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Natural Product Synthesis

Total Synthesis of Zoanthenol**

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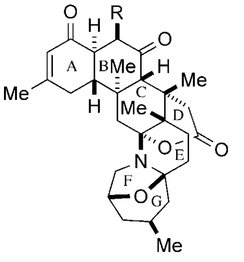
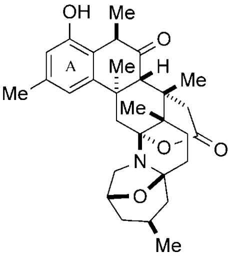
The zoanthamine alkaloids, a family of marine metabolites produced by the zoanthid *Zoanthus* sp., not only have a novel array of structures with stereochemical complexity, but also exhibit distinctive biological and pharmacological properties. For example, norzoanthamine (**1**), isolated from the colonial zoanthid *Zoanthus* sp. by Uemura et al., can suppress the loss of the weight of, and strengthen, bones in ovariectomized mice without problematic side effects[1] and thus is a promising candidate for an anti-osteoporotic drug. Furthermore, zoanthamine (**2**), isolated by Rao, Faulkner and co-workers, exhibits potent inhibitory activity toward phorbol myristate-induced inflammation, along with powerful analgesic effects.[2] The remarkable biological properties of norzoanthamine and zoanthamine, combined with their novel molecular architectures, make this family of alkaloids extremely attractive as synthetic targets.[3] As part of our ongoing synthetic studies of the zoanthamine alkaloids, we have achieved the first total syntheses of **1**[4a,c] and **2**.[4c] These syntheses involved a stereoselective synthesis of the crucial triene precursor using sequential three-component coupling reactions, a key intramolecular Diels–Alder reaction, and subsequent bis(amino)acetalization as the key synthetic steps.[4a] Recently, Kobayashi and co-workers reported the second total synthesis of **1**, which involved an elegant intramolecular Diels–Alder reaction for the construction of the AB ring system as the key step.[5]



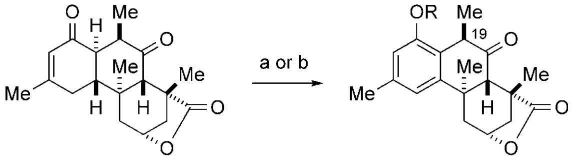
Norzoanthamine (**1**): R = H
Zoanthamine (**2**): R = Me



Zoanthenol (**3**)

Having achieved the efficient chemical syntheses of norzoanthamine and zoanthamine, we focused on the synthesis of zoanthenol (**3**),[6] a member of the zoanthamine alkaloids which is unique as it has an aromatic ring. As with the norzoanthamine derivatives, zoanthenol has been found to exhibit potent anti-platelet activity for human platelet aggregation.[7] In spite of synthetic studies by a number of research groups, employing a variety of distinct strategies, the total synthesis of **3** has yet to be successfully completed.[8–10] Herein, we report the first total synthesis of zoanthenol **3**, using a synthetic intermediate **11** in our synthesis of **1**,[4a,c] and the development of an efficient synthetic route from the commercially available norzoanthamine hydrochloride (**1**·HCl) to **3**.

The only difference in the structures of zoanthenol and zoanthamine is the oxidation pattern of the A ring; therefore, we thought that **3** might be directly synthesized by oxidative aromatization of **2**. To this end, we initially examined the viability of the transformation on the tetracyclic enone **4** as a model substrate. Two efficient procedures were found that successfully effected this transformation (Scheme 1). Thus, when enone **4** was treated with $CuBr_2$ in CH_3CN in the presence of LiBr,[11] compound **5**, now containing an aromatic ring, was obtained as a single product in 83 % yield. The stereochemical structure of **5** was unambiguously confirmed using NOE measurements, which indicated that epimerization at the C19 benzylic position did not occur at all. A second procedure for the aromatization of **4**, by treatment with Ac_2O



4

5: R = H
6: R = Ac

Scheme 1. Model studies on oxidative aromatization of the tetracyclic enone **4**. Reagents and conditions: a) For **5**: $CuBr_2$, LiBr, CH_3CN, 60 °C, 83 % yield. b) For **6**: $Yb(OTf)_3$, Ac_2O, O_2 (1 atm), dioxane, 70 °C, 86 % yield. Tf = trifluoromethanesulfonyl.

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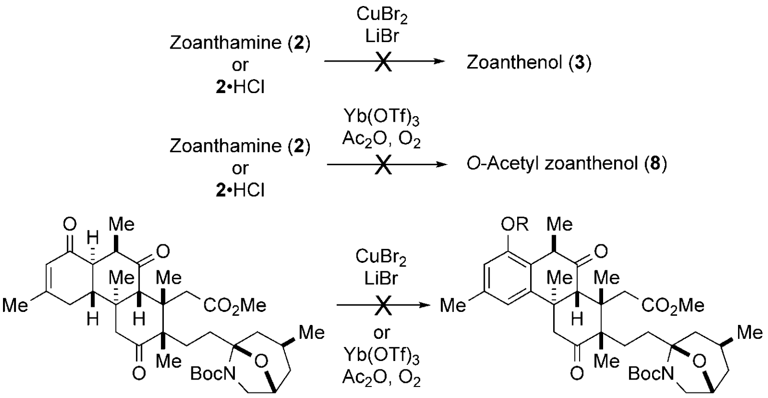
and $Yb(OTf)_3$ in dioxane under an oxygen atmosphere, also produced the aromatic acetate **6** in high yield (86 %), whereupon oxygen was found to be critical for this reaction. Although the reaction mechanism for the latter oxidation is not clear at present, a related air oxidation of 4-oxo-4,5,6,7-tetrahydroindoles with Ac_2O and TsOH (4-methyl benzenesulfonic acid), leading to 4-acetoxyindoles, was reported recently by Ishikawa and Saito.[12]

Having established these two efficient synthetic procedures using tetracyclic enone **4**, we studied the oxidative aromatization of zoanthamine and its synthetic intermediate **7** as potential routes to the total synthesis of zoanthenol (Scheme 2). Although we investigated the reaction conditions in detail for these transformations, particularly focusing on the reaction temperature, solvent, and Lewis acid (e.g. $Sc(OTf)_3$), we were unable to obtain any of the corresponding aromatized compounds (**3**, **8**–**10**) from zoanthamine, zoanthamine hydrochloride (**2**•HCl), or their synthetic intermediate **7**. When the oxidation was performed using $CuBr_2$ and LiBr, only a trace amount of starting material was recovered; $Yb(OTf)_3$-mediated oxidation resulted in the formation of unidentified degradation products. Because copper salts have been known to be coordinated by amines, we postulated that the aminoacetal moiety in the substrates might be labile and decompose under the reaction conditions. Therefore, we decided not to consider this route further.



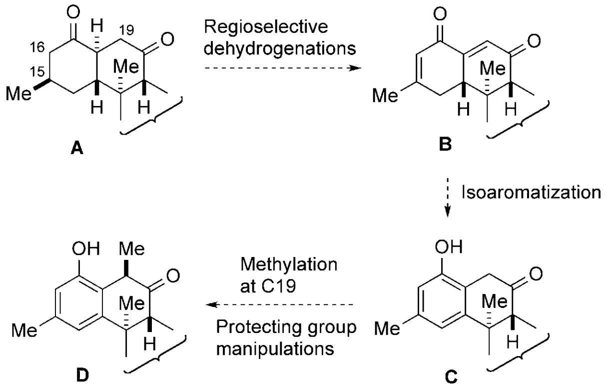
7

9: R = H
10: R = Ac

Scheme 2. Attempts toward the oxidative aromatization of zoanthamine, zoanthamine hydrochloride (**2**•HCl), and its synthetic intermediate **7**. Boc = *tert*-butoxycarbonyl.

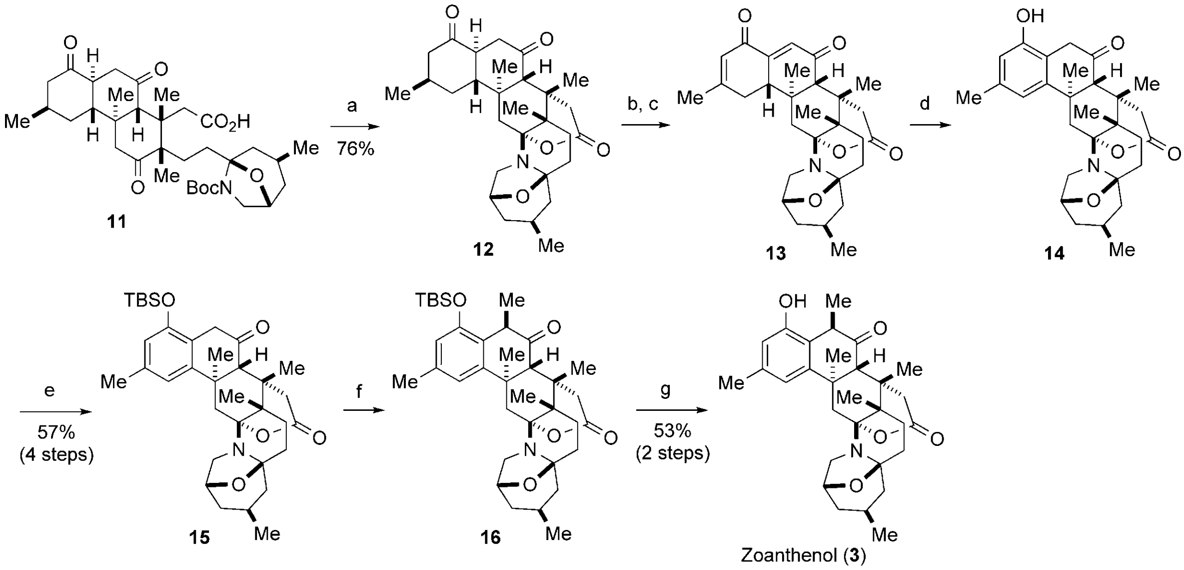
We then turned our attention to the aminoacetalization steps in the total synthesis of norzoanthamine (**1**).[4] This synthesis involved removal of the *tert*-butoxy carbonyl group and formation of an iminium ion by treatment with aqueous acetic acid, and subsequent aqueous TFA (trifluoroacetic acid)-mediated hydrolysis of the methyl ester and lactonization. In these reactions, the use of Brønsted acids did not affect the aminoacetal moiety or the ABC ring system to any appreciable extent. Therefore, we proposed a synthetic route for the construction of aromatic ring **C** using a Brønsted acid mediated isoaromatization[13] of the bis(enone) **B**, by way of a double tautomerization (Scheme 3). Bis(enone) **B** could be derived from diketone **A**, by a regioselective dehydrogenation reaction at the C15–C16 and C18–C19 bonds. The crucial construction of the AB ring system, culminating in the total synthesis of zoanthenol (Scheme 3, **D**), would be achieved by stereoselective introduction of a methyl group at the C19 position.

Indeed, we were able to accomplish the first total synthesis of **3**, using our new synthetic strategy (Scheme 4), starting from the tricyclic ketoacid **11**.[4] First, **11** was converted into dihydronorzoanthamine (**12**) by treatment with aqueous acetic acid at 100 °C in 76 % yield. The crucial precursor for the aromatization step, bis(enone) **13**, was successfully derived from **12** using the Ito–Saegusa method.[14] Thus, the treatment of **12** with LDA (8 equiv) and TMSCl (6 equiv) in THF at −50 °C regioselectively furnished trimethylsilyl enol ethers on the ketone functionalities in the AB ring system; subsequent treatment of the bis(silyl enol ether) with $Pd(OAc)_2$ and $CaCO_3$ in CH_3CN afforded the desired bis(enone) **13** in good yield. As the labile silyl enol ether in the B ring was readily hydrolyzed by acetic acid generated in situ, addition of $CaCO_3$ was critical during the latter reaction.[15] The key aromatization step was successfully performed by treatment of **13** with TFA at 50 °C for 1.5 h to produce the long-awaited aromatic compound **14**, that is, norzoanthenol.[16] It should be noted that this is the first isolation and characterization of norzoanthenol (**14**); isolation of norzoanthenol from natural sources has not yet been reported.



Scheme 3. Isoaromatization route to zoanthenol.

The remaining task for the total synthesis of zoanthenol is the regio- and stereoselective introduction of a methyl group onto the B ring. For this purpose, the phenolic compound **14** was initially transformed into its TBS ether (**15**) in 57 % overall yield from **12**. The stereoselective introduction of the methyl group at the C19 position in the desired product (**16**) was successfully performed by treatment of **15** with LDA (lithium diisopropylamide; 1.5 equiv)[18] in THF at −78 °C followed by addition of MeI (20 equiv). Finally, desilylation of the TBS ether **16** with TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate)[19] in acetone furnished the crude zoanthenol which

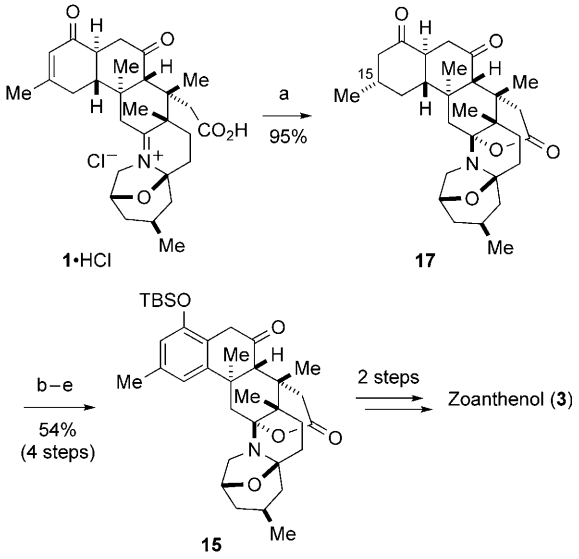


Scheme 4. Total synthesis of zoanthenol. Reagents and conditions: a) AcOH (aq.), 100 °C, 76%. b) TMSCl, LDA, THF, −50 °C. c) $Pd(OAc)_2$, $CaCO_3$, CH_3CN, 55 °C. d) TFA, 50 °C. e) $TBSNO_3$, pyridine, THF, RT, 57% (4 steps). f) LDA, THF, −78 °C, then MeI. g) TASF, acetone, RT, 53% (2 steps). TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl, LDA = lithium diisopropylamide.

was purified by reverse-phase HPLC ($MeOH/H_2O$, 1:1) to give the pure zoanthenol in 53% yield in two steps. The spectroscopic data of the synthetic compound were in agreement with those of the natural product, including optical rotation ($[\alpha]_D^{20} = +7.0\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.18\ \mathrm{g\,cm^{-3}}$, $CHCl_3$); natural zoanthenol:[6] $[\alpha]_D^{20} = +7.1\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.24\ \mathrm{g\,cm^{-3}}$, $CHCl_3$)), IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry.

Although the proposed structure of **3** was successfully verified by the present synthesis, we should point out that all of the aromatic compounds (**14**–**16**), as well as **3**, are highly air-sensitive, probably resulting in oxidation at the benzylic position, and ultimately decomposition. For example, approximately one third of zoanthenol decomposed during the 36 h ^{13}C NMR acquisition time in $CDCl_3$ (neutralized by basic Al_2O_3), and circa 30% of neat TBS ether **16** decomposed over several days of refrigerated storage (−20 °C). Therefore, to minimize oxidative decomposition in air, these compounds were handled under an argon atmosphere with studious care taken in their isolation and purification.

We also studied an alternative synthetic approach from commercially available norzoanthamine hydrochloride (**1**•HCl)[20] to zoanthenol, because Uemura and co-workers have reported the efficient conversion of the former into (15*S*)-15,16-dihydronorzoanthamine (**17**),[1c] the C15 epimer of **12**, by simple catalytic hydrogenation (Scheme 5). Thus, norzoanthamine hydrochloride was hydrogenated over Pd/C in methanol to produce **17** (95% yield), which was transformed into the TBS ether **15** by a four-step reaction sequence, similar to that from **12** to **15**, in 54% overall yield. All of the spectral data for ether **15** was identical with that of the compound previously synthesized from **11** (Scheme 4). In this way, we have established an alternative, efficient, synthetic route from commercially available norzoanthamine hydrochloride to zoanthenol. The overall yield was 27% in seven steps.



Scheme 5. Conversion of norzoanthamine hydrochloride into zoanthenol. Reagents and conditions: a) Pd/C, H_2 (1 atm), MeOH, RT, then Et_3N, 95%. b) TMSCl, LDA, THF, −50 °C. c) $Pd(OAc)_2$, $CaCO_3$, CH_3CN, 55 °C. d) TFA, 50 °C. e) $TBSNO_3$, pyridine, THF, RT, 54% (4 steps).

In conclusion, we have achieved the first total synthesis of zoanthenol (**3**), which features the key TFA-promoted isoaromatization of the bis(enone) **13** to the aromatic compound norzoanthenol (**14**). We have established another efficient synthetic route for zoanthenol, starting from commercially available norzoanthamine hydrochloride (**1**•HCl), in seven steps. The chemistry described herein opens up a completely new chemical avenue to **3**, to the hitherto unknown norzoanthenol, and to aromatic members of the zoanthamine alkaloids and their synthetic derivatives.

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Keywords: alkaloids · isoaromatization · natural products · total synthesis · zoanthenol

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[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] a) C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkatateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen, J. Clardy, *J. Am. Chem. Soc.* **1984**, *106*, 7983–7984; b) C. B. Rao, A. S. R. Anjaneyulu, N. S. Sarma, Y. Venkatateswarlu, R. M. Rosser, D. J. Faulkner, *J. Org. Chem.* **1985**, *50*, 3757–3760.

[3] For an excellent review of synthetic studies of the zoanthamine alkaloids, see: D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 2400–2421; *Angew. Chem. Int. Ed.* **2008**, *47*, 2365–2386.

[4] a) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495–499; b) M. Miyashita, *Pure Appl. Chem.* **2007**, *79*, 651–655; c) F. Yoshimura, M. Sasaki, I. Hattori, K. Komatsu, M. Sakai, K. Tanino, M. Miyashita, *Chem. Eur. J.* **2009**, *15*, 6626–6644.

[5] a) Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 1428–1431; *Angew. Chem. Int. Ed.* **2009**, *48*, 1400–1403; b) D. Yamashita, Y. Murata, N. Hikage, K. Takao, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 1432–1434; *Angew. Chem. Int. Ed.* **2009**, *48*, 1404–1406.

[6] A. H. Daranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1999**, *55*, 5539–5546.

[7] R. M. Villar, J. Gil-Longo, A. H. Daranas, M. L. Souto, J. J. Fernández, S. Peixinho, M. A. Barral, G. Santafé, J. Rodriguez, C. Jiménez, *Bioorg. Med. Chem.* **2003**, *11*, 2301–2306.

[8] a) G. Hirai, H. Oguri, M. Hirama, *Chem. Lett.* **1999**, 141–142; b) S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, M. Hirama, *Tetrahedron Lett.* **2000**, *41*, 6669–6673; c) G. Hirai, H. Oguri, S. M. Moharram, K. Koyama, M. Hirama, *Tetrahedron Lett.* **2001**, *42*, 5783–5787; d) G. Hirai, Y. Koizumi, S. M. Moharram, H. Oguri, M. Hirama, *Org. Lett.* **2002**, *4*, 1627–1630; e) G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram, M. Hirama, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2647–2651; f) N. Sugano, Y. Koizumi, G. Hirai, H. Oguri, S. Kobayashi, S. Yamashita, M. Hirama, *Chem. Asian J.* **2008**, *3*, 1549–1557.

[9] D. R. Williams, D. C. Ihle, T. A. Brugel, S. Patnaik, *Heterocycles* **2006**, *70*, 77–82.

[10] a) D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, *119*, 4155–4158; *Angew. Chem. Int. Ed.* **2007**, *46*, 4077–4080; b) J. L. Stockdill, D. C. Douglas, B. M. Stoltz, *Tetrahedron Lett.* **2009**, *50*, 3182–3184; c) J. L. Stockdill, D. C. Douglas, B. A. McClory, B. M. Stoltz, *Tetrahedron* **2009**, *65*, 6571–6575.

[11] D. Bondon, Y. Pietrasanta, B. Pucci, *Tetrahedron Lett.* **1977**, *18*, 821–824.

[12] M. Arai, Y. Miyauchi, T. Miyahara, T. Ishikawa, S. Saito, *Synlett* **2009**, 122–126.

[13] The isoaromatization of 6-alkylidene-2-cyclohexen-1-one derivatives to 2-alkylphenols has been reported by several groups: a) T. Kobayashi, S. Kumazawa, T. Kato, Y. Kitahara, *Chem. Lett.* **1975**, 301–304; b) E. Campbell, J. J. Martin, J. Bordber, E. F. Kleinman, *J. Org. Chem.* **1996**, *61*, 4806–4809; c) K. Yoshida, R. Narui, T. Imamoto, *Chem. Eur. J.* **2008**, *14*, 9706–9713.

[14] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.

[15] Other acid scavengers, such as MS4 A, K_2CO_3, and 2,6-di-*tert*-butylpyridine, were fruitless.

[16] As **13** and **14** were labile on silica gel, the crude products were directly used in the subsequent reactions.

[17] G. H. Hakimelahi, Z. A. Proba, K. K. Ogilvie, *Tetrahedron Lett.* **1981**, *22*, 4775–4778.

[18] Use of an excess amount of LDA resulted in the formation of a C19-dimethylated compound as the major product, along with **16**.

[19] K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436–6437.

[20] Norzoanthamine hydrochloride (**1**·HCl) is commercially available from Wako Pure Chemical Industries Ltd., and also can be easily prepared by treatment of norzoanthamine with HCl in methanol.[1c]