Natural Products Synthesis (2)

DOI: 10.1002/anie.200804546

# Total Synthesis of (−)-Norzoanthamine**

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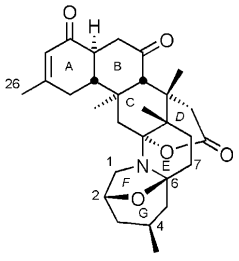
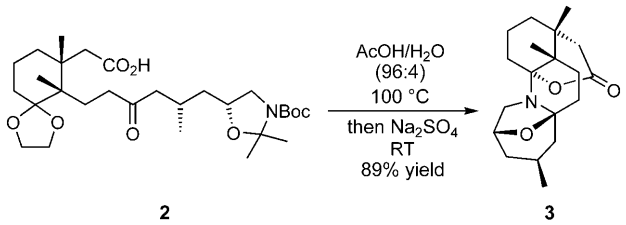
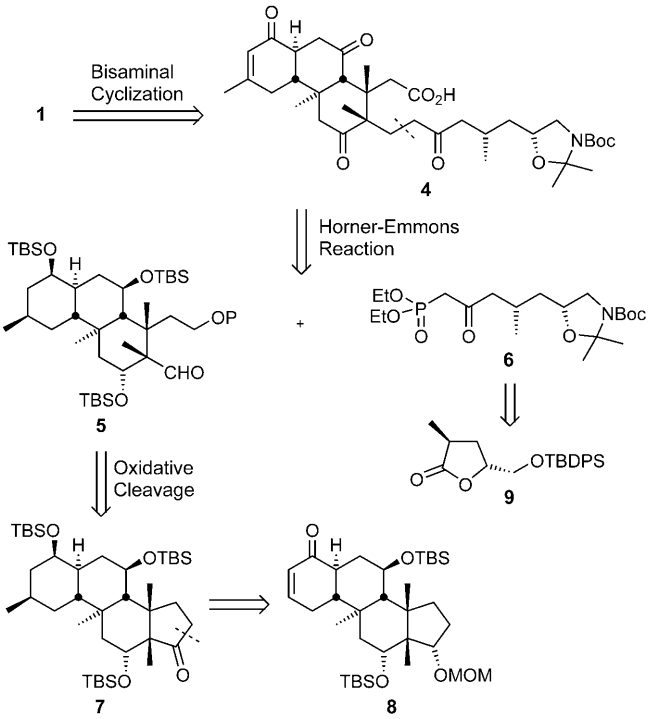
The *Zoanthus* alkaloids, to which zoanthamines and (−)-norzoanthamine (**1**) belong, have attracted a great deal of attention in the synthetic community owing to their significant biological activity[1] as well as their unique and complex heptacyclic structure. Although several groups have attempted the synthesis of these alkaloids,[2–4] only the Miyashita research group has accomplished a total synthesis.[4] The most challenging steps towards the total synthesis of (−)-norzoanthamine are the construction of the bisaminal skeleton in the CDEFG ring moiety and a stereocontrolled construction of the densely functionalized C ring, which contains four quaternary chiral centers. During the course of our studies, we have already developed an excellent methodology for bisaminal formation (Scheme 1),[3] and have reported a synthesis of the ABC ring moiety in the preceding paper.[5] Herein, we report the total synthesis of (−)-norzoanthamine from the key intermediate **8**.




***Scheme 1.*** Model study of bisaminal formation. Boc = *tert*-butoxycarbonyl.

Our synthetic strategy for the preparation of **1**, starting from **8**, is shown in Scheme 2. (−)-Norzoanthamine could be synthesized from a ketoacid **4** or its equivalent based on our efficient method of bisaminal formation. The cyclization precursor **4**, in turn, could be derived from the aldehyde **5** by the Horner–Emmons reaction with nitrogen-containing ketophosphonate **6**, which can be prepared from lactone **9**.[6] As mentioned in the preceding paper, we envisioned that the cyclopentanol moiety in tetracyclic **8** might serve as a handle for introducing the remaining C1–C7 fragment. Thus, oxidative cleavage of cyclopentanone **7** and subsequent functional group transformation would provide the requisite aldehyde **5**. For these manipulations, the key intermediate **8** was first converted into cyclopentanone **7**, in which the α,β-unsaturated cyclohexenone moiety in ring A is masked as cyclohexanol after introducing the methyl group at C26.




***Scheme 2.*** Retrosynthetic analysis. MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Synthesis of aldehyde **5**, a substrate for the Horner–Emmons reaction, was commenced with 1,4-addition of enone **8** for introducing the methyl group at C26 (Scheme 3). Treatment of enone **8** with Gilman reagent led to the corresponding ketone in 91% yield, which was then

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[**] This research was supported in part by a Grant-in-Aid for Scientific Research (B; KAKENHI No.18390010) from the Japan Society for the Promotion of Science. We thank Prof. Dr. Keiji Tanino (The Hokkaido University) for helpful suggestions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804546.


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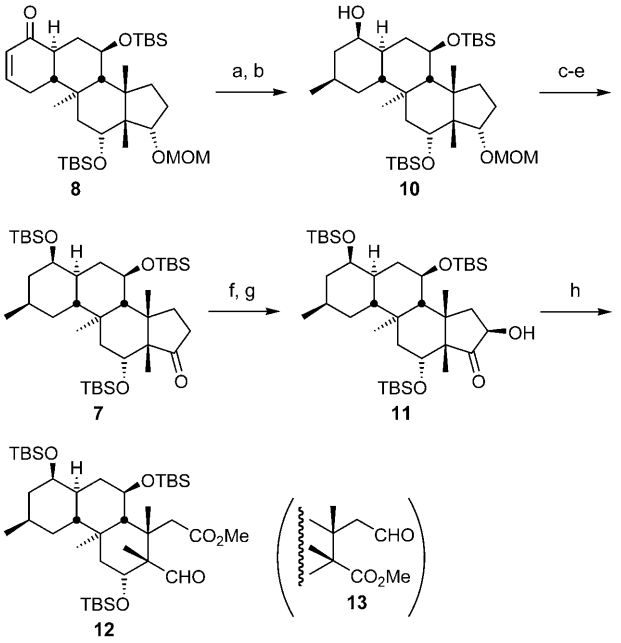



***Scheme 3.*** Synthesis of formyl ester **12**. Reagents and conditions: a) $Me_2CuLi$, $Et_2O$, −78–0 °C, 91 %; b) $NaBH_4$, MeOH, 0 °C–RT, 79 %; c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C–RT, 95 %; d) *B*-bromocatecholborane, $CH_2Cl_2$, −78 °C, 87 %; e) DMP, $CH_2Cl_2$, 0 °C–RT, quant.; f) *n*BuLi, TMSCl, THF, −78–0 °C; g) $O_3$, $CH_2Cl_2$, MeOH, −78 °C, 79 % (over 2 steps); h) $Pb(OAc)_4$, benzene, MeOH, 0 °C–RT, 77 %. DMP = Dess–Martin periodinane, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

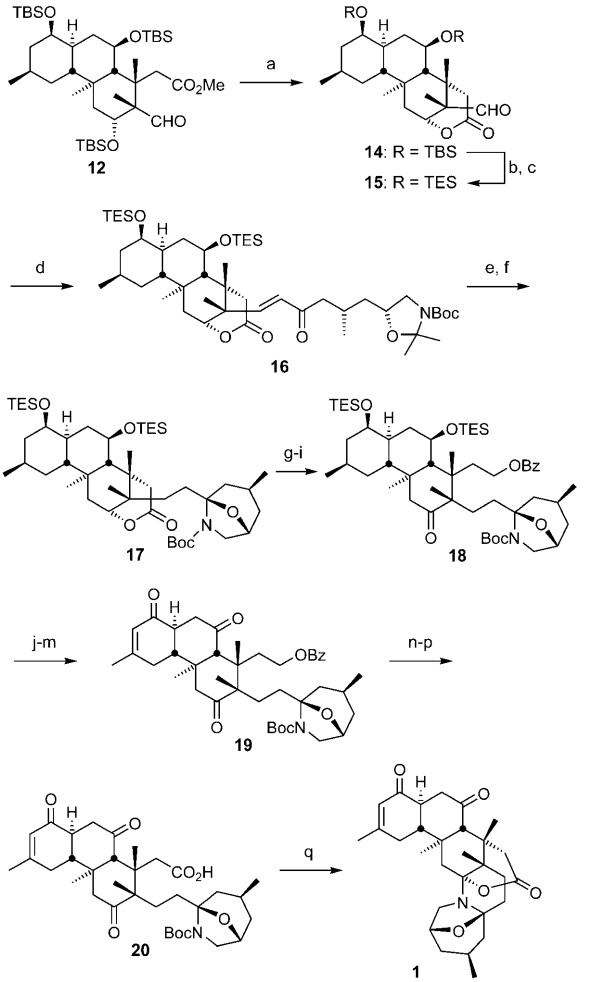
reduced with $NaBH_4$ in MeOH to afford alcohol **10** in good yield. Both the conjugate addition and the reduction reactions proceeded in a highly stereoselective manner to afford **10** as a single isomer. The assignment of the configuration was based on NMR experiments.[7] Protection of the hydroxy group in **10** as the TBS ether, removal of the MOM group,[8] and successive oxidation of the resulting hydroxy group afforded the cyclopentanone derivative **7** in 83 % overall yield.

To cleave the cyclopentanone moiety, **7** was subjected to an α oxidation by using conventional procedures. However the enolization step proved to be very difficult, probably owing to the sterically encumbered carbonyl group resulting from the buttressing effect of the angular methyl groups. We were delighted that deprotonation proceeded cleanly to afford the desired trimethylsilyl enol ether after successive silylation reactions by using *n*BuLi as a base.[9]

Interestingly, ozonolysis of the silyl enol ether provided α-hydroxy ketone **11** as a single diastereomer in 79 % overall yield from ketone **7**, rather than the expected dicarbonyl compound.[10] The configuration of the hydroxy group was determined by use of the modified Mosher method.[11] To obtain formyl ester **13**, we next examined the oxidative cleavage of hydroxy ketone **11** with the process established by Criegee using $Pb(OAc)_4$ in benzene/MeOH.[12] Surprisingly, rather than the anticipated **13**, the formyl ester **12** was obtained in 77 % yield as the sole product. A plausible mechanism for this unprecedented oxidation process is outlined in the Supporting Information. Nonetheless, **12** is a desirable intermediate because it can be directly employed as a substrate for the Horner–Emmons reaction with **6**.

It should be emphasized that the sterically congested bicyclic skeleton, with contiguous quaternary methyl groups, facilitated an unexpected but desirable selectivity during these last few steps. The remaining steps for the completion of the synthesis of (−)-norzoanthamine were: 1) coupling of formyl ester **12** and ketophosphonate **6**, and 2) formation of the bisaminal framework at the very end of the synthesis (Scheme 4).

We first attempted the reaction of formyl ester **12** and ketophosphonate **6**. However, all attempts failed and only starting materials were recovered. The low reactivity of the formyl group can be attributed to the presence of the neighboring acetate and *tert*-butyldimethylsilyloxy groups. Fortunately, selective removal of the TBS group on the C ring




***Scheme 4.*** Completion of the total synthesis of (−)-norzoanthamine (**1**). Reagents and conditions: a) TBAF, THF, 0 °C–RT, quant.; b) aq. HF (4 N), $CH_3CN$, RT, quant.; c) TESCl, imidazole, $CH_2Cl_2$, RT, 76 %; d) **6**, LiCl, $iPr_2NEt$, $CH_3CN$, 60 °C, 67 % (94 % based on the recovered starting material); e) $H_2$, Pd/C, EtOH, RT, 96 %; f) AcOH, $H_2O$, 50 °C, 56 %; g) $AlH_3{\cdot}EtNMe_2$, toluene, 50 °C, 59 %; h) BzCl, $NEt_3$, $CH_2Cl_2$, 0 °C–RT, 88 %; i) DMP, $CH_2Cl_2$, RT, quant.; j) aq. HF (0.5 N), $CH_3CN$, 0 °C–RT, 94 %; k) DMP, $CH_2Cl_2$, RT, quant.; l) LHMDS, TMSCl, THF, −78 °C; m) cat. $Pd(OAc)_2$, $O_2$, DMSO, 60 °C, 74 % (over 2 steps); n) $K_2CO_3$, MeOH, RT; o) DMP, $CH_2Cl_2$, RT; p) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH, $H_2O$, RT, 66 % (over 3 steps); q) AcOH, $H_2O$, 100 °C, 92 %. Bz = benzoyl, DMSO = dimethyl sulfoxide, LHMDS = lithium hexamethyldisilazanide, TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl.

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was possible by simple treatment with TBAF. The resulting hydroxy ester underwent a simultaneous cyclization to afford lactone **14** quantitatively. Upon deprotection, the formyl group in **14** was rendered more reactive. At this stage, two TBS groups in the AB rings of **14** were replaced by TES groups.[13] The Horner–Emmons reaction of **15** and **6** was best carried out under the conditions developed by Masamune, Roush, and co-worker[14] and afforded **16** in good yield. Thus, **16** contains the complete carbon skeleton in (−)-norzoanthamine.

After catalytic hydrogenation the resulting saturated ketone was treated with aqueous AcOH at 50 °C to result in the formation of the monoaminal and afford **17** in 56 % yield, along with desilylated and uncyclized by-products. The by-products were again exposed to aqueous AcOH and treated with TESCl/imidazole to afford **17** in 39 % yield (95 % total yield). Although our original scenario involved the formation of a bisaminal at the final stage of the synthesis, early formation of a monoaminal proved useful for the further transformations. Attempted alcoholysis and hydrolysis of the lactone in **17** failed. The cleavage of the lactone moiety was only achieved by treatment with $AlH_3$ in toluene. Selective protection of the primary hydroxy group, followed by oxidation using DMP [15] gave **18** in 88 % yield (over 2 steps). TES groups in the AB rings of **18** were removed, and the diol was subjected to oxidation with DMP to produce a triketone (not shown). The triketone was then subjected to a selective silyl enol etherification according to the protocol developed by Miyashita and co-workers,[4] and subsequent Saegusa oxidation[16] afforded the enone **19**. The benzoyl group was cleaved and the primary hydroxy group was converted into the carboxylic acid **20** in 66 % overall yield for the three steps.[17] Finally, a solution of **20** in aqueous AcOH was heated at 100 °C to complete the total synthesis of (−)-norzoanthamine (**1**). The spectroscopic data ($^1H$,$^{13}C$ NMR and IR spectra, HRMS, optical rotation) for the final product were, in all respects, identical to those of natural (−)-norzoanthamine.

In conclusion, we have achieve the total synthesis of (−)-norzoanthamine in 47 steps starting from the (−)-Hajos–Parrish ketone. Some of the key features of our synthesis include: 1) stereocontrol of the C ring was realized by utilizing a bicyclo[4.3.0]nonane system, 2) the AB rings were constructed by a highly diastereoselective intramolecular Diels–Alder reaction, 3) a cyclopentanone moiety served as a handle for installing the remaining bisaminal segment after oxidative cleavage, 4) the DEFG ring moiety was constructed by stepwise bisaminal formation using AcOH/$H_2O$. Finally, we would like to emphasize that the cyclopentanone moiety of the (−)-Hajos-Parrish ketone played an important role throughout the synthesis, even though the ring was not incorporated into (−)-norzoanthamine in its original form.

Received: September 16, 2008
Published online: December 3, 2008

**Keywords:** alkaloids · cleavage reactions · Horner–Emmons reaction · natural products · total synthesis

[1] a) S. Fukuzawa, Y. Hayashi, D. Uemura, A. Nagatsu, K. Yamada, Y. Ijuin, *Heterocycl. Commun.* **1995**, *1*, 207 – 214; b) M. Kuramoto, K. Hayashi, Y. Fujitani, K. Yamaguchi, T. Tsuji, K. Yamada, Y. Ijuin, D. Uemura, *Tetrahedron Lett.* **1997**, *38*, 5683 – 5686; c) M. Kuramoto, K. Hayashi, K. Yamaguchi, M. Yada, T. Tsuji, D. Uemura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771 – 779.

[2] For a review, see: D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 2400 – 2421; *Angew. Chem. Int. Ed.* **2008**, *47*, 2365 – 2386.

[3] a) N. Hikage, H. Furukawa, K.-i. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6237 – 6240; b) N. Hikage, H. Furukawa, K.-i. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6241 – 6244; c) N. Hikage, H. Furukawa, K.-i. Takao, S. Kobayashi, *Chem. Pharm. Bull.* **2000**, *48*, 1370 – 1372.

[4] M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495 – 499.

[5] Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2008**, DOI:10.1002/ange.200804544; *Angew. Chem. Int. Ed.* **2008**, DOI:10.1002/ange.200804544.

[6] The synthetic route for ketophosphonate **6** from the known lactone **9** can be found in the Supporting Information.

[7] See the Supporting Information.

[8] R. K. Boeckman, Jr., J. C. Potenza, *Tetrahedron Lett.* **1985**, *26*, 1411 – 1414.

[9] No addition product was formed.

[10] a) R. D. Clark, C. H. Heathcock, *Tetrahedron Lett.* **1974**, *15*, 2027 – 2030; b) R. D. Clark, C. H. Heathcock, *J. Org. Chem.* **1976**, *41*, 1396 – 1403.

[11] a) T. Kusumi, T. Fukushima, I. Ohtani, H. Kakisawa, *Tetrahedron Lett.* **1991**, *32*, 2939 – 2942; b) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092 – 4096.

[12] a) R. Criegee, *Ber. Dtsch. Chem. Ges. B.* **1931**, *64*, 260 – 266; b) J. R. Hazen, *J. Org. Chem.* **1970**, *35*, 973 – 978.

[13] Removal of the TBS groups in the corresponding silyl ether **17** required harsh reaction conditions, which caused the undesired loss of the Boc group.

[14] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183 – 2186.

[15] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156.

[16] a) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011 – 1013; b) R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, D. Zheng, *Tetrahedron Lett.* **1995**, *36*, 2423 – 2426.

[17] As the resulting primary alcohol was unstable during column chromatography on silica gel, subsequent DMP oxidation of the crude alcohol was carried out without purification.

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