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Absolute Configuration of the Spiroacetal Portion of Zooxanthellatoxin-A.

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Abstract: By synthesizing the MTPA ester **11**, an enantiomer of the degradation product **1**, the absolute configuration of the spiroacetal portion (C79-C95) of zooxanthellatoxin-A was determined to be 81*R*, 85*R*, and 93*S*. Copyright © 1996 Elsevier Science Ltd

Zooxanthellatoxin-A (ZT-A) and ZT-B were isolated from the symbiotic dinoflagellate, zooxanthella *Synbiodinium* sp., as vasoconstrictive compounds[1a] and found to be an activator of rabbit platelets aggregation.[1b] The structures were determined on the basis of their degradation experiments and extensive spectral analyses.[2] These contain as common structure the largest lactone ring among known natural products. In order to investigate their biogenesis and the mechanism of the bioactivities, we initiated a combination of synthetic and spectroscopic studies to determine their stereochemistry and reported the absolute stereochemistry of the tetrahydropyran portion of the common terminal acid in zooxanthellatoxins.[3] In this paper, we will report the absolute stereochemistry of the spiroacetal portion of ZT-A.

Oxidation of ZT-A and ZT-B with large excess of $NaIO_4$ gave peracetates **1** and **2** (R=Ac) of the corresponding spiroacetal alcohols, respectively, after reduction with $NaBH_4$ followed by acetylation (Fig. 1). The relative configurations of the spiroacetal moiety of **1** and **2** were determined on the basis of spin coupling constants and NOE data. The stereochemistry at the acyclic portions could not be elucidated. Since the amount of the compound is limited, we started to synthesize one of the possible isomers of the spiroacetal **1** based on its C_2 symmetry as shown in Scheme 1.

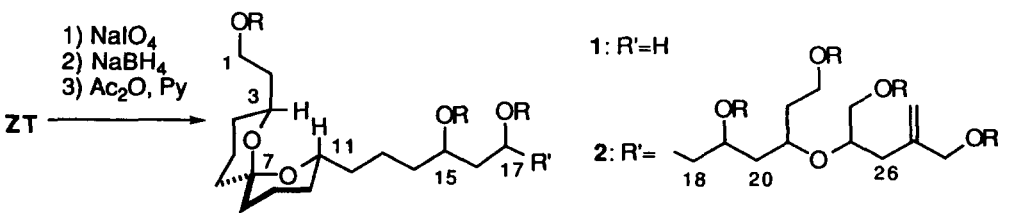
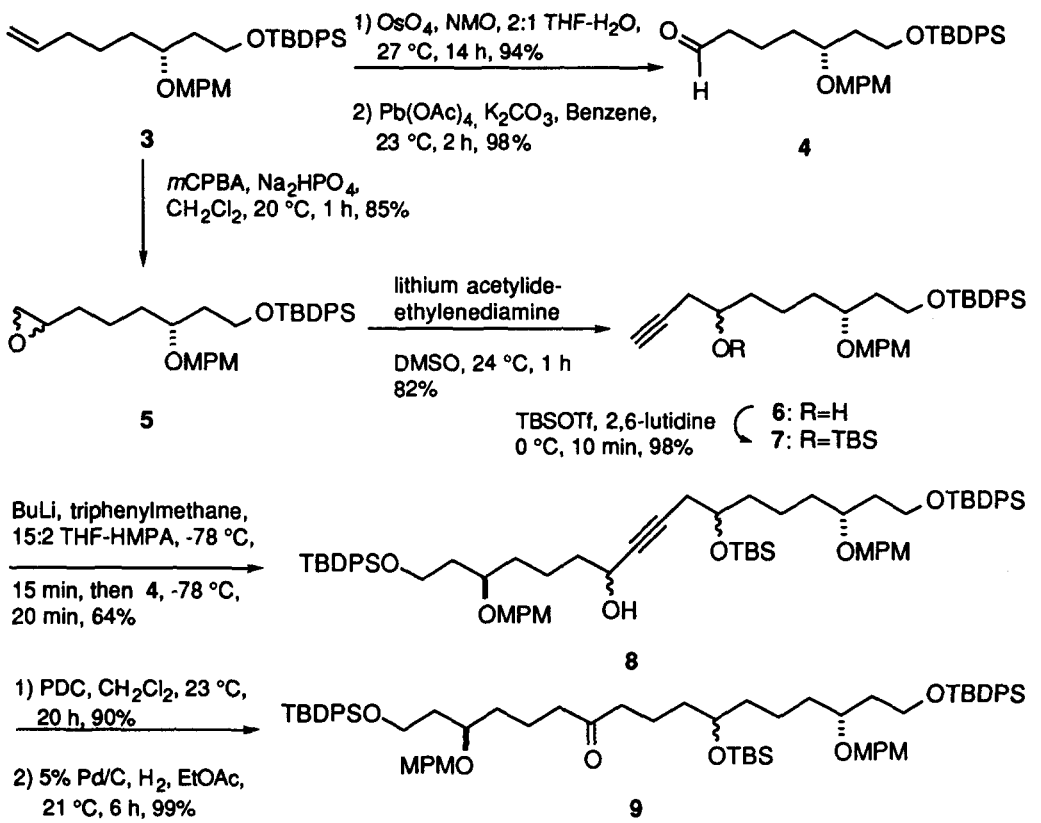


Fig. 1. Degradation experiments of zooxanthellatoxins (ZT).

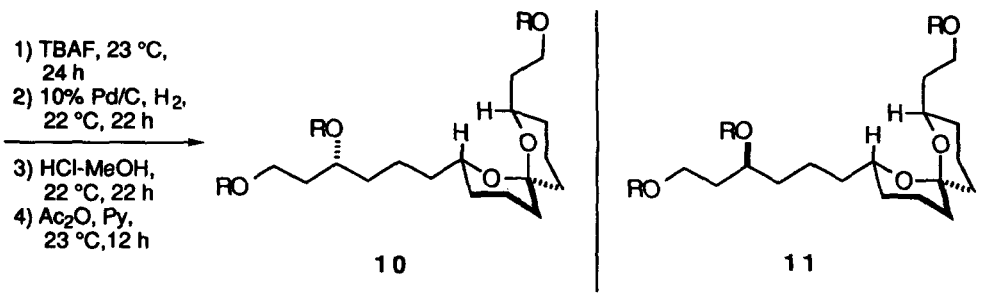
The common building unit **3** for the synthesis[4] was prepared from 5-hexen-1-ol in 8 steps including Sharpless epoxidation (97% ee) in a total yield of 38%.[5] OsO_4 oxidation of **3** followed by glycol cleavage with $Pb(OAc)_4$ gave aldehyde **4**. On the other hand, epoxidation of **3** with *m*CPBA yielded a 1:1 diastereo-mixture of epoxide **5**, which was treated with lithium acetylide to afford alkyne **6**. After protection of the hydroxyl group with TBS, **7** was subjected to the coupling reaction with the aldehyde **4** in the presence of a small amount of triphenylmethane as an indicator to afford a diastereo-mixture of alcohol **8**. The precursor of spiroacetalization **9** was prepared in 90% yield from **8** by oxidation of the hydroxyl group followed by hydrogenation of the triple bond.

Scheme 1



Spiroacetalization of **9** was performed with HCl-MeOH following two deprotection steps with TBAF and H_2-10% Pd/C, respectively (Scheme 2). After acetylation, the most stable spiroacetal **10** (R=Ac) was obtained in 10% yield from **9** and the other unstable spiroacetal isomers were not isolated in pure form. Hydrolysis of the acetate with K_2CO_3 in MeOH afforded triol **10** (R=H). The ^1H NMR spectra of both triol and triacetate **10** were very similar to those of the triol and the triacetate **1** prepared from ZT-A, respectively, suggesting that their relative configurations in the spiroacetal unit were identical, though the configuration in the acyclic portion could not be determined at this stage.

Scheme 2



Absolute configuration of **1** was deduced by converting the triols to their diastereomeric esters of α-methoxy-α-trifluoromethyphenylacetic (MTPA) acid and comparing the spectral data with those of esters **10** [R=(*R*)-MTPA, **10-(*R*)-MTPA**] and **11** [R=(*R*)-MTPA, **11-(*R*)-MTPA**] prepared from **10** (R=H) under normal [DCC, (*R*)-MTPA acid, CH_2Cl_2] and Mitsunobu [(*R*)-MTPA acid, triphenylphosphine, diethyl azodicarboxylate, THF, 22 °C, 7 h and then 40 °C, 2 h] conditions, respectively. Comparison of the spectrum of the acyclic portions of the esters **1**, R=(*R*)-MTPA [**1-(*R*)-MTPA**] and R=(*S*)-MTPA [**1-(*S*)-MTPA**], suggested *R*-configuration at C15.[8] Since the spectrum of **1-(*S*)-MTPA** was identical with that of **11-(*R*)-MTPA** , the absolute configuration of **1** is opposite to that of **11**, *i.e.*, 3*S*, 11*R*, and 15*R*.

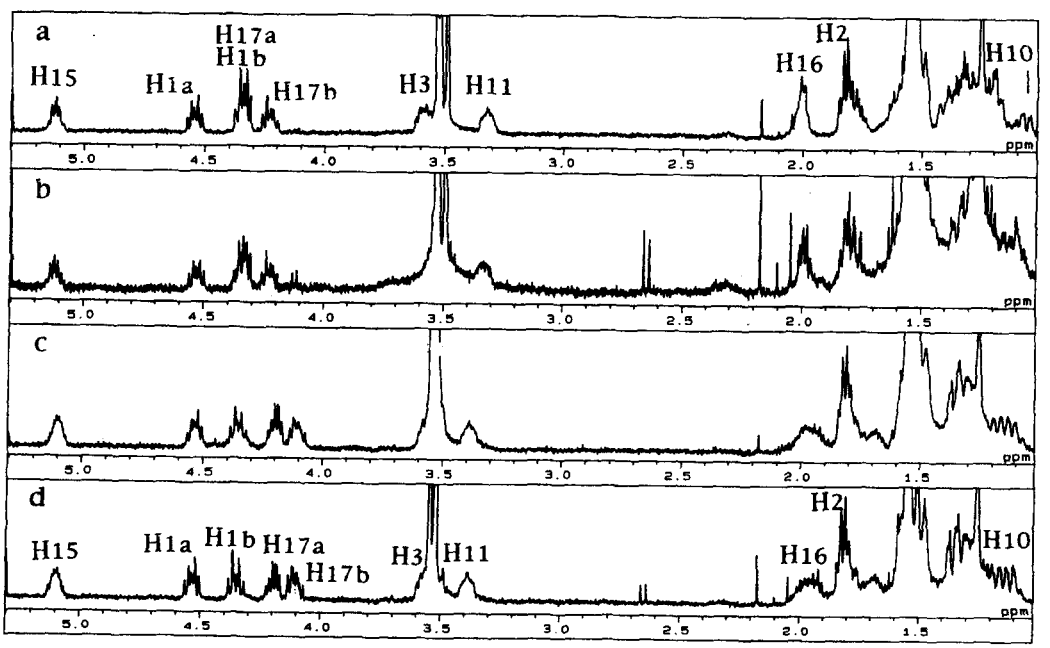


Fig. 2. 400 MHz ^{1}H NMR spectra of the tris-MTPA esters of spiroacetal triols **1**, **10**, and **11** in $CDCl_3$: **a**; **1-(*R*)-MTPA**, **b**; **10-(*R*)-MTPA**, **c**; **11-(*R*)-MTPA**, **d**; **1-(*S*)-MTPA**.

In spite of the rapidly increasing number of reports dealing with highly oxygenated marine toxins having moderate to large molecular weights, little is known about the absolute configuration of these marine toxins and

their biogenesis.[9,10] Since the number of enzymes involved in their biogenesis is limited, it thus appears that a general pathway to control configuration at the chiral centers is feasible. The absolute stereochemistry of the degradation product **1** was determined as 3*S*, 11*R*, and 15*R* which correspond to C93, C85, and C81 of ZT-A, respectively. The absolute configuration of the spiroacetal portion found in the congener ZT-B might be the same to that of ZT-A as in the common terminal acid portion. Studies on the absolute configuration and biogenesis of zooxanthellatoxins are in progress in our laboratory.

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References and Notes

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4. All new compounds gave satisfactory spectral data.
5. 1) PDD, 2) $Ph_3P{=}CHCO_2CH_3$, 3) DIBAH, 4) Sharpless epoxidation with (-)-DET, 5) Red-Al, 6) *p*-anisaldehyde, PTS, 7) DIBAH, and 8) TBDPSCl, imidazole.
6. Triacetae **10**: $[\alpha]_D^{20}$ -48 (*c* 0.20, $CHCl_3$); IR (film) 2940, 1746, 1442, 1252, 1100, 980, 856, and 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (2H, m), 1.22-1.70 (12H, m), 1.63 (3H, s), 1.72 (3H, s), 1.80 (3H, s), 1.93 (2H, m), 3.53 (1H, br m), 3.75 (1H, br m), 3.99 (1H, dt, *J*=11, 6 Hz), 4.15 (1H, dt, *J*=11, 5 Hz), 4.29 (1H, dt, *J*= 11, 6 Hz), 4.37 (1H, dd, *J*=11, 7 Hz), and 5.14 (1H, br m); HR-EIMS m/z 442.2566 $(M)^+$. Calcd for $C_{23}H_{38}O_8$ 442.2538.
7. Triol **10**: $[\alpha]_D^{22}$ -58 (*c* 0.10, CH_3OH); IR (film) 3360, 2868, and 1096 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.10-1.78 (20H, m), 1.78-2.00 (2H, m), 3.62 (1H, m), 3.65-3.75 (1H, m), 3.68 (2H, t, *J*=7 Hz), 3.70 (2H, t, *J*=7 Hz), and 3.80 (1H, m); HR-EIMS m/z 316.2242 $(M)^+$. Calcd for $C_{17}H_{32}O_5$ 316.2250.
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