exclusive formation of **1** seems to be reasonable judging from the results of MM2* calculation using MacroModel 6.5 for the relative energies of the compounds, which suggested that the potential energy of **1** would be > 3.5 kcal mol^{-1} lower than any others. In addition, the axial preference of the C–O bond of the cyclic acetal would be enhanced by the presence of an α-ketone due to the cyclic stereoelectronic effect of π-electron donation. The acetalization in THF proceeded under the kinetic control, while the thermodynamic effect played an important role in the case of MeCN. The difference between the selectivities in MeCN and THF were induced by the solvation effect, which appeared in the glycosidation, involving the intermediacy of the acetonitrilium ion.[15] Thus, the one-step assembling reaction of the tetraketone to the complicated acetal was achieved to provide selectively the pentacyclic compound in an excellent yield. Further synthetic study is now under way in our laboratory.

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan (11780410, J. I.).

Notes and references

† **1**: colorless oil. $[\alpha]_D^{22}$ +19.7 (*c* 0.14, $CHCl_3$); ^{1}H-NMR (C_6D_6, 400 MHz) δ 7.32 (2H, d, *J* 8.5 Hz), 7.25–7.06 (5H, m), 6.85 (2H, d, *J* 8.5), 4.79 (1H, d, *J* 6.8), 4.68 (1H, dd, *J* 1.3, 4.6), 4.65 (1H, d, *J* 6.8), 4.51–4.43 (2H, m), 4.43 (1H, d, *J* 11.2), 4.43–4.32 (3H, m), 4.23 (1H, d, *J* 12.2), 3.85 (1H, dd, *J* 6.6, 10.0 Hz), 3.82 (1H, dd, *J* 8.3, 8.7), 3.69 (1H, dd, *J* 8.3, 8.7), 3.67–3.58 (3H, m), 3.57 (1H, dd, *J* 1.3, 3.4), 3.30 (3H, s), 2.83 (1H, ddd, *J* 2.4, 8.8, 12.2), 2.62 (1H, ddd, *J* 7.4, 12.7, 14.6), 2.37–2.28 (1H, m), 2.32 (1H, dd, *J* 6.8, 14.2), 2.25–2.13 (3H, m), 2.08–1.96 (4H, m), 1.94–1.83 (1H, m), 1.79-1.65 (3H, m), 1.63–1.53 (2H, m), 1.46–1.17 (4H, m), 1.13 (3H, d, *J* 6.8), 0.98 (2H, t, *J* 8.5), and −0.01 (9H, s); ^{13}C-NMR (C_6D_6, 100 MHz) δ 201.5, 159.7, 138.7, 131.4, 129.4, 128.6, 127.9, 114.1, 108.9, 108.7, 108.5, 94.8, 78.3, 77.8, 73.8, 73.5, 73.0, 70.0, 68.5, 68.1, 67.2, 65.4, 54.9, 45.6, 40.1, 38.6, 35.9, 35.2, 34.0, 33.0, 32.5, 31.3, 30.3, 29.5, 20.6, 18.4, and 17.0; IR (neat), ν_{max} 2926, 2855, 1733, 1612, 1514, 1454, 1367, 1303, 1249, 1099, 1036, 984, 952, 861, 836, 749, and 698 cm^{-1}; FD-HR-MS: found: 796.4228, calcd. for $C_{44}H_{64}O_{11}Si$ (M^+): 796.4218.

‡ SEM = 2,2-(trimethylsilyl)ethoxymethyl. TBS = *tert*-butyldimethylsilyl. MMTr = 4-methoxyphenyldiphenylmethyl. DMPI = Dess-Martin periodinane {IUPAC name: 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one}. MPM = 4-methoxybenzyl.

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