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Synthetic Studies of Zoanthamine/Norzoanthamine Alkaloids: Advanced Intermediate for the Heterocyclic Aminal Core

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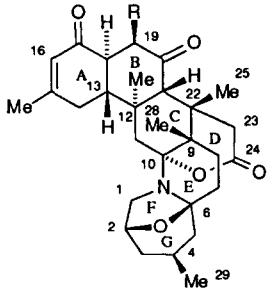
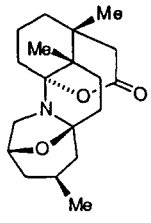
Abstract: *An advanced intermediate for the heterocyclic aminal core of zoanthamine/norzoanthamine alkaloids was prepared in an enantio and stereoselective manner. Contiguous quaternary chiral centers were selectively constructed utilizing a stereoselective cuprate addition to the readily available (+)-Wieland-Miescher ketone.* © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: alkaloids; Aminals; Amino ketones; Marine metabolites.

Zoanthamine[2] (**1**) and norzoanthamine[3] (**2**) are marine alkaloids which show significant biological activities such as inhibitory effects toward phorbol myristate-induced inflammation[2b] for **1** and IL-6 production[3c] for **2**. In particular, norzoanthamine (**2**) is considered to be a promising osteoporotic drug because it strongly suppresses the decrease in bone weight and strength in ovariectomized mice without showing the serious side effects observed in the case of 17β-estradiol.[3c] These alkaloids are structurally quite unique, possessing a rather complicated heptacyclic ring system, along with five quaternary chiral centers, and are considered a challenging target molecule from the synthetic point of view.[4] Indeed, enantiocontrolled construction of the hemiaminal moiety of related 28-deoxyzoanthenamine was very recently reported by Williams and coworker.[5] During the course of our studies directed toward total synthesis of norzoanthamine, we examined an enantioselective route to the fully functionalized heterocyclic aminal core **3**. Pentacyclic heterocycle **3** contains four of the five chiral quaternary centers, including three contiguous ones, in zoanthamine and norzoanthamine. The present paper focuses on the enantioselective preparation of **4**, an advanced intermediate for **3**, and the accompanying paper describes the construction of aminal core **3**.



Zoanthamine (**1**) : R = Me
Norzoanthamine (**2**) : R = H



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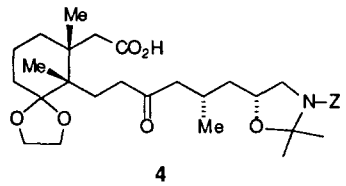

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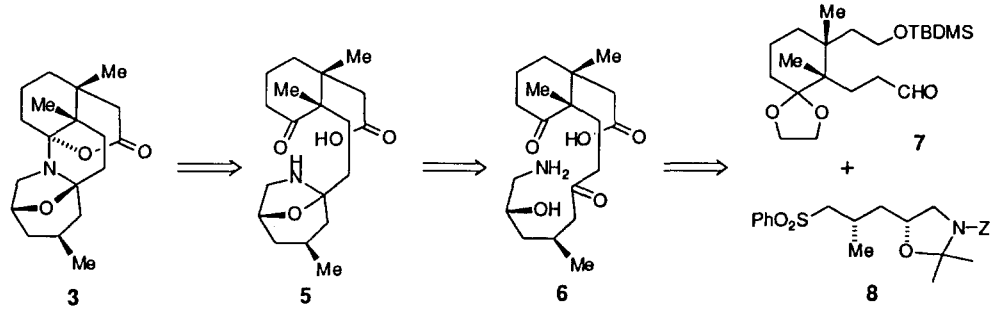
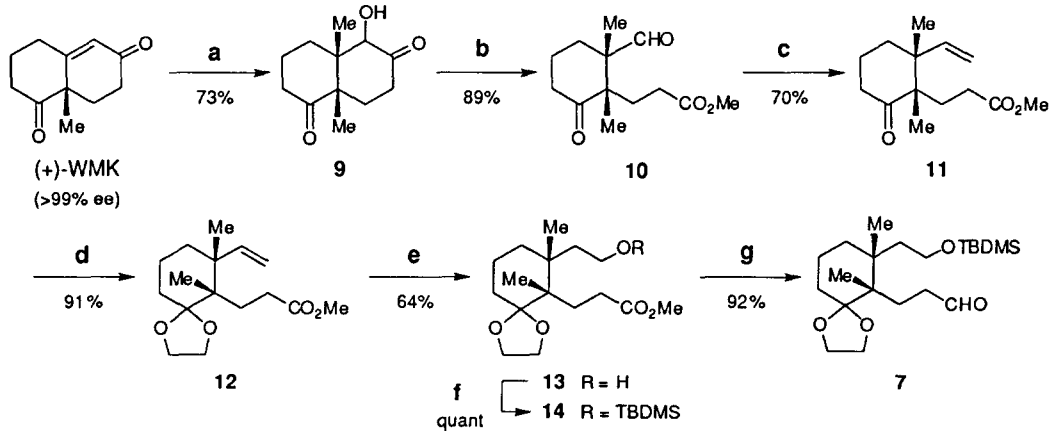
Our strategy for the pentacyclic aminal ring system is shown in Scheme 1. Thus, we expected that the fully functionalized monocyclic precursor **6** or its suitably protected derivative might undergo sequential cyclization through aminal **5** under particular conditions to produce **3**. We envisaged that partially protected **4** would serve as a potential intermediate for the synthesis of **3**, and that **4** could be derived from the aldehyde **7** and the sulfone **8**. The most crucial point in the preparation of **7** is the construction of the two contiguous quaternary centers which correspond to C-9 and C-22.[6] Our approach was to utilize the stereoselective cuprate addition to the readily available (+)-Wieland-Miescher ketone (WMK).[7]

Scheme 1



Highly diastereoselective cuprate addition to (+)-WMK was carried out according to the Piers method,[8] and the reaction was quenched with TMSCl and Et_3N to obtain the silyl enol ether. The crude silyl enol ether was subjected to MCPBA oxidation, followed by treatment with CSA to afford the hydroxy ketone **9**[9] in 73% yield from (+)-WMK. Hydroxyketone **9** was then oxidatively cleaved with $Pb(OAc)_4$, and the resulting monocyclic ketoaldehyde **10** was reacted with $Ph_3P{=}CH_2$ under ice-water cooling to give **11** in good yield. The undesirable Wittig reaction at the ketonic part or intramolecular aldol-type reaction did not proceed under these conditions.

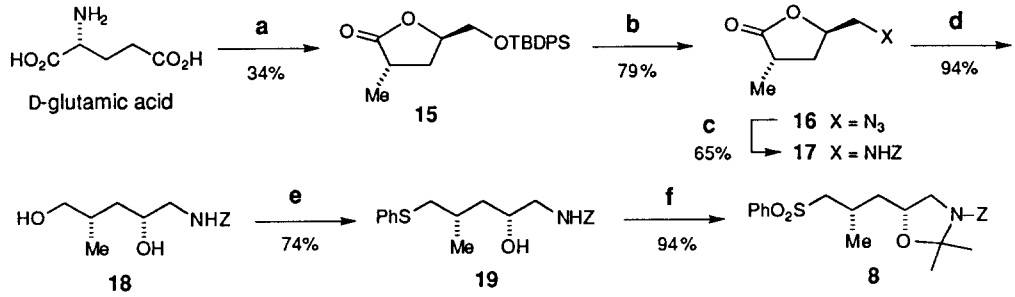
Scheme 2



Reagents and conditions: **a** (i) Me_2CuLi/Et_2O, -25°C, 0.5h, then TMSCl, Et_3N, -25 to 0°C, 2h; (ii) MCPBA/hexane, r.t., 2h; (iii) CSA/acetone, r.t. 16h; 73% from (+)-WMK. **b** (i) $Pb(OAc)_4$/benzene-MeOH, 0°C, 0.5h, 89%. **c** $Ph_3P^+CH_3\ Br^-$, $NaNH_2$/THF, 5°C, 2h, 70%. **d** $TMSO(CH_2)_2OTMS$, TMSOTf/CH_2Cl_2, r.t., 17h, 91%. **e** (i) $BH_3{\cdot}SMe_2$/THF, r.t., 2h, then 35% H_2O_2/3*N* NaOH, r.t; (ii) CH_2N_2/Et_2O; 64%. **f** TBDMSCl, imidazole/CH_2Cl_2, 0°C, 0.5h, quant. **g** DIBAL/CH_2Cl_2, -78°C, 15min, 92%.

Then, the ketone was protected with ethyleneketal by Noyori's method[10] to give **12**, and the vinyl group was transformed to the hydroxyethyl group by hydroboration followed by oxidative work-up and esterification to give **13**. After protection of the hydroxyl group as TBDMS ether, the methoxycarbonyl group of **14** was reduced with DIBAL to obtain the key intermediate **7**.

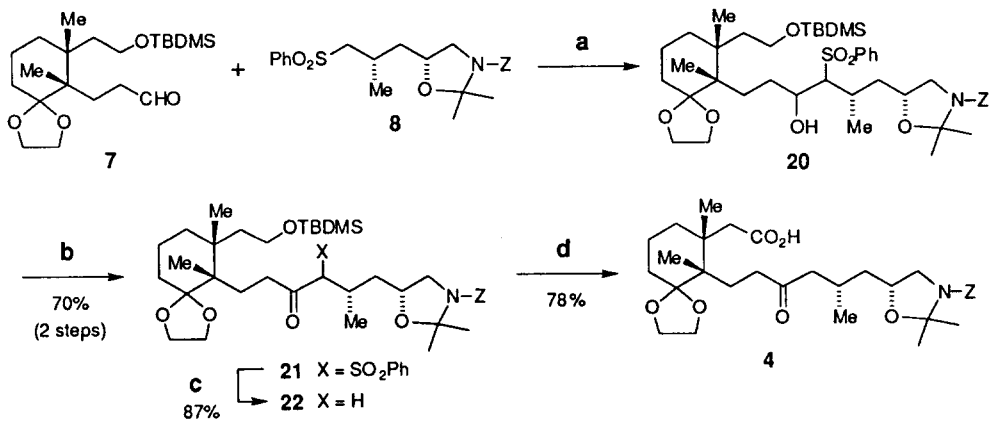
Scheme 3



Reagents and conditions: **a** (i) $NaNO_2/H_2O$; (ii) BH_3•SMe_2/THF; (iii) TBDPSCl, imidazole/DMF; (iv) LDA, MeI/THF, -78°C, 34%. **b** (i) TBAF/THF, r.t., 1h; (ii) MsCl, Et_3N/CH_2Cl_2, r.t., 1h; (iii) NaN_3/DMF, 90°C, 2h, 79%. **c** (i) H_2, Pd/C/THF, r.t., 2h; (ii) $ClCO_2Bn$, Et_3N/THF, 65%. **d** $NaBH_4$/THF-MeOH (4:1), 60°C, 15min, 94%. **e** PhSSPh, *n*-Bu_3P/pyridine, r.t., 1h, 74%. **f** (i) 2,2-dimethoxypropane, *p*-TsOH/acetone, r.t., 1h, (ii) MCPBA, $NaHCO_3/CH_2Cl_2$, 0°C, 1h, 94%.

The preparation of the C1-C5 segment **8** is summarized in Scheme 3. Thus, D-glutamic acid was converted to α-methyl-γ-butyrolactone **15** by the reported procedure.[11] Two chiral centers in **8** are already established with **15**.[12] After transformation to the Z-amino derivative **17** by the conventional method, lactone **17** was reduced to the diol **18**.[13] Then, the primary hydroxyl group of **18** was selectively converted to the phenylthio group with PhSSPh and *n*-Bu_3P.[14] Protection of the aminoalcohol moiety with an isopropylidene group and final oxidation of the phenylthio group with MCPBA afforded the sulfone **8**.

Scheme 4



Reagents and conditions: **a** *t*-BuLi/THF, -78°C, 0.5h. **b** Dess-Martin periodinane, pyridine/CH_2Cl_2, r.t., 2h, 70% from **7**. **c** 5% Na-Hg, Na_2HPO_4/MeOH, r.t., 2h, 87%. **d** (i) TBAF/THF, r.t., 18h; (ii) Dess-Martin periodinane, pyridine/CH_2Cl_2, r.t., 2h; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*-BuOH-H_2O, r.t., 1h, 78%.

With these two segments in hand, the coupling of **7** and **8** was next examined. (Scheme 4) Thus, the sulfone **8** (2 equiv) was treated with *t*-BuLi (2 equiv) in THF at -78°C, and the resulting lithiated **8** was then reacted with the aldehyde **7** giving a diastereomeric mixture of hydroxysulfone **20** along with the recovery of excess sulfone **8**. Without separation, the mixture was oxidized with Dess-Martin periodinane[15] to result in the ready separation of the ketosulfone **21** (70% yield based on **7**) and **8**. Reductive desulfurization of **21** was carried out with 5% Na-Hg in 87% yield. Finally, carboxylic acid **4**[16] was obtained in 78% overall yield by conventional transformation.

As described above, preparation of the advanced intermediate **4** was successfully achieved starting from (+)-Wieland-Miescher ketone and D-glutamic acid. Cyclization to the pentacyclic aminal core **3** is the subject of the accompanying paper.

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References and Notes

1. Visiting scientist from Sankyo Co., Ltd.
2. (a) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkateswarlu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7983-7984. (b) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkateswarlu, Y.; Rosser, R. M.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 3757-3760. (c) Rao, C. B.; Rao, D. V.; Raju, V. S. N.; Sullivan, B. W.; Faulkner, D. J. *Heterocycles* **1989**, *28*, 103-106. (d) Rahman, A.-U.; Alvi, K. A.; Abbas, S. A.; Choudhary, M. I.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 6825-6828.
3. (a) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocyclic Communications*, **1995**, *1*, 207-214. (b) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683-5686. (c) Kuramoto, M.; Hayashi, K.; Yamaguchi, K.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771-779.
4. (a) Tanner, D.; Andersson, P. G.; Tedenborg, L. Somfai, P. *Tetrahedron* **1994**, *50*, 9135-9144. (b) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217-1223.
5. Williams, D. R.; Cortez, G. S. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.
6. The carbon numbers are expressed according to the norzoanthamine numbering in this paper.
7. Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167-168.
8. Piers, E.; de Waal, W.; Britton, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5113-5120.
9. All new compounds were fully characterized by ^{1}H-NMR (500 or 270 MHz) and IR spectra, and satisfactory high-resolution MS was obtained for them.
10. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357-1358.
11. Hanessian, S.; Roy, R. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. J. *J. Org. Chem.* **1990**, *55*, 5766-5777.
12. A similar strategy was also employed by Williams *et al.*[5]
13. Soai, K.; Oyamada, H.; Takase, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2327-2328.
14. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *16*, 1409-1412.
15. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287
16. The structure of **4** was characterized as follows: $[\alpha]_D^{20}$ -18.6° (c 1.13, $CHCl_3$); IR (neat) 3200, 2939, 1709, 1693, 1413, 1356, 1215, 1113, and 1068 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, d, *J*=6.6Hz), 1.04 (6H, s), 1.47-1.67 (15H, m), 1.83-1.93 (1H, m), 2.09-2.13 (1H, m), 2.22-2.31 (2H, m), 2.39-2.65 (3H, m), 3.08 (1H, t, *J*=9.6Hz), 3.20 (1H, d, *J*=13.5Hz), 3.73-3.86 (3H, m), 3.90-4.02 (2H, m), 4.07-4.17 (1H, m), 5.11 (2H, s), 7.36 (5H, s); ^{13}C-NMR ($CDCl_3$) δ 16.6, 19.0, 20.1, 22.4, 23.4, 24.2, 25.3, 26.5, 30.2, 32.1, 39.8, 40.5, 41.3, 45.8, 50.1, 50.8, 62.5, 65.1, 66.5, 72.3, 77.2, 93.7, 113.9, 127.9, 128.0, 128.5, 136.7, 152.2, 178.6, 211.2. HRMS calcd for $C_{32}H_{47}O_8N$ 573.3302, found 573.3290.