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TETRAHEDRON: *ASYMMETRY*

Synthesis and absolute configuration of an exomethylene portion of zooxanthellatoxin-A

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Abstract

The absolute configuration of the exomethylene portion of zooxanthellatoxin-A (ZT-A) was established as 71*R*,73*R*,74*S*,75*R* by comparing an MTPA ester of an acyclic degradation product of ZT-A with those of the compound synthesized from methyl-α-D-glucopyranoside.

Zooxanthellatoxin-A (ZT-A) and -B were isolated from the symbiotic dinoflagellate, *Synbiodinium* sp. (strain Y-6) as vasoconstrictive compounds[1a] and found to be activators of rabbit platelet aggregation.[1b–d] The structures were determined on the basis of degradation experiments coupled with extensive spectral analyses.[2] In order to investigate their biogenesis and mechanisms of the bioactivities, we started to determine their stereochemistry by a combination of synthetic and spectroscopic studies and have reported the absolute configuration of the tetrahydropyran portion of the common terminal acid (L) in zooxanthellatoxins and the spiroacetal portion of zooxanthellatoxin-A.[3] Since major differences of the structures between ZT-A and the congener ZT-B were seen around the exomethylene containing portion, it was interesting to know the differences of the stereochemistry of their exomethylene units from a biosynthetic point of view. Here we report the absolute configuration of an exomethylene portion of ZT-A.

Under the selected oxidation conditions with a use of limited amounts of $NaIO_4$, the tetraacetate **1b** was obtained after reduction with $NaBH_4$ followed by acetylation. The relative configuration of the tetrahydropyran structure of **1b** was determined on the basis of coupling constants and NOE data. Due to low reproducibility of the degradation experiments, it was difficult to obtain enough **1** to determine the absolute configuration. We selected a final glycol cleavage product with $NaIO_4$ **2a** as a key compound to determine the absolute configuration by comparing NMR data of its MTPA esters. For this purpose either **1a** or its C73 and/or C74 epimers could be used as a precursor of **2a**.

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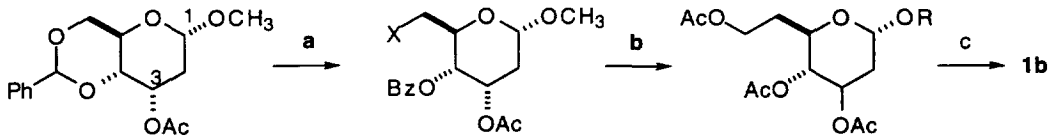
Bromination of the readily available acetate **3**[4,5] derived from α-methyl-D-glucoside with NBS gave bromide **4**[4,6] which was transformed to cyano compound **5**[4] upon treatment with KCN in DMSO. Successive reduction of **5** with DIBALH followed by $NaBH_4$ afforded a triol which was isolated as a triacetate **6** after acetylation.[7] After several unsuccessful attempts to introduce a C4 unit to the tetrahydropyran ring of **6** with an allylsilane $AcOCH_2CH_2C(CH_2)CH_2TMS$,[8] we attempted the C-glycosidation reaction after acetolysis of **6**.[5a] Treatment of **6** with Ac_2O:H_2SO_4 (100:1) gave a mixture of acetates, from which a tetraacetate **7**[9] was obtained in 40% yield. Under acetolysis conditions, inversion of the acetoxy group at the C3 position occurred, in which a cyclic acetoxonium intermediate between C1 and C3 carbons might be involved. C-Glycosidation of **7** with allylsilane smoothly proceeded at 0°C to afford **1b** in a moderate yield of 33% (Scheme 1). ^1H NMR spectra of the synthetic **1b**[10] and the degradation product **1b** from ZT-A were superimposable, thus the relative configuration of the exomethylene portion of ZT-A was unambiguously established. After deacetylation of **1b**, the tetraol **1a**[11] was subjected to $NaIO_4$ oxidation to give a synthetic acyclic tetraol **2a**.[12] Because the ^1H NMR spectra of the (*R*)- and (*S*)-MTPA esters (synthetic **2c** and **2d**) were distinguishable,[13,14] it is possibe to establish the absolute configuration by an MTPA ester of the degradation product **2a** derived from ZT-A.



3 **4**: X=Br **5**: X=CN **6**: R=CH_3, 3α **7**: R=Ac, 3β

Reagents and conditions: a) 1) NBS, AIBN, $BaCO_3$, CCl_4, reflux, 40 min, 2) KCN, DMSO, 50 °C, 4 h, 67% for two steps; b) 1) DIBALH, CH_2Cl_2, -78 °C, 1 h, 2) $NaBH_4$, EtOH, 0 °C, 2 h , 3) Ac_2O, Py, DMAP, 23 °C, 21.5 h, 58% for three steps, 4) Ac_2O, H_2SO_4, 23 °C, 4 h, 40%; c) $AcOCH_2CH_2C(CH_2)CH_2TMS$, BF_3•Et_2O, CH_3CN, 0 °C, 1.3 h, 33%.

Scheme 1.

A seco-acid of ZT-A was treated with $NaIO_4$ followed by reductive work-up and acetylation to afford a mixture of acetates containing the exomethylene portion. Since cleavage of the glycols was incomplete, the mixture was further treated with $NaIO_4$ after deacetylation. Reductive work-up followed by desalting by ion exchange gave a mixture of alcohols. The mixture was acylated with (*R*)-MTPA acid, DCC and DMAP to yield an (*R*)-MTPA ester of **2a**. The ^1H NMR spectrum of the MTPA ester were identical to that of the (*R*)-MTPA ester of the synthetic product **2a**, by which the absolute configuration of the exomethylene portion of ZT-A was proved to be 71*R*,73*R*,74*S*,75*R* as shown in Fig. 1.

Studies on the absolute configuration of the other parts of zooxanthellatoxins such as an exomethylene portion of zooxanthellatoxin-B are in progress.

Acknowledgements

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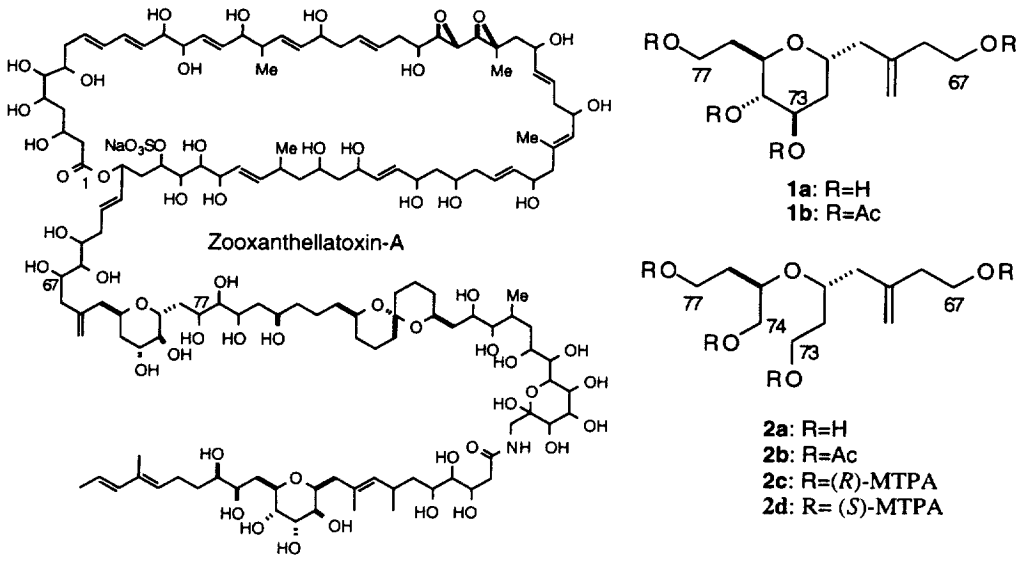

Fig. 1.

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9. Tetraacetate **7**: $[\alpha]_D^{22}$ +90.8 (*c* 1.02, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.20 (1H, brddd, 4 Hz, H1), 5.28 (1H, ddd, 5, 10, 12 Hz, H3), 4.86 (1H, t, 10 Hz), 4.16, 4.10 (each 1H, m, H7), 3.93 (1H, dt, 3, 10 Hz, H5), 2.25 (1H, brdd, 5, 14 Hz, H2α), 2.12, 2.07 (each 3H, s, OAc), 2.03 (6H, s, OAc), 1.93 (1H, ddd, 4, 12, 14 Hz, H2β), 1.83 (1H, m, H6), 1.76 (1H, tdd, 6, 10, 15 Hz, H6); HR-EIMS: *m/z* 287.1114 $(M-OAc)^+$. Calcd for $C_{13}H_{19}O_7$ 287.1131.
10. Tetraacetate **1b**: $[\alpha]_D^{21}$ +35.6 (*c* 0.52, $CHCl_3$); IR (KBr) νmax 3022, 2962, 2932, 2866, 1740, 1371, 1242, 1074, 1050, 753 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 5.32 (1H, ddd, 5, 8, 10 Hz, H73), 4.98 (1H, t, 8 Hz, H74), 4.80, 4.79 (each 1H, brs, exomethylene), 4.22, 4.21 (each 1H, td, 7, 10 Hz, H77), 4.09 (2H, t, 7 Hz, H67), 3.91 (1H, tdd, 5, 6, 9 Hz, H71), 3.78 (1H, dt, 4, 8 Hz, H75), 2.34 (1H, dd, 9, 14 Hz, H70), 2.18 (2H, t, 7 Hz, H68), 1.88–1.94 (2H, m, H76), 1.89 (1H, dd, 6, 14 Hz, H70), 1.78 (1H, td, 5, 13 Hz, H72α), 1.75, 1.74, 1.72, 1.71 (each 3H, s, OAc), and 1.67 (1H, ddd, 5, 9, 13 Hz, H72β); HR-EIMS *m/z* 354.1684 $(M-AcOH)^+$. Calcd for $C_{18}H_{26}O_7$ 354.1678.
11. Tetraol **1a**: $[\alpha]_D^{21}$ +40.9 (*c* 0.12, MeOH); ^1H NMR (400 MHz, CD_3OD, 35°C) δ 4.89, 4.87 (each 1H, brs, exomethylene), 4.14 (1H, dtd, 2, 6, 9 Hz, H71), 3.73 (1H, ddd, 5, 9, 11 Hz, H73), 3.66 (2H, t, 7 Hz, H67), 3.66 (1H, m, H77), 3.58 (1H, td, 7, 11 Hz, H77), 3.51 (1H, dt, 3, 9 Hz, H75), 3.00 (1H, t, 9 Hz, H74), 2.57 (1H, dd, 9, 15 Hz, H70), 2.29 (2H, t, 7 Hz,

H68), 2.23 (1H, dd, 6, 15 Hz, H70), 2.05 (1H, dtd, 3, 7, 14 Hz, H76), 1.90 (1H, ddd, 2, 5, 14 Hz, H72α), 1.69 (1H, ddd, 6, 11, 14 Hz, H72β), and 1.63 (1H, m, H76); EI-MS *m/z* 161 [(M−C_5H_9O)$^+$, 13%], 149 (28%), 143 (6%), and 125 (100%); HR-FDMS *m/z* 247.1518 (M+H)$^+$. Calcd for $C_{12}H_{23}O_5$ 247.1545.

12. Tetraol **2a**: $[\alpha]_D^{21}$ −1.8 (*c* 0.11, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.95, 4.94 (each 1H, s, exomethylene), 3.81 (1H, ddt, 5, 6, 7 Hz, H71), 3.72 (2H, t, 6 Hz, H67), 3.68 (2H, t, 7 Hz, H73), 3.70–3.65 (1H, m, H75), 3.70–3.65 (2H, m, H77), 3.64 (1H, dd, 4, 11 Hz, H74), 3.53 (1H, dd, 5, 11 Hz, H74), 2.38 (1H, dd, 6, 14 Hz, H70), 2.31 (2H, t, 6 Hz, H68), 2.22 (1H, dd, 7, 14 Hz, H70), 1.81 (1H, ddd, 5, 7, 14 Hz, H72), 1.72 (1H, m, H72), and 1.81–1.70 (2H, m, H76); HR-FDMS *m/z* 249.1702 (M+H)$^+$. Calcd for $C_{12}H_{25}O_5$ 249.1702.
13. (*R*)-MTPA ester of **2c**: $[\alpha]_D^{26}$ +47.6 (*c* 0.087, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (8H, m), 7.34 (12H, m), 4.76, 4.73 (each 1H, brs, exomethylene), 4.37 (1H, td, 6, 11 Hz, H73), 4.36 (1H, td, 6, 11 Hz, H77), 4.31 (2H, t, 7 Hz, H67), 4.26 (1H, ddd, 5, 7, 11 Hz, H77), 4.20 (1H, dd, 4, 12 Hz, H74), 4.17 (1H, ddd, 5, 7, 11 Hz, H73), 4.07 (1H, dd, 5, 12 Hz, H74), 3.54 (1H, m, H75), 3.51, 3.48, 3.47, 3.46 (each 3H, OMe), 3.42 (1H, tt, 6, 7 Hz, H71), 2.24 (2H, t, 7 Hz, H68), 2.12 (1H, dd, 6, 15 Hz, H70), 1.95 (1H, dd, 7, 15 Hz, H70), 1.80, 1.74 (each 1H, m, H76), 1.72 (1H, dtd, 6, 7, 15 Hz, H72), and 1.62 (1H, dtd, 5, 6, 15 Hz, H72); HR-EIMS *m/z* 811.2158 (M−$C_{15}H_{16}O_3F_3$). Calcd for $C_{37}H_{36}O_{10}F_9$, 811.2164; HR-FABMS *m/z* 1113.3380 (M+H)$^+$. Calcd for $C_{52}H_{53}O_{13}F_{12}$, 1113.3294.
14. (*S*)-MTPA ester of **2d**: $[\alpha]_D^{24}$ −40.2 (*c* 0.063, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (8H, m), 7.36 (12H, m), −7.35 (20H, m, Ph), 4.77, 4.72 (each 1H, brs, exomethylene), 4.40 (1H, td, 6, 11 Hz, H77), 4.32 (2H, t, 7 Hz, H67), 4.27 (2H, m, H73), 4.21 (1H, dd, 4, 12 Hz, H74), 4.20 (1H, td, 6, 11 Hz, H77), 4.08 (1H, dd, 4, 12 Hz, H74), 3.51, 3.50, 3.48, 3.47 (each 3H, OMe), 3.49 (1H, m, H75), 3.47 (1H, m, H71), 2.24 (2H, t, 7 Hz, H68), 2.14 (1H, dd, 5, 14 Hz, H70), 1.89 (1H, dd, 7, 14 Hz, H70), 1.78 (1H, m, H72), 1.77 (2H, m, H76), and 1.61 (1H, m, H72); HR-EIMS *m/z* 811.2126. Calcd for $C_{37}H_{36}O_{10}F_9$, 811.2164.