Studies on the Stability of 1,7,9-Trioxadispiro[5.1.5.2]pentadecane System: The Common Tricyclic Acetal Moiety in Pinnatoxins

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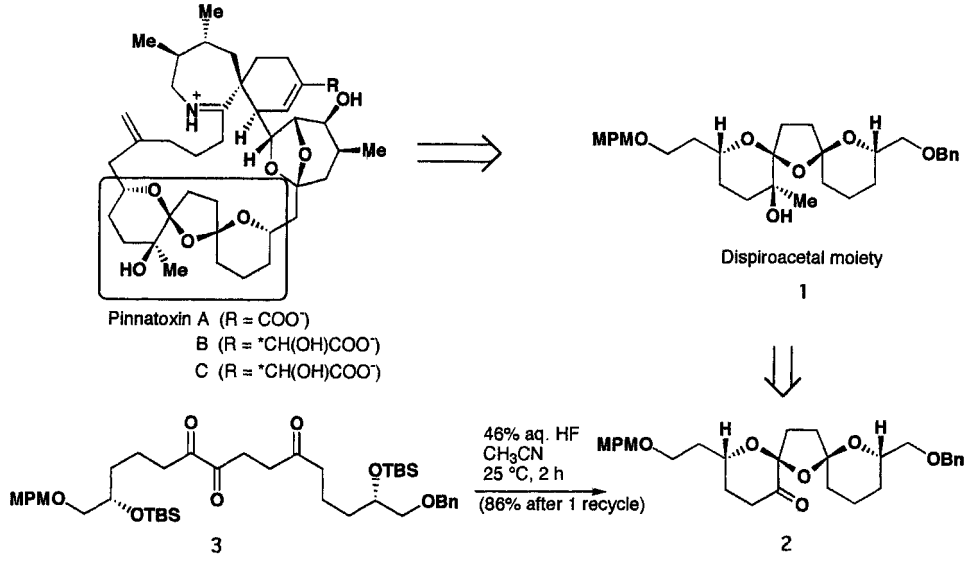
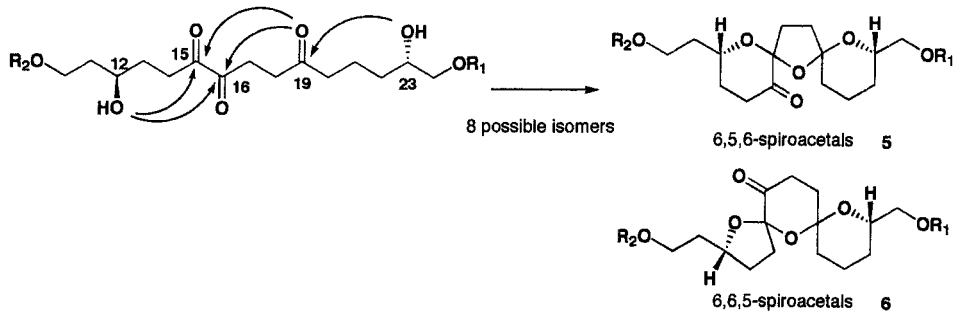
Abstract: The stability of the common dispiroacetal moiety in pinnatoxins, the 1,7,9-trioxadispiro[5.1.5.2]pentadecane system, was investigated. The tricyclic keto acetal, of the natural form, was most favored among the possible isomers, however, its methylated form was not so preferential to be isomerized readily in the presence of acid. These stability results were supported by MM2 and AM1.

The trioxadispiroacetal moieties usually appear in nature in polyether ionophores,[1)] and the construction of these tricyclic systems, linked in a spiro fashion, represents a synthetic challenge. The favored conformation of the spiroacetal would be predictable on the basis of stabilizing anomeric and *exo*-anomeric effects that direct C-O bonds to axial positions on the respective rings.[2)] Although several syntheses of the dispiroacetal systems were reported,[3)] the formation of spiroacetals provided low selectivity to afford a mixture of anomers due to the cumulative stereoelectronic and steric effects of the isomers. Very recently, we have reported the construction of the common trioxadispiro-acetal moiety **1** of pinnatoxins, shellfish poisons, isolated from *Pinna muricata*,[4, 5)] with high selectivity *via* methylation of the corresponding tricyclic ketone **2**.[6)] Compound **2** was rather stable in the presence of acid, whereas the methylation product, **1**, was labile under the same condition. In this paper, we describe the stability studies of the 1,7,9-trioxadispiro[5.1.5.2]pentadecane system.

In our previous studies,[6)] when triketone **3** was subjected to HF in CH_3CN, cleavage of the silyl groups and the subsequent cyclization proceeded stereoselectively to afford the desired tricyclic compound **2** in 78% yield, along with several isomers. The isomers could be transformed into **2** on further treatment under the same conditions, thus the total conversion yield of **3** to **2** amounted to 86% (Scheme 1). The acetalization of **3** could provide eight possible isomers, which includefour 6,5,6-tricyclic keto-acetals **5** and four 6,6,5-tricyclic ketones **6** (Scheme 2). The predominant product indicated that **2** would be thermodynamically most preferable in CH_3CN. In order to investigate the stability of the trioxadispiro-acetal system, we reviewed the additional acidic conditions.[7)] First, for the purpose of elucidating solvent effects, the similar treatment of **3** with HF in THF for 24 h was attempted (Table 1). The cyclization provided **2** as a major spiroacetal in 63%, however, removal of the TBS group proceeded slowly to be



Scheme 1



Scheme 2

accompanied with decomposition products (entries 1 and 2). On the other hand, when purified **2** was treated with aqueous HCl in THF, the starting material was recovered in 69%, along with a mixture of dicyclic products (entry 3). Under a nonaqueous condition, exposure of **2** to PTS·H_2O in THF provided **2** (quant.) without any isomerization (entry 5). It was clarified that **2** would be the thermodynamically most favored tricyclic acetal in both CH_3CN and THF, and the energy differences between **2** and the isomers would be significant. Next, we explored the energy calculation of the dispiro compounds.

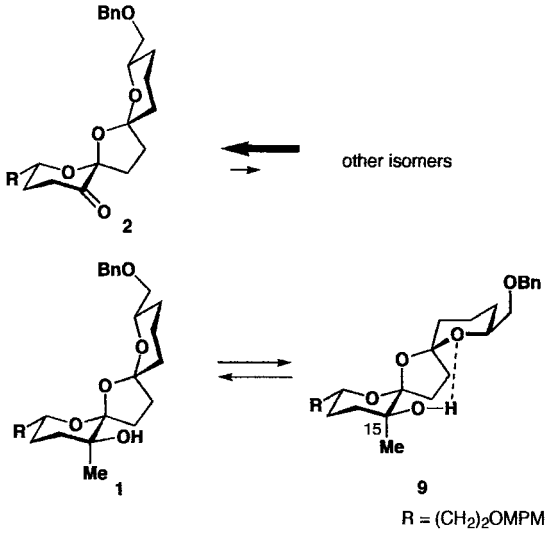
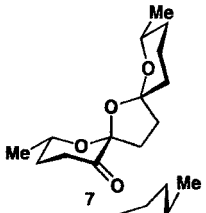
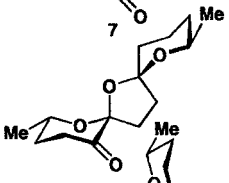
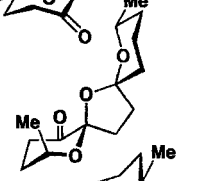
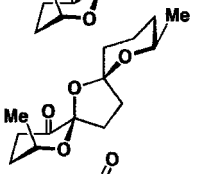
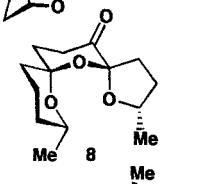
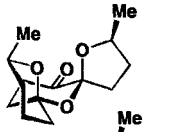
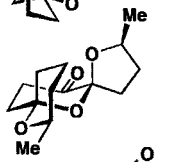
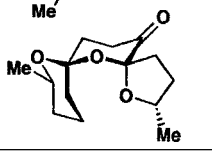


Table 1. The acid treatment of **1**, **2**, and **3**

entry	substrate		results
1	**3**	HF-CH_3CN (20:1), 25 °C, 2 h	**2** (78%)
2		HF-THF (9:1), 22 °C, 24 h	**2** (63%)
3	**2**	1 M HCl-THF (10:1), 22 °C, 44 h	**2** (69%)
4		PPTS-THF, 22 °C, 24 h	**2** (82%)
5		PTS-THF, 22 °C, 24 h	**2** (quant)
6	**1**	trace HCl-$CDCl_3$, 22 °C, 12 h	**1**:**9** (3:2) (quant)
7		trace HCl-THF, 22 °C, 41.5 h	**1**:**9** (3:1) (quant)
8		PPTS-THF, 22 °C, 24 h	no reaction
9		PTS-THF, 22 °C, 24 h	**1**:**9** (3:1) (quant)
10	**9**	PTS-THF, 24 °C, 24 h	**1**:**9** (3:1) (quant)

To simplify the calculation, we selected dimethyl compound **7** as a model. Table 2 depicts the energy of the possible isomers relative to **7**.[8] Most of the 6,5,6-tricylic acetals would be more favored than the 6,6,5-tricyclic ketones. There might be significant 1,3-diaxial repulsion in the central ring of 6,6,5-tricyclic systems. It should be noted that the optimal conformations of α-keto acetal in all isomers came from the consequence of the stabilizing anomeric effect. The anomer effect would be increased by the carbonyl group in the α-keto spiroacetal, which can be attributed to the stereoelectronic effect of the carbonyl π-orbital.[9] Based on the calculations by MM2, *cis*-6,5,6-tricyclic isomer **7** was most preferred energetically, and the difference in potential energy from the next stable isomer, **8** was evaluated as more than 1.8 kcal/mol (entries 1 and 5). It could be rationalized that the structure of **7** would maximize the anomeric stabilization and minimize any destabilizing 1,3-diaxial and dipole repulsion. AM1 calculations also suggested the predominance of **7**. Accordingly, it is accepted that naturally occurring acetal **2** would be the most stable among the possible isomers.

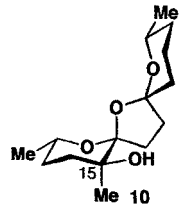
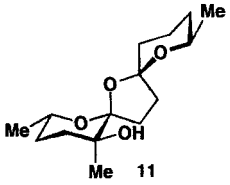
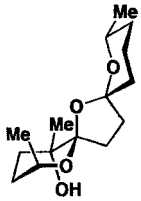
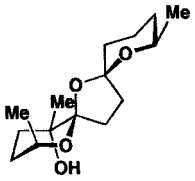
Table 2. The relative energy of the isomers against **7**

entry		(kcal/mol) MM2	AM1
1		0.0	0.0
2		2.2	2.5
3		2.3	1.7
4		5.3	6.0
5		1.8	2.5
6		3.3	6.1
7		4.1	2.8
8		6.8	6.3

The tricyclic ketone **2** was converted to **1** in 90 % yield as a single stereoisomer. Unexpectedly, when **1** was allowed to stand in old $CDCl_3$ in an NMR tube for 12 h, the isomerization occurred to give a mixture of two isomers (3:2);[10] one was recovered **1**, another was compound **9**.[11] Similar transformations were observed by treatment with fresh $CDCl_3$ in the presence of a trace of HCl (Table 1, entry 6). The evidence of destabilization was so intriguing that we examined the isomerization of **1** (Table 1). Exposure to HCl or PTS in THF provided a mixture of **1** and **9** in a ratio of 3:1 (entries 7 and 9). Since analogous operation of pure **9** furnished a mixture of **1** and **9** in the same ratio (entry 10), the isomerization was suggested to be in thermodynamic equilibrium. It was apparent that **1** would be unstable under acidic conditions, compared to the precursor **2**. Next, the calculations of the relative energy of the possible isomers was evaluated again (Table 3). MM2 calculation predicted that **10** would be the most favored isomer, however, the differential energy was estimated to be only 0.5-1.1 kcal/mol (entries 1,

2, and 3) and the preference for naturally occurring isomer, **10**, would be small. Based on AM1 level calculations, **11** was found to be the most preferential isomer. These results were coincident to the experimental observation of **1**. It is considered that the keto-acetal **2** would be stabilized by the anomeric effect enhanced by the presence of α-ketone, while methyl compound **1** would be destabilized by the repulsion of the central ring against the methyl or the hydroxyl group at C-15, as well as the lack of above α-keto enhanced anomeric effect. Furthermore, the hydrogen bonding of the hydroxyl group at C-15 with the tetrahydropyranyl oxygen atom might probably exist in **9**.[12] The isomerization ratios between **1** and **9** were slightly different in $CDCl_3$ and THF due to the difference in solvation effect. It was realized that **9** increased in relatively low dielectric solvent $CDCl_3$ (ε=4.7), compared to THF (ε=7.4). In consequence, extreme predominance of **1** would be lost over the isomers and would be isomerized partly to **9** easily.

Table 3. The relative energy of possible isomers

entry		(kcal/mol) MM2	AM1
1		0.0	0.0
2		1.1	-1.4
3		0.5	0.2
4		3.6	5.7

It was thus concluded that the ketone **2** would be more available as a synthetic key intermediate, whereas the corresponding methyl compound **1** has an ability to isomerize readily in the presence of acid.[13]

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References and Notes

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6) Sugimoto, T.; Ishihara, J.; Murai, A. *Tetrahedron Lett*. **1997**, *38*, 7379.

7) Exposure of **3** to a mixture of Bu_4NF (3.4 eq) and AcOH (10 eq) in THF at 25 °C for 1.5 h resulted in no reaction, whereas treatment with Bu_4NF (10 eq) and AcOH (10 eq) afforded complex mixtures.

8) All structures in the Table show the optimum conformations. Based on the calculation, the central five-membered ring is able to have two envelope conformations, which are estimated to have almost the same energy. The ^{1}H-NMR measurements at variable temperatures supported the existence of two conformers of the tetrahydrofuran ring in equilibrium.

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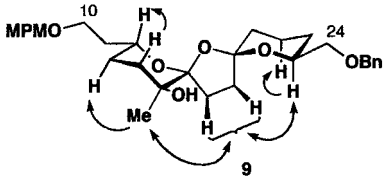
10) The ratios of the mixture were determined by ^{1}H-NMR analysis.

11) The structure of **9** was determined by ^{1}H- and ^{13}C-NMR, NOE, COSY, HMBS, and HSQC spectra. The selected NOE correlations of **9** are shown as follows:



9

9: colorless oil, $[\alpha]_D^{22}$ -34 (*c* 0.17, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$), δ 1.20 (3H, s, H-37), 1.36 (1H, m, H-22), 1.45 (1H, m, H-13ax), 1.47 (1H, m, H-13eq), 1.54 (1H, m, H-22), 1.58 (1H, m, H-14eq), 1.59 (1H, m, H-11), 1.64 (1H, m, H-17α), 1.64 (1H, m, H-20), 1.67 (1H, m, H-21), 1.68 (1H, m, H-11), 1.77 (1H, m, H-21), 1.79 (1H, m, H-18α), 1.93 (1H, dt, *J*= 4.9, 13.2 Hz, H-14ax), 2.24

(1H, m, H-18β), 2.25 (1H, m, H-17b), 3.43 (1H, dd, *J*= 6.3, 10.3 Hz, H-24), 3.46-3.54 (2H, m, H-10), 3.59 (1H, dd, *J*= 6.3, 10.3 Hz, H-24), 3.77 (3H, s, MPM), 3.79-3.84 (1H, m, H-23), 3.94-4.01 (1H, m, H-12), 4.39 (2H, s, MPM), 4.88 (2H, s, Bn), 6.87 (2H, d, *J*= 8.8 Hz, MPM), 7.22 (2H, d, *J*= 8.8 Hz, MPM), and 7.25-7.36 (5H, m, Bn); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 21.32 (C21), 22.15 (C37), 27.87 (C22), 30.67 (C17), 31.51 (C13), 32.58 (C18), 36.43 (C14), 36.79 (C11), 37.24 (C20), 55.66 (MPM), 67.73 (C10), 68.14 (C12), 70.41 (C15), 73.68 (MPM), 74.06 (C24), 74.18 (Bn), 75.00 (C23), 110.49 (C19), 112.15 (C16), 114.67, 128.70, 128.95, 129.38, 130.53, 131.64, 139.53, and 160.79 (Ar); IR (neat), 3544, 3064, 2938, 2860, 1614, 1518, 1458, 1365, 1302, 1248, 1149, 1098, 1035, 1002, 960, 822, 735, and 696 cm^{-1}; IR ($CHCl_3$), 3520, 3018, 3005, 2947, 2866, 1612, 1514, 1456, 1364, 1302, 1248, 1194, 1175, 1148, 1096, 1036, 1003, 957, 860, 826, 766, 748, 700, and 671 cm^{-1}.

12) On measurement of IR analysis of **9** in 0.03 M $CHCl_3$, a broad signal was observed at 3520 cm^{-1}, which was assignable to the hydrogen bonded hydroxyl group, whereas IR absorption of **1** in 0.03 M $CHCl_3$ solution displayed a sharp signal at 3568 cm^{-1}, corresponding to a free hydroxyl group.

13) It was also reported that the unexpected rearrangements of the trioxadispiroacetal compounds proceeded in the presence of acid. see: Dorta, R. L.; Martín, A.; Suárez, E.; Betancor, C. *J. Org. Chem.* **1997**, *62*, 2273.