Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 7087-7090, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01580-8

Determination of the Absolute Configuration of Yessotoxin, a Polyether Compound Implicated in Diarrhetic Shellfish Poisoning, by NMR Spectroscopic Method Using a Chiral Anisotropic Reagent, Methoxy-(2-naphthyl)acetic Acid

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Abstract: The absolute configuration of yessotoxin (**1**), a potent diarrhetic toxin causative of shellfish poisoning, was determined by NMR-spectroscopy using a chiral anisotropic reagent, methoxy-(2-naphthyl)acetic acid (2NMA), which was applied to a monoacetate of bisdesulfated yessotoxin (**3**). Copyright © 1996 Elsevier Science Ltd

A significant number of polyethers, most of them having potential biological activities, has been isolated from marine organisms.[1] Their intriguing structures have been investigated mainly by NMR spectroscopy and X-ray crystallography. As they are present in extremely minute amounts in the organisms, however, the stereochemistry of their structures are proposed relatively, except for very few examples such as brevetoxins, the absolute configuration of which has been established by CD.[2]

Yessotoxin (**1**: YTX) is a brevetoxin-type polyether that has been isolated from scallops as a diarrhetic shellfish poison.[3] Its planar structure and the relative stereochemistry have been elucidated by spectroscopic methods, although the absolute configuration has remained undetermined.

We have been developing new chiral anisotropic reagents, such as 2NMA [methoxy-(2-naphthyl)acetic acid],[4,5] 9ATMA (9-anthrylmethoxyacetic acid),[4,5] 2ATMA (2-anthrylmethoxyacetic acid),[6] and PGME (phenylglycine methyl ester),[7] which make it possible to determine the absolute configurations of organic compounds by NMR. Among these reagents, 2NMA is the most convenient for

secondary alcohols in that (i) the anisotropy of its naphthalene ring is much greater than that of the benzene ring of MTPA (conventional modified Mosher's method[8]), giving greater $\Delta\delta$ (δ_R - δ_S) values, and (ii) the enantiomerically pure reagent is easily prepared in substantial amounts.[9] This report deals with determination of the absolute configuration of YTX by means of 2NMA.

Attempted esterification at 32-OH of YTX with 2NMA was unsuccessful because of its axial orientation. Therefore, we focused on introducing 2NMA at 4-position, which is blocked by a sulfate group. Solvolysis of YTX was facilitated by heating a solution of YTX in pyridine-dioxane (1 : 1, 120 °C, 3 h) to give bisdesulfated YTX (**2**: DS-YTX). When DS-YTX (1.6 mg) was treated with an excess of acetic anhydride (50 μL) in pyridine (50 μL) at 0 °C for 45 min, a mixture of recovered DS-YTX (300 μg), monoacetate (**3**: 600 μg),[10] and diacetate (**4**: 300 μg), separable by HPLC (Mightysil RP-18; MeOH : MeCN : H_2O = 9 : 1 : 1), was obtained. The secondary OH at C-32 was intact in **3** and **4**.

Monoacetate **3** having free OH at C-4 was divided in two portions (300 μg each), and each portion was treated with (*R*)- and (*S*)-2NMA (1.1 mg), EDC[11] (3.9 mg), DMAP (1.5 mg), and NEt_3 (2.8 μL) in chloroform (500 μL) for 43.5 h at ambient temperature. The reaction mixture was successively washed with 10% aq citric acid, H_2O, 5% aq $NaHCO_3$, and H_2O, and the solvent was removed. Each residue was purified by HPLC (see above) to give pure (*R*)- (**5**: 200 μg) and (*S*)-2NMA esters (**6**: 200 μg), respectively. The ^{1}H-NMR spectra of **3**, **5**, and **6** are shown in Fig. 1.

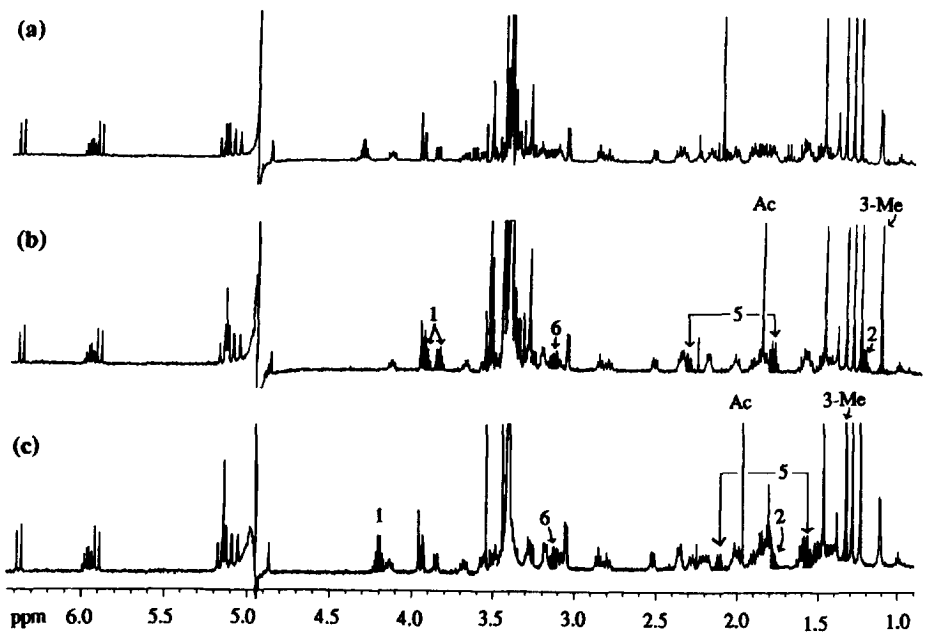
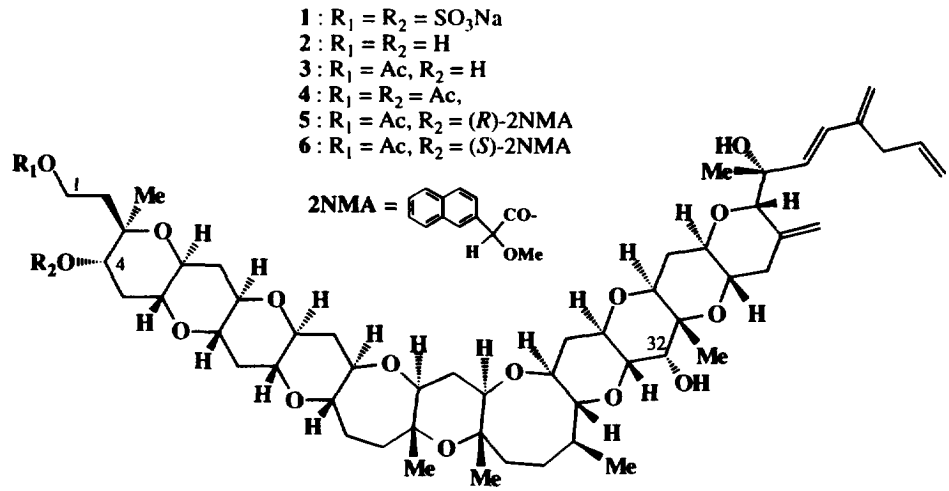
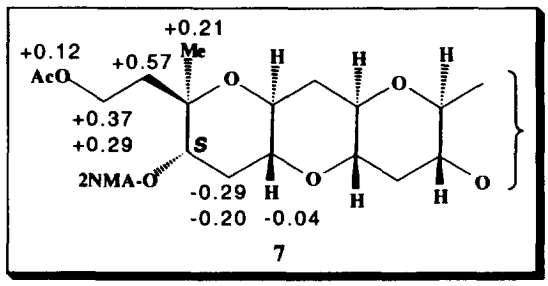


Figure 1. A part of the ^{1}H-NMR spectra (600 MHz, CD_3OD) of (a) monoacetate (**3**), (b) monoacetyl-(*S*)-2NMA ester (**6**) and (c) monoacetyl-(*R*)-2NMA ester (**5**) of DS-YTX. Spectra were recorded using a presaturation technique irradiating at the strong OH bands at 4.95 ppm except during acquisition.





By analyzing the COSY and HOHAHA spectra of **5** and **6**, much higher $\Delta\delta$ values [$\delta_{R(5)} - \delta_{S(6)}$] of the protons with much greater magnitude than those anticipated for MTPA were obtained. They are indicated in partial structure **7**.

From these results, the absolute configuration of the hydroxy group at C-4 was determined to be *S*, and, since the relative stereochemistry of the other asymmetric centers has been established, the present finding led to the absolute configuration of YTX as shown in **1**.

This is the second report (the first one on brevetoxin B[2]) on the absolute configuration of a ladder-like polyether, and the present methodology is expected to be applicable to the stereochemical as well as biosynthetic studies on other important polyethers.

Acknowledgement. We are grateful to Dr. Michio Murata, Tokyo University, for his encouragement and discussions. This work is financially supported by a Grant-in-Aid from the Japanese Ministry of Education and also by Ono Pharmaceutical Co., Ltd. (T. K.) and Suntory Institute for Bioorganic Research (H. T.).

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10. This sample is contaminated with less than 10% of another monoacetate (**3'**: R_1 = H, R_2 = Ac). This minor product could be eliminated by HPLC after conversion into 2NMA esters.
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(*Received in Japan* 4 *July* 1996; *revised* 5 *August* 1996; *accepted* 12 *August* 1996)