Synthetic Studies of Zoanthamine/Norzoanthamine: Biogenetic-like One-Step Construction of the Heterocyclic Aminal Core (CDEFG Ring) from a Monocyclic Precursor

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Biogenetic-like one-step construction of the pentacyclic aminal core of zoanthamine/norzoanthamine alkaloids was accomplished in high yield from the suitably protected monocyclic aminohydroxy diketocarboxylic acid 7 by heating in aqueous acetic acid.

Key words aminal; alkaloid; norzoanthamine; polycycle; tandem reaction

Zoanthamine[3)] (**1**) and norzoanthamine[4)] (**2**) are marine alkaloids having significant biological activities. For example, norzoanthamine and its hydrochloride strongly suppress the decrease in bone weight and strength in ovariectomized mice without showing serious side effects such as are observed in the case of 17β-estradiol, and has been considered to be a promising osteoporotic drug.[4c)] In addition to their interesting biological activities, their unique and complicated heptacyclic structure, including a bisaminal skeleton, has resulted in stimulatimg increasing synthetic efforts.[5)] Uemura proposed a biosynthetic pathway for norzoanthamine which involves the cyclization of an assumed acyclic precursor **3**.[4c)] Although the precise pathway, particularly for the ABC ring, is unclear, it seems plausible that a DEFG ring moiety is constructed from the tricyclic precursor **4** either in an enzymatic or a non-enzymatic way.

During the course of our investigation towards the total synthesis of norzoanthamine, we became interested in the construction of the CDEFG ring moiety by a biogenetic-like cyclization which is most attractive from a synthetic point of view as well. Furthermore, we also envisaged that the construction of this moiety could be achieved at the final stage of the total synthesis. These considerations led us to investigate the development of an efficient methodology for the synthesis of fully functionalized aminal moiety **5**, and we recently reported the first synthesis of the pentacyclic aminal core **5**.[6)] The synthesis of **5** was accomplished in two steps from the protected aminohydroxy diketocarboxylic acid **6** as shown in Chart 1. Thus, **6** was initially converted to the monoaminal **8** by treating with hydrochloric acid in THF in 78% yield, and hydrogenolysis of the Cbz group in **8** resulted in simultaneous cyclization affording the desired pentacyclic **5** in 71% yield after MS3A treatment. Although this is the first entry to the aminal core, it would be more desirable if pentacyclic aminal core **5** could be constructed in one-step from a suitably protected precursor in a similar manner to a plausible biogenetic-like tandem cyclization. Here we wish to describe the successful transformation of Boc derivative **7** to **5**.

The preparation of the cyclization precursor **7** followed the same strategy developed for the preparation of Cbz-derivative **6**.[6)] (Chart 2) Thus, the aldehyde **9**[6)] was coupled with the sulfone **11**, prepared from the corresponding Cbz-derivative **10** by 4 steps[7)] in 99% yield. The resulting hydroxysulfone was further transformed to the cyclization precursor **7** by conventional functional group manipulation in 38% overall yield from **9**.[8)]

We then investigated the cyclization of **7**. At first, **7** was treated with 2 N HCl–THF (1 : 3), the same conditions for the cyclization of Cbz-derivative **6** to monoaminal **8**, to obtain the corresponding monoaminal **12** and spiroketal **13** in 89% and 7% yields, respectively. The structure of **12** was determined by comparison of its ^{1}H-NMR spectrum with that of the corresponding Cbz-derivative **8**. This result indicated that the Boc group remained untouched under these conditions. Deprotection of the Boc group was next examined under various standard conditions[9)] such as HCl–THF, HCl (g)–AcOEt, CF_3CO_2H–CH_2Cl_2, TMSI–CH_3CN, *etc.* However, only decomposition of **12** occurred under these forcing conditions and the formation of **5** could not be detected by TLC. Among a number of unsuccessful efforts, we observed that deprotection of the Boc group was accelerated by adding a small amount of H_2O in CH_3CO_2H, and we focused on an H_2O–CH_3CO_2H system for deprotection of the Boc group.

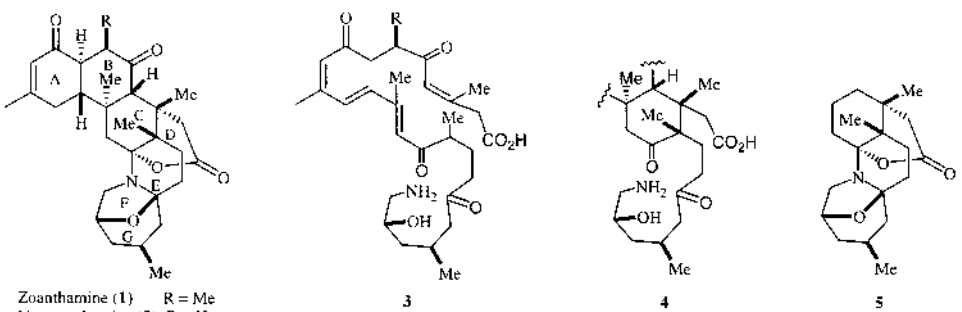

Fig. 1

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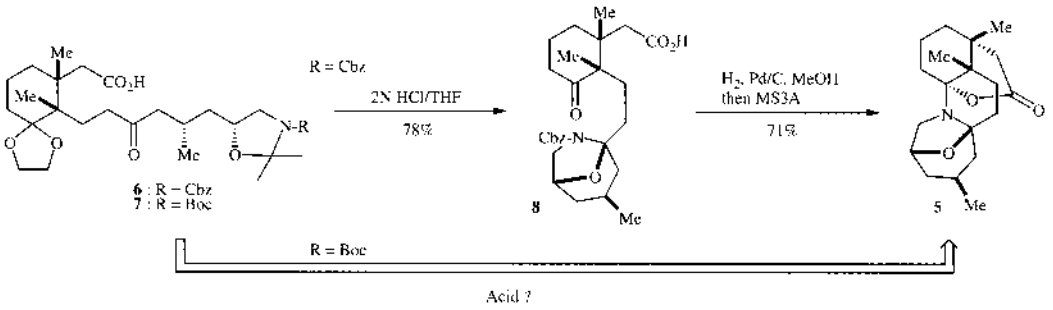

Chart 1

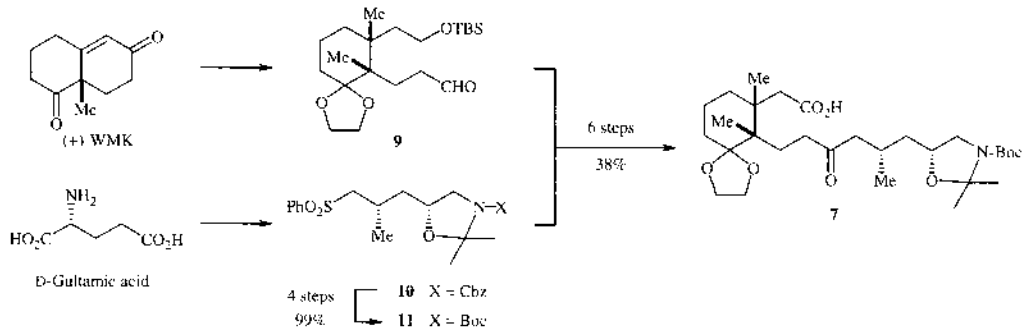

Chart 2

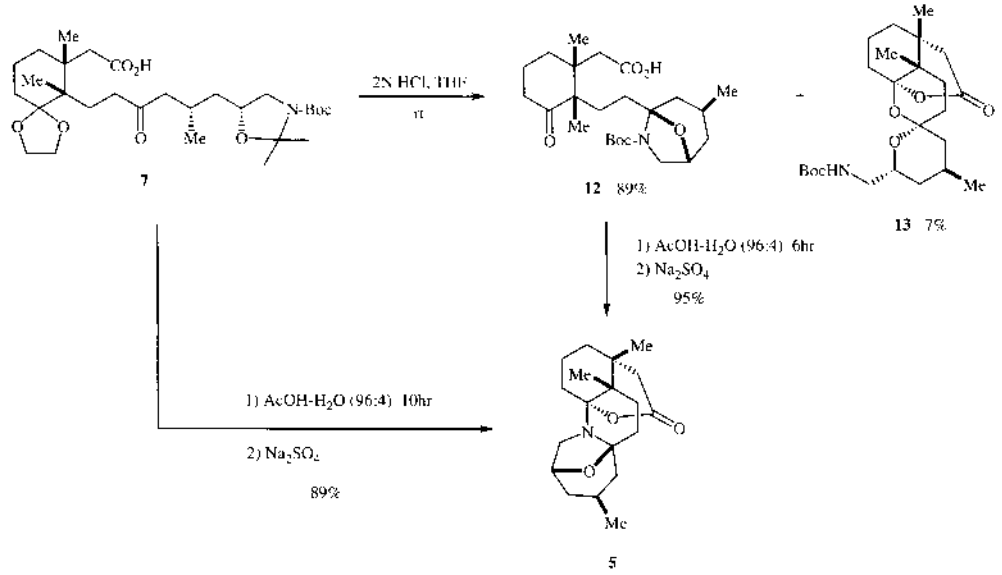

Chart 3

After a systematic survey of varying ratios ($CH_3CO_2H : H_2O$) and reaction temperatures, we were finally able to obtain the pentacyclic aminal **5** in 95% yield by heating at 100 °C in CH_3CO_2H–H_2O (96 : 4) for 6 h, followed by the addition of anhydrous Na_2SO_4. Without Na_2SO_4 treatment, aminal **5** could not be isolated. The obtained **5** was unambiguously identified by comparing its NMR spectrum with that of the authentic sample prepared by the previous method.[6] Further, the present conditions, CH_3CO_2H–H_2O (96 : 4) at 100 °C, were found to be effective for the one-step and biogenetic-like conversion of **7** to **5**. Thus, pentacyclic **5** was produced in 89% yield from **7**.

In summary, we were able to establish an efficient methodology for the construction of the fully functionalized CDEFG ring moiety **5** of the zoanthamine and norzoanthamine family. It should be emphasized that a pentacyclic aminal system could be constructed from the monocyclic Boc-derivative **7** in one-step by finding the appropriate acidic conditions. We think that the present conditions might be applicable to the final step of the total synthesis of norzoanthamine, and studies along this line are now in progress.

Experimental

General NMR spectra were recorded on a JEOL JNM-LA-400, JNM AL-300 or JNM-EX-270 spectrometer. Chemical shifts are shown in ppm downfield internal tetramethylsilane. The abbreviations used in ^{1}H-NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. IR were recorded on a Horiba FT-210 spectrometer. Optical rotations were measured on JASCO DIP-360 or JASCO P-1030 spectrometer. Mass spectra were obtained on a JEOL JMS-BU20, JMS-SX102A or JMS-700 spectrometer.

2-[(1*R*,2*S*)-2-{2-[(1*S*,3*S*,5*S*)-6-Aza-6-*tert*-butoxycarbonyl-3-methyl-8-oxa-bicyclo[3.2.1]oct-5-yl]ethyl}-1,2-dimethyl-3-oxo-cyclohexyl] Acetic Acid (12) and (1*R*,3*S*,6*S*,7*R*)-6,7-Dimethyl-2,10-dioxa-9-oxo-tricyclo-[4.4.3^{1,7}]decane-3-spiro-1′-[(3′*S*,5′*S*)-2′-oxa-5′-methyl-3′-(*tert*-butoxycarbonylaminomethyl)]Cyclohexane (13) To a stirred solution of **7** (24.1 mg, 44.7 μmol) in THF (3 ml) was added 2 M HCl (1 ml) at room temperature. After stirring for 21 h, the reaction mixture was poured into saturated $NaHCO_3$ (5 ml), and the mixture was extracted with AcOEt (20 ml). The organic layer was washed with saturated NaCl (5 ml), dried and concentrated. The residual oil was subjected to chromatography (1 : 1 hexane/AcOEt) to give monoaminal **12** (17.4 mg, 89%) and spiroketal **13** (1.3 mg, 7%).

Monoaminal (**12**): $[\alpha]_D^{27}$ +59.2° (c=0.53, $CHCl_3$). IR (film) cm^{-1}: 3440, 2981, 1674, 1394. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, d, J=6.4 Hz), 0.97 (3H, s), 0.98 (3H, s), 1.07—1.30 (3H, m), 1.45 (9H, s), 1.37—1.45 (1H, m), 1.57 (1H, dt, J=5.2, 12.0 Hz), 1.69—1.82 (3H, m), 1.89—2.17 (5H, m), 2.21—2.54 (4H, m), 3.35—3.55 (2H, m), 4.39 (1H, br s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5, 21.2, 21.5, 21.8, 24.1, 26.5, 28.4, 31.0, 31.9, 37.6, 38.3, 41.5, 42.2, 42.8, 51.2, 55.5, 72.4, 80.5, 93.9, 152.8, 176.7, 215.2. FAB-MS m/z: 438 (M+H), 338, 198. HRMS: Calcd for $C_{24}H_{40}NO_6$ (M+H), 438.2856. Found 438.2846.

Spiroketal (**13**): $[\alpha]_D^{27}$ −53.7° (c=0.12, $CHCl_3$). IR (film) cm^{-1}: 2934, 1701, 1510, 1367, 1290. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, J=5.4 Hz), 0.88 (3H, s), 0.87—0.94 (2H, m), 0.99 (1H, t, J=12.7 Hz), 1.15 (3H, s), 1.18—1.35 (3H, m), 1.46 (9H, s), 1.51—1.98 (8H, m), 2.00—2.12 (1H, m), 2.31 (1H, d, J=19.0 Hz), 2.58 (1H, d, J=19.0 Hz), 3.11 (1H, ddd, J=4.6, 7.8, 13.5 Hz), 3.26 (1H, ddd, J=2.7, 5.2, 13.5 Hz), 4.24 (1H, tdd, J=2.7, 4.6, 11.7 Hz), 5.79 (1H, br s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 16.6, 18.1, 20.6, 21.7, 22.0, 25.0, 29.7, 31.9, 35.3, 36.9, 37.3, 40.9, 44.6, 46.2, 69.0, 78.4, 98.5, 107.8, 156.9, 171.1. FAB-MS m/z: 438 (M+H), 338, 198. HRMS: Calcd for $C_{24}H_{40}NO_6$ (M+H), 438.2856. Found 438.2847.

Bisaminal (5) A solution of **12** (7.9 mg, 18.1 μmol) in AcOH–H_2O (96 : 4, 2 ml) was stirred at 100 °C for 6 h. After the reaction mixture was cooled to room temperature, anhydrous Na_2SO_4 was added to the mixture. The mixture was stirred for 1 h, and filtered and washed with MeOH. The filtrate was concentrated. The residual oil was subjected to silica gel chromatography (4 : 1 $CHCl_3$/MeOH) and passed through activated alumina column (1 : 1 $CHCl_3$/MeOH) to give **5** (5.2 mg, 95%) as a colorless oil.

$[\alpha]_D^{27}$ +3.7° (c=0.82, $CHCl_3$). IR (film) cm^{-1}: 2941, 1709, 1458, 1250, 1159. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, J=6.6 Hz), 0.90 (3H, s), 1.08 (1H, t, J=12.4 Hz), 1.20 (3H, s), 1.23—1.28 (1H, m), 1.44 (1H, dt, J=2.9, 12.9 Hz), 1.53—1.66 (3H, m), 1.67—1.94 (6H, m), 2.02 (1H, dd, J=4.7, 14.0 Hz), 2.10 (1H, dd, J=5.1, 12.4 Hz), 2.23—2.31 (1H, m), 2.25 (1H, d, J=19.0 Hz), 2.55 (1H, dd, J=2.2, 19.0 Hz), 3.20 (1H, t, J=6.7 Hz), 3.25 (1H, d, J=6.7 Hz), 4.52—4.53 (1H, m). ^{13}C-NMR (68 MHz, $CDCl_3$) δ: 18.2, 18.4, 21.7, 22.9, 23.2, 24.9, 29.7, 30.1, 35.5, 38.8, 40.8, 44.4, 47.4, 89.8, 105.6, 173.3. EI-MS m/z: 319 (M^+), 279. HRMS: Calcd for $C_{19}H_{29}NO_3$ 319.2147. Found 319.2148.

Bisaminal (5) (One-Step Cyclization) A solution of **7** (16.7 mg, 30.9 μmol) in AcOH–H_2O (96 : 4, 2 ml) was stirred at 100 °C for 10 h. After the reaction mixture was cooled to room temperature, anhydrous Na_2SO_4 was added to the mixture. The mixture was stirred for 1 h, and filtered and washed with MeOH. The filtrate was concentrated. The residual oil was subjected to chromatography (3 : 1 $CHCl_3$/MeOH) and passed through activated alumina column (1 : 1 $CHCl_3$/MeOH) to give **5** (8.8 mg, 89%) as a colorless oil.

Acknowledgments We thank Prof. Daisuke Uemura (Nagoya University) for helpful discussions. This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, and CREST, Japan Science and Technology Corporation.

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7) (i) 4 N HCl/THF, (ii) H_2, Pd–C/MeOH, (iii) Boc_2O, 1 N NaOH–dioxane, (iv) 2,2-dimethoxypropane, *p*-TsOH/benzene.
8) (i) *t*-BuLi/THF, −78 °C, (ii) Dess–Martin periodinane, pyridine/CH_2Cl_2, r.t., (iii) 5% Na-Hg, Na_2HPO_4/MeOH, r.t., (iv) TBAF/THF, r.t., (v) PCC, MS4A, CH_2Cl_2, r.t., (vi) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*-BuOH–H_2O, r.t.
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