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Synthetic Studies of the Zoanthamine Alkaloids: Total Synthesis of Zoanthenol Based on an Isoaromatization Strategy

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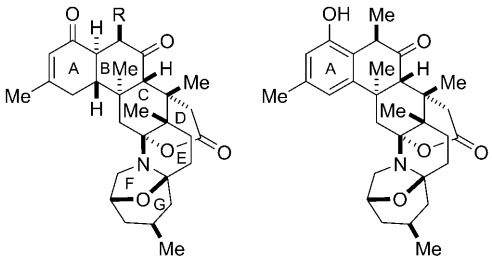
Abstract: The total synthesis of zoanthenol, a unique aromatic member of the zoanthamine alkaloids, which has exhibited potent anti-platelet activities on human platelet aggregation, is described in full detail. The key step involves a Brønsted acid-promoted isoaromatization in the AB ring system to install the crucial aromatic ring. We have not only succeeded in the first total synthesis of zoanthenol, but also established an alternative efficient synthetic route from the commercially available norzoanthamine hydrochloride to zoanthenol.

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

Introduction

The zoanthamine alkaloids, isolated from the genus *Zoanthus* sp., not only have a unique array of structural and stereochemical complexity but also display a range of distinctive biological and pharmaceutical properties. Namely, norzoanthamine (**1**) isolated by Uemura et al. in 1995,[1] can suppress the loss of bone weight and strength in ovariectomized mice and has been expected to be a promising candidate for an anti-osteoporotic drug.[1c,d] On the other hand, zoanthamine (**2**), isolated by Rao and Faulker et al. in 1984,[2] has exhibited potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects.[2b] The remarkable biological properties of norzoanthamine (**1**) and zoanthamine (**2**), combined with their novel molecular architectures make this family of alkaloids extremely attractive targets for chemical synthesis. Indeed, great synthetic efforts have been devoted to the total synthesis of the zoanthamine alkaloids, which Stoltz and co-workers recently described in their excellent Review.[3]



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

Zoanthenol (**3**)

We have been engaged in synthetic studies of the zoanthamine alkaloids[4] and already achieved the first total syntheses of norzoanthamine (**1**) in 2004[4b] and that of zoanthamine (**2**) in 2009, respectively.[4d] As shown in Scheme 1, the total syntheses of norzoanthamine (**1**) and zoanthamine (**2**) feature 1) the stereoselective synthesis of the requisite triene **4** for an intramolecular Diels–Alder reaction using the sequential three-component coupling reactions, and subsequent photosensitized oxidation of the furan ring, 2) the key intramolecular Diels–Alder reaction to construct the ABC carbon framework bearing two quaternary asymmetric carbon atoms, and 3) the crucial bis-(amino)acetalization for the construction of the DEFG ring system.

Recently, Kobayashi et al. reported the second total synthesis of **1**, which involved an elegant intramolecular Diels–Alder reaction to construct the AB ring system, and subsequent synthesis of the DEFG ring system including bisaminal structures as the key steps.[5]

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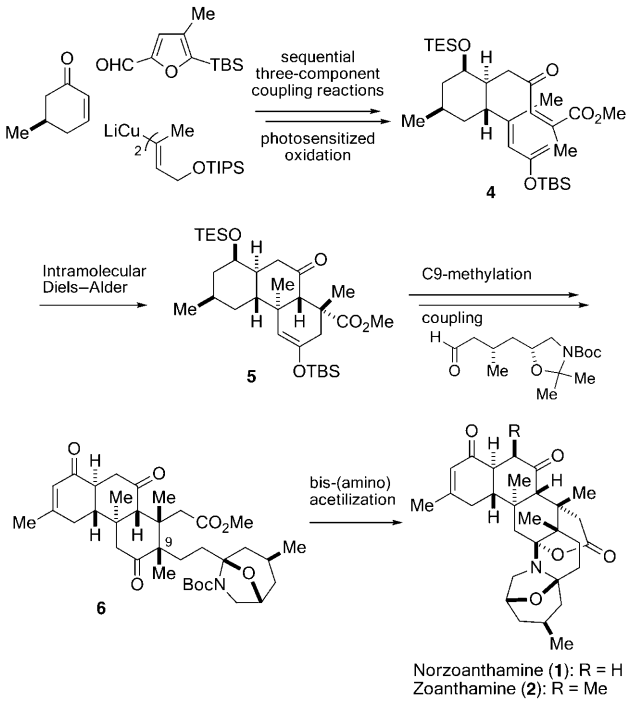


Scheme 1. Strategy for the total synthesis of norzoanthamine (**1**) and zoanthamine (**2**).

Having achieved the efficient total syntheses of **1** and **2**, we next focused on the synthesis of zoanthenol (**3**),[6] another representative member of the zoanthamine alkaloids bearing a unique aromatic ring. As with norzoanthamine derivatives, Zoanthenol (**3**) has been reported to exhibit potent anti-platelet activity on human platelet aggregation.[7] The unique biological properties of zoanthenol (**3**), combined with its novel chemical structure make this alkaloid an extremely attractive target for total synthesis as well as norzoanthamine (**1**) and zoanthamine (**2**). Indeed, a number of research groups have extensively studied the chemical synthesis of zoanthenol (**3**) based on their distinctive strategies.[8–10] However, until we accomplished the first synthesis of **3** in 2009,[11] the total synthesis of **3** had seriously been impeded, owing to its densely functionalized complex stereostructure. In this article, we will discuss not only the first total synthesis of zoanthenol (**3**), using a synthetic intermediate **27** in our synthesis of norzoanthamine (**1**), and an efficient alternative synthetic route from the commercially available norzoanthamine hydrochloride to zoanthenol (**3**) in full detail.[11]

Abstract in Japanese:

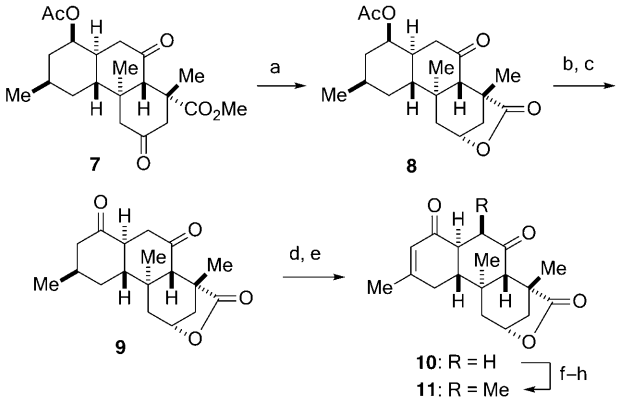
特異な化学構造と顕著な生物活性を有するゾアンタミン系アルカロイドは内外の注目を集めており、活発な合成研究が展開されている。しかし非常に複雑な立体構造を有するため全合成研究は難航している。著者らは代表的な化合物であるノルゾアンタミンの最初の化学合成に成功するとともに、最近ゾアンタミンおよびゾアンテノールの全合成を達成した。本論文はユニークな芳香環を含むゾアンテノールの最初の化学合成について、合成戦略、最重要課題である芳香環構築法の開発、ノルゾアンタミン塩酸塩からゾアンテノールへの効率的変換などを中心に実験項を含め詳細に記述している。

Results and Discussion

The only difference in the structures of zoanthenol (**3**) and zoanthamine (**2**) is the oxidation pattern of the A ring. Therefore, we envisioned two possible routes toward the total synthesis of zoanthenol. Namely, one is the straightforward synthesis of **3** from zoanthamine (**2**) by aromatization of the A ring in the latter. The other includes aromatization of the A ring in an appropriate synthetic intermediate in the total syntheses of **1** and **2**, and subsequent transformation into zoanthenol (**3**). First, we set about synthetic studies of **3** based on the former strategy. The key issue in the synthesis of zoanthenol (**3**) depended on, of course, development of an efficient synthetic method that makes the construction of the aromatic ring possible without affecting the densely functionalized structure of zoanthamine (**2**).

One-step oxidative aromatization approach

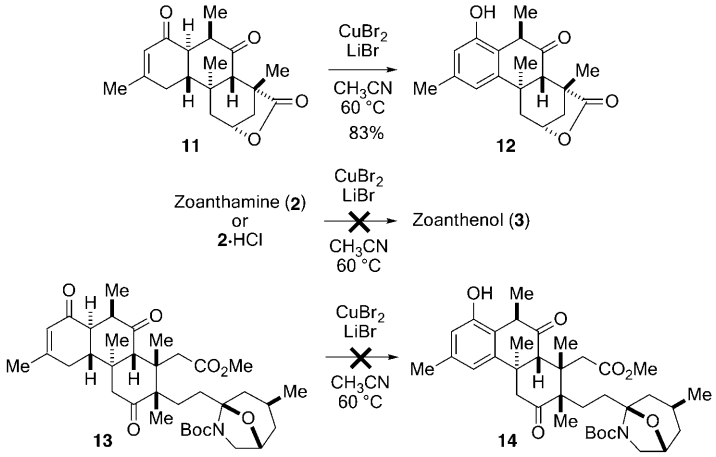
At first, we thought that zoanthenol (**3**) might be derived from zoanthamine (**2**) by oxidative aromatization of the A ring in one step. To probe such possibility effectively, we chose tetracyclic enone **11** as a model compound. The requisite substrate **11** was synthesized from the diketo ester **7**,[4] the key intermediate in the total synthesis of **1** and **2**, according to Scheme 2. Thus, **7** was converted into the keto



Scheme 2. Synthesis of the tetracyclic enone **11**. a) K-Selectride, THF, CH_2Cl_2, −78 °C, 89 %; b) $Ti(OEt)_4$, toluene, 100 °C; c) Dess–Martin periodinane, CH_2Cl_2, RT, 73 % (2 steps); d) TMSCl, LiHMDS, THF, −65 °C; e) $Pd(OAc)_2$, CH_3CN, 50 °C, 93 % (2 steps); f) TBSOTf, Et_3N, CH_2Cl_2, −65 °C; g) LDA, THF, −55 °C, then MeI, −50 °C; h) AcOH (aq.), RT, 86 % (3 steps).

lactone **8** by treatment with K-Selectride in THF and CH_2Cl_2 at −78 °C. After removal of the acetyl group in **8** by treatment with $Ti(OEt)_4$ in toluene at 100 °C,[12] the resulting alcohol was oxidized with Dess–Martin periodinane[13] to afford the diketo lactone **9** in 65% overall yield from **7**. Regioselective introduction of a double bond into the A ring was successfully performed by the Ito–Saegusa method,[14] which involved regioselective formation of trimethylsilyl enol ether in the A ring by treatment with lithium hexamethyldisilazide (LiHMDS) and trimethylsilyl chloride (TMSCl) in THF at −65 °C, and subsequent oxidation of the resulting trimethylsilyl (TMS) enol ether with $Pd(OAc)_2$ in CH_3CN at 50 °C, provided the desired enone **10** in 93% yield. The tetracyclic enone **10** was transformed into the targeted compound **11** by a three-step reaction sequence: 1) conversion of the enone moiety into dienol TBS ether by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and Et_3N in CH_2Cl_2 at −65 °C; 2) stereoselective introduction of a methyl group at the C19 position by treatment of the TBS ether with lithium diisopropylamide (LDA) and MeI in tetrahydrofuran (THF) at −50 °C; 3) hydrolysis of the resulting dienol TBS ether with aqueous AcOH, in 86% overall yield from **10**.

With the model compound **11** in hand, we studied the key oxidative aromatization of **11**, which led to the aromatic compound **12** (Scheme 3). Initial attempts to aromatize the

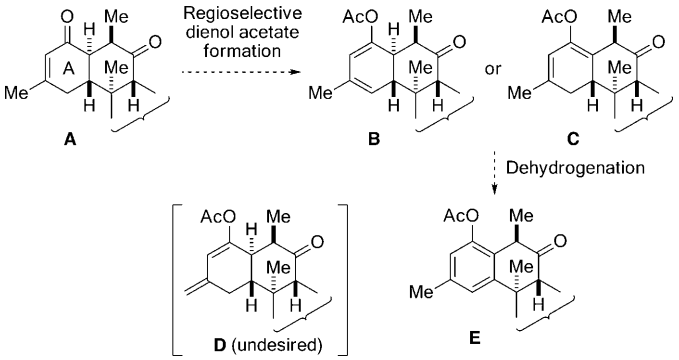


Scheme 3. Attempts at one-step oxidative aromatization using $CuBr_2$/LiBr.

A ring by refluxing with an excess amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene or dioxane merely resulted in recovery of the starting material. After a number of trials, we eventually found that the procedure of Pucci and co-workers[15] was effective for this particular transformation. Thus, when **11** was treated with $CuBr_2$ (4 equiv) and LiBr (2 equiv) in CH_3CN at 60 °C, the desired product **12** was obtained as a single product in 83% yield. The structure of **12** was unambiguously confirmed by NOE measurements, which indicated that our apprehensive epimerization at the benzylic position did not occur at all (see the Supporting Information). The excellent preliminary result led us to apply the Pucci procedure to zoanthamine (**2**) and its synthetic intermediate **13**[4] toward the synthesis of zoanthenol (**3**). However, the reactions of **2**, zoanthamine hydrochloride,[16] and **13** gave a complex mixture in every case under these reaction conditions, and none of the corresponding aromatic compound was detected. In spite of many attempts by screening the solvent effects and stoichiometry of the reagents as well as the reaction temperature, we were unable to obtain the targeted compounds. As copper salts have been known to coordinate with amines, we deduced that the aminoacetal moiety in these substrates might be decomposed under the reaction conditions.

Stepwise dehydrogenation approach

We next examined another approach to construct the aromatic ring **E**, using homoannular dienol acetate **B** or its regioisomer **C,** by means of dehydrogenation with DDQ or chloranil as shown in Scheme 4, though an alternative possi-



Scheme 4. Stepwise dehydrogenation approach to zoanthenol (**3**).

ble regioisomer **D** may not undergo aromatization. The requisite dienol acetates **B** and/or **C** will probably be derived from the dienone precursor **A** by treatment with an appropriate base and acetic anhydride (Ac_2O). In this context, regioselective generation of dienolate anions from 3-methyl-2-cyclohexenone derivatives have been reported in the literature.[17] Alternatively, **B** and/or **C** may be derived by acid-catalyzed enol acetylation of **A**.

Toward this end, we first examined the reaction of the tetracyclic enone **11** (Scheme 5). Thus, when **11** was treated with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C followed by an addition of Ac_2O, a mixture of the exocyclic dienol acetate **15** and endocyclic isomer **16** was obtained in 20% and 33% yield, respectively. Interestingly, the homoannular dienol acetate **18** was not produced under these reaction conditions. As we expected, aromatization of **16** with DDQ (2 equiv) smoothly occurred in dioxane at 80 °C to afford the aromatic compound **17** in 85% isolated yield. To improve the yield of **16**, several bases were examined, however, the use of LDA and LiHMDS did not substantially affect the yield and ratio of the product **16**:**16**

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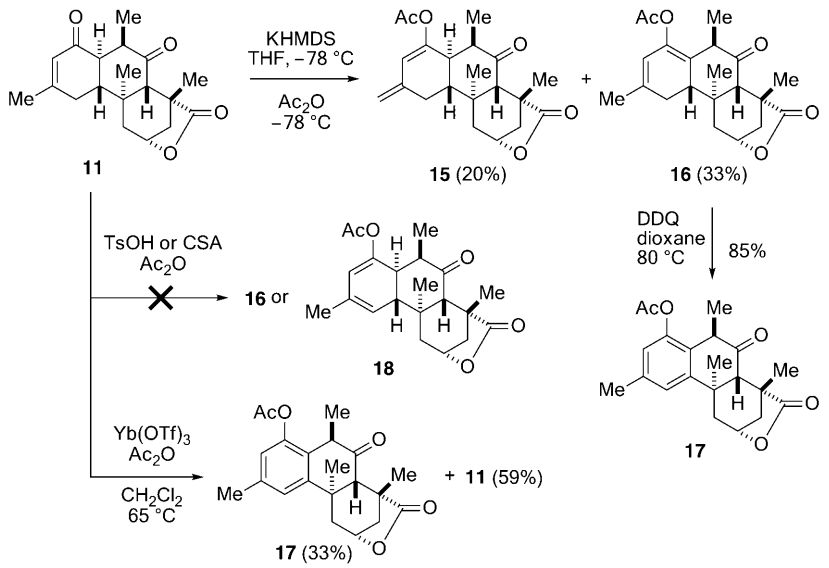


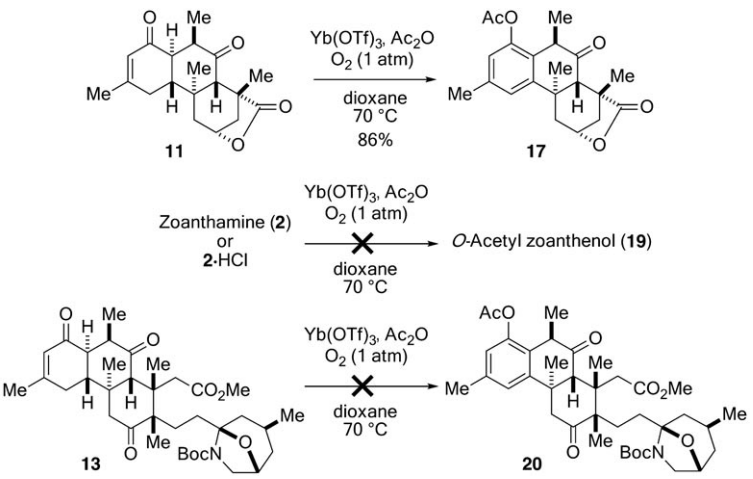
Scheme 5. Synthesis of dienol acetates and an aromatic compound.

(26%) and **15** (37%) with LDA; exclusive formation of **15** (43%) with LiHMDS.

Encouraged by the experiment that the dienol acetate **16** was an efficient precursor for aromatization, we next focused on the synthesis of **16** and/or **18** under acidic conditions. However, all the reactions with TsOH or camphorsulfonic acid (CSA) in the presence of Ac_2O did not occur at all and only the starting material was recovered unchanged.

At this stage, we anticipated that the use of a rare-earth metal triflate might act as an effective catalyst for this particular transformation, since it is well known that rare-earth metal triflates effectively catalyze acylation of alcohols with acid anhydrides, and formation of geminal diacetate from aldehydes with Ac_2O.[18] In addition, these catalysts are known to be active even in the presence of Lewis bases containing nitrogen and oxygen atoms,[19] and this seems to be ideally suited for the highly functionalized zoanthamine alkaloids. Thus, when **11** was treated with Ac_2O and $Yb(OTf)_3$ in 1,2-dichloroethane at 65°C, surprisingly, the aromatic acetate **17**[20] was directly obtained in 33% isolated yield, along with the starting material (59%). Neither the expected dienol acetates (**16**, **18**) nor the *exo*-dienol acetate **15** was produced under the conditions.

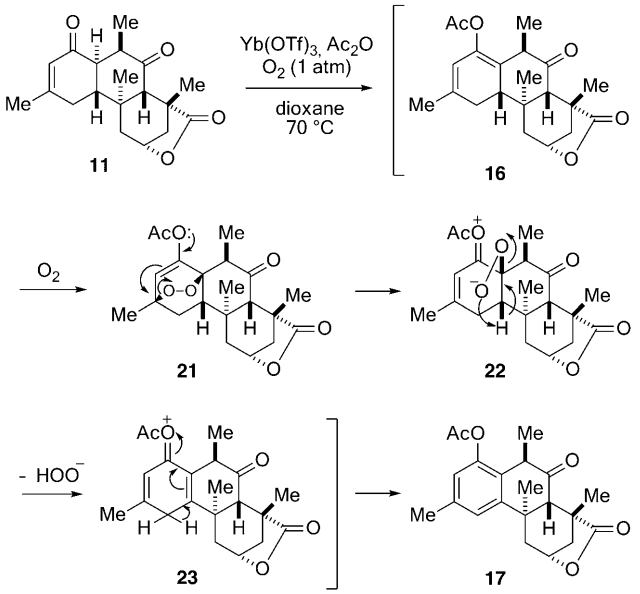
The unexpected but gratifying result prompted us to investigate $Yb(OTf)_3$-mediated aromatization of **11**, thus leading to **17** in detail, particularly focusing on solvent effects, the stoichiometry of catalyst, and the reaction temperature as well as the use of other Lewis acids (e.g. $Sc(OTf)_3$). Soon, we noticed that oxygen was of critical importance for this particular oxidation reaction. After a number of experiments, we eventually found that the aromatization of **11** smoothly occurred under the following optimized conditions, using a combination of $Yb(OTf)_3$ (1 equiv), Ac_2O (10 equiv), and oxygen (1 atm) in dioxane at 70°C for 4 hours afforded the desired product **17** in 86% yield (Scheme 6). In addition, the experiment confirmed that this aromatization reaction was extremely retarded or did not



Scheme 6. $Yb(OTf)_3$-mediated oxidative aromatization to aromatic acetates.

occur in the dark. Therefore, the following reaction mechanism may be most probable (Scheme 7): 1) formation of the enol acetate **16** in situ; 2) a Diels–Alder reaction with oxygen leading to **21**; 3) elimination of a hydroperoxide anion from **22**; 4) aromatization with a cross-conjugated oxonium ion **23** giving rise to the product **17**. A similar reaction mechanism, including 1,4-adducts of enol acetates with singlet oxygen, was recently reported by Ishikawa and Saito;[21] this involved in air oxidation of 4-oxo-4,5,6,7-tetrahydroindoles with TsOH and Ac_2O, leading to various 4-acetoxyindoles.

With this new methodology in hand for oxidative aromatization, with the use of a $Yb(OTf)_3$ catalyst, this methodology was applied to zoanthamine (**2**), zoanthamine hydrochloride (**2**·HCl), and its synthetic intermediate **13** toward the total synthesis of zoanthenol (**3**; Scheme 6). However, disap-



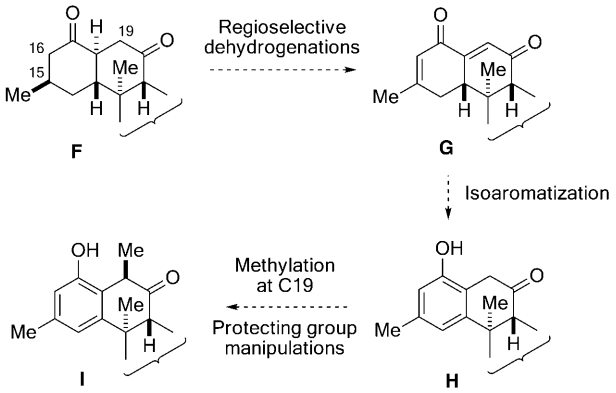
Scheme 7. Possible reaction mechanism of aromatization.

pointingly, all the reactions gave a complex mixture, which is probably due to decomposition of the aminoacetal moiety under the reaction conditions. Consequently, we employed another synthetic approach toward the synthesis of zoanthenol (**3**).

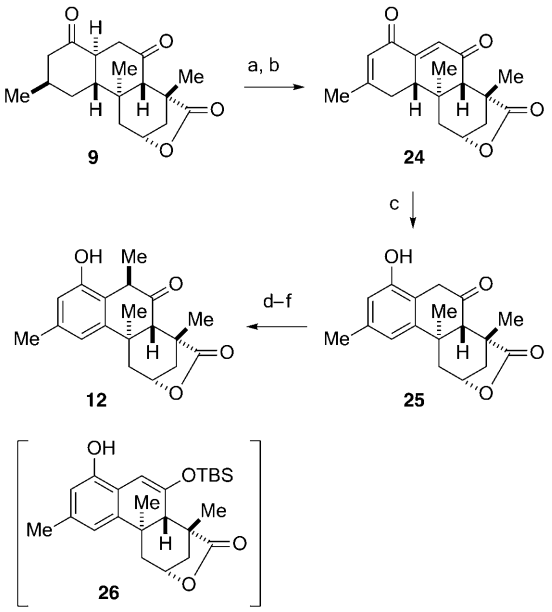
Synthetic approach by means of isoaromatization

At this stage, we remembered the aminoacetalization steps (cf. **6**→**1**, Scheme 1) in the total synthesis of norzoanthamine (**1**),[4] which involved the following reaction sequence: 1) removal of the *tert*-butoxycarbonyl (Boc) group and subsequent formation of an iminium ion by treatment with aqueous AcOH at 100 °C; 2) hydrolysis of the methyl ester followed by lactonization with aqueous trifluoroacetic acid (TFA) at 110 °C. These reactions suggest that the use of Brønsted acids did not essentially affect the aminoacetal moiety. Based on such assumption, we designed a new strategy for construction of the aromatic ring (**H**) by means of a Brønsted acid-mediated isoaromatization[22] of bis(enone) (**G**) through double tautomerization, as shown in Scheme 8. The requisite bis(enone) (**G**) may be derived from diketone (**F**) by a regioselective dehydrogenation reaction at the C15–C16 and C18–C19 bonds. The new strategy for aromatization, based on isoaromatization, followed by a stereoselective introduction of a methyl group at the C19 position could direct us to the summit of zoanthenol (**I**).

We first synthesized the bis(enone) **24** as a model substrate (Scheme 9). Fortunately, **24** was readily derived from the diketone **9** by means of the Ito–Saegusa method, which involved regioselective formation of the bis(silyl enol ether) by treatment with LDA and TMSCl at −70 °C followed by oxidation with $Pd(OAc)_2$ in CH_3CN at 50 °C. Since the bis(enone) **24** was highly susceptible to silica gel, the crude product was directly used in the next aromatization reaction.



Scheme 8. Synthetic strategy for zoanthenol (**3**) based on isoaromatization.



Scheme 9. Model studies on isoaromatization. a) LDA, TMSCl, THF, −70 °C; b) $Pd(OAc)_2$, CH_3CN, 50 °C; c) TFA, 50 °C, 42 % (3 steps); d) $TBSNO_3$, pyridine, THF, RT, 82 %; e) LiHMDS, THF, −78 °C, then MeI, −78 °C; f) TASF, acetone, RT, 86 % (3 steps).

Although acetic acid induced isoaromatization of **24** at 100 °C was not reproducible, the expected result was obtained by treatment of **24** with TFA at 50 °C, thereby giving rise to the aromatic compound **25** in 42 % overall yield from **9**. On the other hand, treatment of **24** with other Brønsted acids such as TfOH at 0 °C, or SiO_2 in EtOAc at 80 °C, did not give satisfactory results.[23]

Having discovered the new synthetic methodology for aromatization, the remaining task for the synthesis of the targeted compound **12**, corresponding to the ABC ring system of zoanthenol (**3**), was a stereoselective introduction of a methyl group at the benzylic position. For this purpose, the phenolic hydroxy group in **25** was initially protected as a TBS ether by treatment with $TBSNO_3$[24] in THF in the presence of pyridine (82 % yield). It should be noted that when

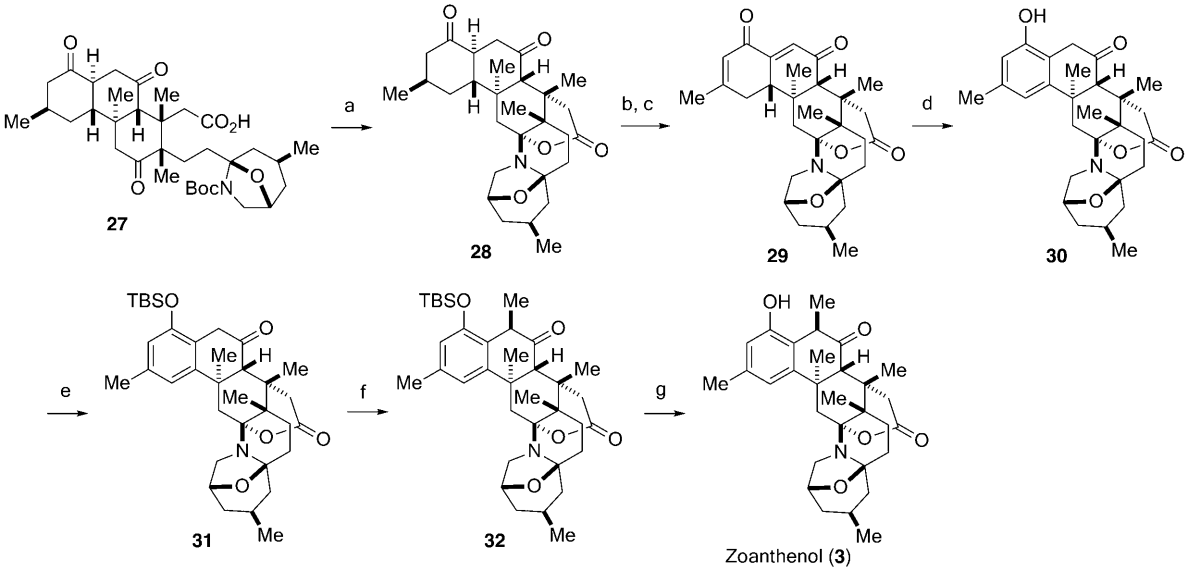
silylation was carried out under the generally used conditions (e.g., $TBSCl/Et_3N$ or TBSCl/imidazole), the TBS enol ether **26** was produced as the major product. In addition, the silylation reaction of **25** with 1-(*tert*-butyldimethylsilyl)-imidazole[25] in 1,2-dichloroethane resulted in formation of the phenolic TBS ether of **25** in lower yield (58%), and a substantial amount of the starting material was recovered. Thus, the use of $TBSNO_3$ was of critical importance for this particular silylation reaction. The subsequent key methylation reaction at the benzylic position was successfully performed by treatment of the phenolic TBS ether of **25** with LiHMDS and MeI in THF at −78°C. Finally, deprotection of the TBS group with TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate)[26] in acetone furnished the targeted compound **12** in 86% overall yield from **25**. We should point out that all other conditions examined to remove the TBS group, such as aqueous AcOH, TFA, 1 M HCl (aq.) in THF, and tetrabutylammonium fluoride (TBAF) in THF, afforded lower yields of **12**.

Total synthesis of zoanthenol

With the new synthetic methodology for construction of the aromatic ring in hand, we focused on the total synthesis of zoanthenol (**3**), starting from the key intermediate **27**[4] in the total synthesis of norzoanthamine (**1**) and zoanthamine (**2**) (Scheme 10). First, **27** was converted into dihydronorzoanthamine (**28**) by treatment with aqueous AcOH at 100°C in 76% yield. The crucial precursor bis(enone) **29** for aromatization was derived from **28** by means of the Ito–Saegusa method. Thus, treatment of **28** with an excess amount of LDA (8 equiv) and TMSCl (6 equiv) in THF at −50°C furnished TMS enol ethers at the ketone functions in the AB ring, and subsequent treatment of the bis(silyl enol ether) with $Pd(OAc)_2$ and $CaCO_3$ in CH_3CN produced the desired bis(enone) **29** in good yield.[27] As the silyl enol ether in the B ring was readily hydrolyzed by acetic acid generated in situ, an addition of $CaCO_3$ was of critical importance for the latter reaction, while other acid scavengers, such as MS4 Å, K_2CO_3, and 2,6-di-*tert*-butylpyridine, were fruitless. The key aromatization was performed by treatment of **29** with TFA at 50°C for 1.5 h to provide the long-awaited aromatic compound **30**,[28] that is, norzoanthenol. It should be pointed out that norzoanthenol (**30**) was isolated and characterized for the first time by the present synthesis; isolation of norzoanthenol from natural sources has not been reported yet.

The remaining task for the total synthesis of zoanthenol (**3**) was the regio- and stereoselective introduction of a methyl group onto the B ring. For this purpose, **30** was initially transformed into the TBS ether **31** by treatment with $TBSNO_3$ and pyridine in THF in 57% overall yield from **28**. The subsequent introduction of a methyl group at the C19 position was performed by treatment of **31** with LDA (1.5 equiv) in THF at −78°C followed by an addition of MeI (20 equiv) to afford the methylated product **32** in a stereoselective manner.[29] Finally, desilylation of the TBS ether **32** with TASF in acetone furnished the crude zoanthenol, which was purified by reverse phase HPLC (Inertsil ODS-3, $MeOH/H_2O = 1:1$), thereby giving rise to the pure zoanthenol (**3**) in 53% yield over two steps. The spectral data of the synthetic compound were in agreement with those of the natural product, including optical rotation ($[\alpha]_D^{28} = +7.0$ ($c = 0.18$ in $CHCl_3$); natural zoanthenol:[6] $[\alpha]_D^{25} = +7.1$ ($c = 0.24$ in $CHCl_3$), ^1H and ^{13}C NMR spectra, IR, and mass spectra.

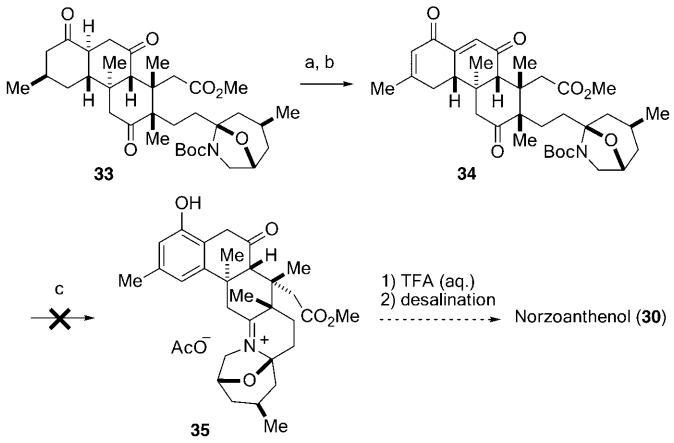
Although the proposed structure of zoanthenol (**3**) was verified by the present synthesis, we should point out that all the aromatized compounds (**30**–**32**), as well as zoanthenol (**3**), were highly sensitive to air, probably resulting in air oxidation at the benzylic position and ultimately decomposi-



Scheme 10. Total synthesis of zoanthenol (**3**). 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).

tion.[30] For example, approximately one third of zoanthenol (**3**) was decomposed during the 36 hours ^{13}C NMR acquisition time in $CDCl_3$ (neutralized by basic Al_2O_3), and circa 30% of neat TBS ether **31** decomposed over several days of refrigerated storage (−20°C). Therefore, in order to minimize decomposition in air, these compounds were handled under an argon atmosphere with studious care taken in their isolation and purification.

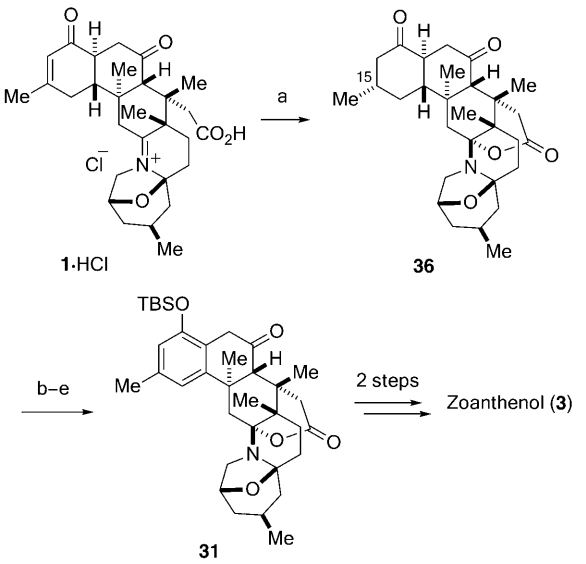
On the other hand, aiming at an alternative synthesis of zoanthenol (**3**), one-pot manipulation including isoaromatization, deprotection of the Boc group, and subsequent iminium ion formation, was examined using bis(enone) **34**. The bis(enone) **34** was prepared from the keto ester **33**[4] in two steps as shown in Scheme 11. Contrary to our expectation, however, treatment of **34** with aqueous AcOH at 100°C caused decomposition and the cyclized iminium ion **35** was not detected at all.



Scheme 11. Unsuccessful synthetic route to zoanthenol through **34**. a) LDA, TMSCl, THF, −70°C; b) $Pd(OAc)_2$, CH_3CN, 50°C, >99% (2 steps); c) AcOH (aq.), 100°C.

Conversion of norzoanthamine hydrochloride into zoanthenol

We next studied an alternative synthetic approach from commercially available norzoanthamine hydrochloride (**1**·HCl)[31] to zoanthenol (**3**), as Uemura and co-workers reported the efficient conversion of the former into (15*S*)-15,16-dihydronorzoanthamine (**36**),[1c] the C15 epimer of **28**, by simple catalytic hydrogenation (Scheme 12). Indeed, norzoanthamine hydrochloride was efficiently converted into **36** by hydrogenation over Pd/C in MeOH and subsequent desalination with Et_3N in 95% yield, which was then transformed into the TBS ether **31** by a four-step reaction sequence similar to that from **28** to **31**: 1) regioselective formation of bis-trimethylsilyl enol ethers at the ketone functions in the AB ring; 2) oxidation of the resulting bis(silyl enol ether) with $Pd(OAc)_2$ in the presence of $CaCO_3$ in CH_3CN; 3) isoaromatization with TFA; 4) protection of the phenolic



Scheme 12. Conversion of norzoanthamine hydrochloride to zoanthenol (**3**). 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).

hydroxyl group with $TBSNO_3$ in THF, in 54% overall yield. All the spectral data of the synthetic compound **31** were identical with those of the previously synthesized compound from **28** (Scheme 10). Thus, we have established an alternative efficient synthetic route from commercially available norzoanthamine hydrochloride to zoanthenol (**3**). The overall yield for this particular conversion was 27% in seven steps.

Conclusions

In summary, we have achieved the first total synthesis of zoanthenol (**3**), which involves the novel TFA-promoted isoaromatization of the bis(enone) **29** to the aromatic compound **30**, norzoanthenol, as the key step. We have also established another efficient synthetic route to zoanthenol (**3**), starting from the commercially available norzoanthamine hydrochloride (**1**·HCl), in seven steps. It is noteworthy that three types of the representative zoanthamine alkaloids, norzoanthamine (**1**), zoanthamine (**2**), and zoanthenol (**3**) were efficiently synthesized through the common intermediate **27**.

The chemistry described herein opens up a completely new chemical avenue to zoanthenol (**3**), to the hitherto unknown norzoanthenol (**30**), and to aromatic members of the zoanthamine alkaloids and their synthetic derivatives.

Experimental Section

Materials and methods

All the reactions were carried out in a round-bottomed flask with an appropriate number of necks and sidearms connected to a three-way stop-

cock and/or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by a rotary pump and then flushed with argon prior to use. Solutions and solvents were introduced by a hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry THF was freshly prepared by distillation from sodium benzophenone ketyl before use. Anhydrous acetone, CH_3CN, CH_2Cl_2, dioxane, MeOH, and pyridine were purchased from Kanto Chemical Co. Inc. In order to minimize decomposition by air oxidation, extreme care was taken in the handling and isolation of sensitive compounds, especially for zoanthenol (**3**) and its aromatic precursors (**30**–**32**). These compounds were always handled under an argon atmosphere.

Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer using 5 mm NaCl plates. Wavelength of maximum absorbance are quoted in cm^{-1}. ^1H NMR spectra were recorded on a JEOL ECA-500 (500 MHz) in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard. Chemical shifts are reported in parts per million (ppm), and signals are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ^{13}C NMR spectra were recorded on a JEOL ECA-500 (125 MHz) or JEOL ECA-600 (150 MHz) in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard. Chemical shifts are reported in ppm. High resolution mass spectra (HRMS) were recorded on a JEOL JMS AX-500, JEOL JMS-SX102A or JEOL JMS-T-100GCV at the GC-MS and NMR Laboratory, Graduate School of Agriculture, Hokkaido University. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 6% ethanolic *p*-anisaldehyde (includes 6% conc. sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.

Additional experimental procedures are available in the Supporting Information.

Compound 28: A solution of the carboxylic acid **27**[4] (16.8 mg, 27.9 μmol) in aqueous AcOH (AcOH/H_2O = 24:1, 0.5 mL) was heated at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (1 mL) containing Et_3N (100 μL). The solution was stirred at room temperature for 20 min. Water was added to the mixture and the product was thoroughly extracted with EtOAc (×5). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1:3) afforded 10.2 mg (76%) of dihydronorzoanthamine (**28**) as a colorless solid. M.p. 274–276 °C; $[\alpha]_D^{32} = +33.6$ ($c = 0.21$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 4.55$–4.53 (m, 1H), 3.62 (d, $J = 20.0$ Hz, 1H), 3.25–3.19 (m, 2H), 2.83 (s, 1H), 2.79 (td, $J = 11.9$, 5.5 Hz, 1H), 2.70 (dd, $J = 13.5$, 11.7 Hz, 1H), 2.62–2.54 (m, 2H), 2.35 (d, $J = 20.0$ Hz, 1H), 2.31 (dd, $J = 14.3$, 5.2 Hz, 1H), 2.28–2.21 (m, 1H), 2.14 (d, $J = 14.3$ Hz, 1H), 2.08 (dd, $J = 13.2$, 4.6 Hz, 1H), 2.00 (td, $J = 12.5$, 3.2 Hz, 1H), 1.89 (td, $J = 13.2$, 4.6 Hz, 1H), 1.83–1.78 (m, 2H), 1.67 (td, $J = 13.6$, 3.6 Hz, 1H), 1.55 (dd, $J = 13.7$, 4.6 Hz, 1H), 1.45 (td, $J = 12.7$, 2.9 Hz, 1H), 1.17 (s, 3H), 1.09–1.07 (m, 1H), 1.02 (d, $J = 7.4$ Hz, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.90 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 209.58$, 209.21, 172.54, 101.69, 89.91, 74.16, 59.49, 52.05, 51.04, 47.26, 46.98, 44.39, 42.54, 42.14, 40.45, 39.83, 38.82, 36.44, 35.83, 30.89, 29.93, 29.80, 23.59, 22.91, 21.79, 21.03, 19.56, 18.42, 17.80 ppm; IR (film): $\tilde{\nu} = 2959$, 2927, 2871, 1713, 1383, 1363, 1341, 1320, 1308, 1287, 1277, 1246, 1237, 1186, 923, 910 cm^{-1}; HRMS (FD): *m/z*: calcd for $C_{20}H_{28}O_5$: 483.2985; found: 483.2965 $[M]^+$.

Compound 29: A solution of dihydronorzoanthamine (**28**) (5.7 mg, 11.8 μmol) and TMSCl (9.0 μL, 70.7 μmol) in THF (0.2 mL) was added dropwise to a freshly prepared solution of LDA (1.0 M) in THF (94 μL, 94 μmol) at −78 °C and the mixture was stirred at −50 °C for 1.5 h. A saturated aqueous solution of $NaHCO_3$ containing Et_3N was added to the reaction mixture and the product was extracted with EtOAc. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The crude TMS enol ether was used for the next step without purification.

A mixture of the crude TMS enol ether (11.8 μmol), $CaCO_3$ (12 mg, 118 μmol), and CH_3CN (0.3 mL) was stirred at room temperature for 5 min. Then, $Pd(OAc)_2$ (10.6 mg, 47.4 μmol), and the mixture was stirred at 55 °C for 1.5 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite by the aid of EtOAc (0.5 mL). A saturated aqueous solution of $NaHCO_3$ (0.5 mL) and L-serine (15 mg, 143 μmol) was added to the filtrate and the mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the bis(enone) **29** as a 50:3 mixture with norzoanthamine (**1**). The crude bis(enone) **29** was used for the next step without purification.

Norzoanthenol (30): A solution of the crude bis(enone) **29** (11.8 μmol, a 50:3 mixture with **1**) in TFA (0.5 mL) was heated at 50 °C for 1.5 h. After the mixture was cooled to room temperature, phosphate buffer (pH 7.4, 0.5 mL) and EtOAc (0.5 mL) were added. After being stirred at room temperature for 30 min, the product was throughly extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give norzoanthenol (**30**) as a 50:3 mixture with norzoanthamine (**1**). The crude norzoanthenol (**30**) was used for the next step without purification.

For characterization, further purification by reverse phase HPLC (Inertsil ODS-3, 10 mm x 50 mm, MeOH/H_2O = 1:1) afforded the pure norzoanenol (**30**) as an amorphous solid. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 6.58$ (s, 1H), 6.51 (s, 1H), 5.48–4.87 (br, 1H), 4.61–4.58 (m, 1H), 3.77 (d, $J = 20.6$ Hz, 1H), 3.64 (d, $J = 21.8$ Hz, 2H), 3.43–3.38 (m, 2H), 3.38 (d, $J = 20.6$ Hz, 1H), 3.22 (s, 1H), 2.61 (d, $J = 13.7$ Hz, 1H), 2.53 (d, $J = 13.7$ Hz, 1H), 2.46 (d, $J = 20.6$ Hz, 1H), 2.38–2.32 (m, 4H), 2.31 (s, 3H), 2.13 (dd, $J = 12.9$, 4.9 Hz, 1H), 1.91 (td, $J = 12.7$, 3.8 Hz, 1H), 1.79 (dd, $J = 10.0$, 3.7 Hz, 1H), 1.73 (dd, $J = 13.7$, 4.0 Hz, 1H), 1.63–1.56 (m, 2H), 1.49 (td, $J = 12.6$, 2.7 Hz, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.93 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 208.17$, 200.29, 153.47, 138.04, 115.62, 114.10, 112.79, 102.30, 90.21, 74.52, 57.41, 47.48, 44.61, 41.56, 40.81, 39.98, 39.15, 39.01, 36.88, 35.82, 30.20, 28.60, 23.97, 23.20, 22.90, 22.10, 21.70, 21.51, 18.73 ppm; IR (film): $\tilde{\nu} = 3600$–3000 (br), 2952, 2925, 2870, 1713, 1684, 1591, 1454, 1361, 1269, 1247, 1191, 913, 732 cm^{-1}; HRMS (FD): *m/z*: calcd for $C_{29}H_{37}NO_5$: 479.2672; found: 479.2682 $[M]^+$.

Compound 31: Pyridine (29 μL, 354 μmol) was added to a mixture of norzoanthenol (**30**; 11.8 μmol, a 50:3 mixture with **1**) and $AgNO_3$ (30 mg, 177 μmol) in THF (150 μL), and the resulting mixture was stirred at room temperature for 0.5 h at which point most of silver complex was dissolved. Then TBSCl (18 mg, 118 μmol) was added, and the resulting mixture was stirred at room temperature for 1.5 h. After addition of water, the resulting mixture was filtered through a cotton plug by the aid of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1:1) afforded 4.0 mg (57% from **28**) of the TBS ether **31** as a colorless amorphous solid. The TBS ether **31** was used for next step immidiately due to its instability. $[\alpha]_D^{29} = -11.4$ ($c = 0.34$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 6.60$ (s, 1H), 6.52 (s, 1H), 4.60–4.56 (m, 1H), 3.77 (d, $J = 20.0$ Hz, 1H), 3.62 (d, $J = 22.3$ Hz, 1H), 3.40 (ddd, $J = 13.2$, 7.4, 6.3 Hz, 2H), 3.34 (d, $J = 22.3$ Hz, 1H), 3.20 (s, 1H), 2.60 (d, $J = 13.7$ Hz, 1H), 2.52 (d, $J = 14.3$ Hz, 1H), 2.45 (dd, $J = 20.0$, 1.1 Hz, 1H), 2.37–2.34 (m, 1H), 2.32 (s, 3H), 2.14 (dd, $J = 12.9$, 4.9 Hz, 1H), 1.90 (dt, $J = 13.2$, 6.9 Hz, 1H), 1.78–1.75 (m, 2H), 1.62–1.55 (m, 2H), 1.49 (td, $J = 12.6$, 2.7 Hz, 1H), 1.16 (s, 3H), 1.11 (3H, s), 1.10 (3H, s), 1.00 (s, 9H), 0.93 (d, $J = 6.3$ Hz, 3H), 0.26 (s, 3H), 0.24 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 208.43$, 190.08, 153.33, 150.83, 119.67, 116.77, 115.59, 101.91, 89.95, 74.27, 57.10, 47.22, 44.35, 41.65, 41.34, 39.73, 38.91, 38.81, 36.61, 35.60, 29.97, 29.69, 28.38, 25.73, 24.69, 23.74, 22.96, 21.85, 21.26, 18.48, 18.22, −40.4, −4.17 ppm; IR (film): $\tilde{\nu} = 2953$, 2927, 2857, 1716, 1542, 1457, 1362, 1251, 1189, 836 cm^{-1}; HRMS (FD): *m/z*: calcd for $C_{35}H_{51}NO_5Si$: 593.3537; found: 593.3523 $[M]^+$.

Compound 32: A freshly prepared solution of LDA (1.0 M) in THF (12.4 μL, 12.4 μmol) was added to a solution of the TBS ether **31** (4.9 mg, 8.3 μmol) in THF (100 μL) at −78 °C and the mixture was stirred at the

same temperature for 1 h. Then MeI (10.2 μL, 165 μmol) was added and the mixture was stirred at −78 °C for 2 h. Water was added to the mixture and the product was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the methylation product **32** as a 3:1 mixture with **31**. The crude methylation product **32** was used for next step without purification.

Zoanthenol (3): A solution of TASF (9.0 mg, 33.2 μmol) in acetone (100 μL) was added to the crude methylation product **32** (8.3 μmol, a 3:1 mixture with **31**), and the mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of phosphate buffer solution (pH 7.4, 0.5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by reverse phase HPLC (Inertsil ODS-3, 10 mm x 50 mm, MeOH/H_2O = 1:1) afforded 2.2 mg (53% from **31**) of the pure zoanthenol (**3**) as an amorphous solid. $[\alpha]_D^{28} = +7.0$ ($c = 0.18$ in $CHCl_3$); lit.:[6] $[\alpha]_D^{25} = +7.1$ ($c = 0.24$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.55$ (s, 1H), 6.48 (s, 1H), 4.62–4.57 (m, 1H), 3.91 (d, $J = 20.0$ Hz, 1H), 3.56 (s, 1H), 3.55 (q, $J = 6.9$ Hz, 1H), 3.42 (d, $J = 6.3$ Hz, 1H), 3.37 (t, $J = 6.3$ Hz, 1H), 2.64 (d, $J = 13.7$ Hz, 1H), 2.50 (d, $J = 13.7$ Hz, 1H), 2.44 (dd, $J = 20.0$, 1.1 Hz, 1H), 2.36–2.33 (m, 1H), 2.30 (s, 3H), 2.14 (dd, $J = 13.2$, 5.2 Hz, 1H), 1.92 (td, $J = 13.6$, 4.8 Hz, 1H), 1.82–1.73 (m, 1H), 1.54 (d, $J = 6.9$ Hz, 3H), 1.50–1.39 (m, 1H), 1.17 (s, 3H), 1.13 (dd, $J = 12.0$, 10.3 Hz, 1H), 1.11 (s, 3H), 1.06 (s, 3H), 0.93 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 201.28$, 150.74, 138.17, 116.05, 115.02, 102.28, 90.24, 74.50, 52.54, 47.46, 46.66, 44.68, 41.75, 40.61, 40.04, 39.14, 36.33, 36.01, 32.12, 30.06, 29.57, 23.93, 22.90, 22.06, 21.49, 21.19, 18.52 ppm; IR (film): $\tilde{\nu} = 3700$–3100 (br), 2955, 2922, 2850, 1716, 1457, 1362, 1259 cm^{-1}; HRMS (FD): m/z: calcd for $C_{30}H_{39}NO_5$: 494.2866; found: 494.2860 $[M+H]^+$.

Compound 36: A mixture of the 5% Pd/C (purchased from Nacalai Tesque, Inc., 4.0 mg) and MeOH (1 mL) was stirred under H_2 (1 atm) at room temperature for 15 min. A solution of norzoanthamine hydrochloride (**1**·HCl)[31] (11.2 mg, 21.7 μmol) in MeOH (1 mL) was added to the mixture, and the mixture was vigorously stirred under H_2 (1 atm) for 3 h. The reaction mixture was filtered through a pad of celite with MeOH. The filtrate was concentrated under reduced pressure and the residue was dissolved in MeOH (1 mL) containing Et_3N (15 μL, 108.5 μL) and the solution was stirred at room temperature for 1 h. The mixture was concentrated and the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:3) to afford 10.0 mg (95%) of (15*S*)-15,16-dihydronorzoanthamine (**36**) as an amorphous solid. $[\alpha]_D^{29} = +3.28$ ($c = 0.50$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 4.56$–4.52 (m, 1H), 3.62 (d, $J = 20.0$ Hz, 1H), 3.28–3.22 (m, 2H), 2.80 (s, 1H), 2.74 (td, $J = 11.5$, 4.6 Hz, 1H), 2.70 (q, $J = 12.0$ Hz, 1H), 2.47 (ddd, $J = 13.2$, 4.0, 1.7 Hz, 1H), 2.35 (dd, $J = 11.5$, 4.6 Hz, 1H), 2.32 (dd, $J = 13.7$, 5.2 Hz, 1H), 2.29–2.24 (m, 1H), 2.17 (d, $J = 14.3$ Hz, 1H), 2.08 (dd, $J = 13.2$, 4.6 Hz, 1H), 2.05 (t, $J = 13.2$ Hz, 1H), 1.93–1.83 (m, 2H), 1.76 (dt, $J = 13.0$, 3.4 Hz, 1H), 1.67 (td, $J = 14.0$, 4.0 Hz, 1H), 1.54 (td, $J = 8.7$, 4.2 Hz, 1H), 1.46 (td, $J = 12.6$, 3.2 Hz, 1H), 1.27–1.25 (m, 1H), 1.15 (s, 2H), 1.12–1.05 (m, 1H), 1.11 (d, $J = 6.3$ Hz, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.91 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 209.38$, 208.42, 172.30, 101.48, 89.66, 73.93, 58.94, 56.16, 50.18, 49.09, 46.82, 44.14, 42.21, 41.88, 40.26, 39.55, 38.57, 36.15, 35.57, 33.53, 33.50, 29.64, 23.35, 22.65, 22.12, 21.54, 20.77, 18.07, 17.62 ppm; IR (film): $\tilde{\nu} = 2955$, 2926, 2869, 1714, 1683, 1652, 1455, 1361, 1245, 1187, 983, 912, 729 cm^{-1}; HRMS (FD): m/z: calcd for $C_{29}H_{41}NO_5$: 483.2985: found: 483.2991 $[M]^+$.

Conversion of 36 into 31: A solution of (15*S*)-15,16-dihydronorzoanthamine (**36**) (7.4 mg, 15.3 μmol) and TMSCl (12.0 μL, 91.8 μmol) in THF (0.3 mL) was added dropwise to a freshly prepared solution of LDA (1.0 M) in THF (153 μL, 153 μL) at −78 °C, and the mixture was stirred at −50 °C for 1.5 h. A saturated aqueous solution of $NaHCO_3$ containing Et_3N was added to the reaction mixture and the product was extracted with EtOAc. The organic layer was extracted, dried over Na_2SO_4, and concentrated under reduced pressure. The crude TMS enol ether was used for the next step without purification.

A mixture of the crude TMS enol ether (15.3 μmol), $CaCO_3$ (15.3 mg, 153 μmol), and CH_3CN (0.3 mL) was stirred at room temperature for 2 min. Then $Pd(OAc)_2$ (13.7 mg, 61.2 μmol) was added and the mixture was stirred at 55 °C for 1.5 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite by the aid of EtOAc (0.5 mL). A saturated aqueous solution of $NaHCO_3$ (0.5 mL) and L-serine (15 mg, 143 μmol) was added to the filtrate, and the mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the bis(enone) **29** as a 25:2 mixture with norzoanthamine (**1**). The crude bis(enone) **29** was used for the next step without purification.

A solution of the bis(enone) **29** (15.3 μmol, a 25:2 mixture with **1**) in TFA (0.5 mL) was heated at 50 °C for 1.5 h. After the mixture was cooled to room temperature, phosphate buffer (pH 7.4, 0.5 mL) and EtOAc (0.5 mL) were added. After being stirred for 30 min, the product was throughly extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give norzoanthenol (**30**) as a 25:2 mixture with norzoanthamine (**1**). The crude norzoanthenol (**30**) was used for the next step without purification.

Pyridine (29 μL, 354 μmol) was added to a mixture of norzoanthenol (**30**; 15.3 μmol, a 25:2 mixture with **1**) and $AgNO_3$ (30 mg, 177 μmol) in THF (150 μL), and the resulting mixture was stirred at room temperature for 0.5 h at which point most of the silver complex was dissolved. Then TBSCl (18 mg, 118 μmol) was added, and the resulting mixture was stirred at room temperature for 1.5 h. After addition of water, the resulting mixture was filtered through a cotton plug by the aid of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1:1) afforded 4.9 mg (54% from **36**) of the TBS ether **31** as a colorless amorphous solid. The spectrospcopic data of the synthetic compound **31** from norzoanthamine hydrochloride were all identical with those of the previously synthesized compound from **28**. $[\alpha]_D^{31} = -9.4$ ($c = 0.25$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.60$ (1H, s), 6.52 (s, 1H), 4.62–4.57 (m, 1H), 3.76 (d, $J = 20.6$ Hz, 1H), 3.62 (d, $J = 22.3$ Hz, 1H), 3.43–3.38 (m, 1H), 3.34 (d, $J = 22.3$ Hz, 1H), 3.20 (s, 1H), 2.60 (d, $J = 14.3$ Hz, 1H), 2.52 (d, $J = 13.7$ Hz, 1H), 2.45 (d, $J = 20.0$ Hz, 1H), 2.38–2.32 (m, 1H), 2.32 (s, 1H), 2.14 (dd, $J = 12.9$, 4.9 Hz, 1H), 1.90 (td, $J = 13.6$, 4.6 Hz, 1H), 1.79–1.70 (m, 1H), 1.78 (td, $J = 15.5$, 3.4 Hz, 1H), 1.63–1.51 (m, 2H), 1.49–1.46 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.00 (s, 9H), 0.93 (d, $J = 6.3$ Hz, 3H), 0.26 (s, 3H), 0.24 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 208.43$, 190.08, 153.33, 150.83, 119.67, 116.77, 115.59, 101.91, 89.95, 74.27, 57.10, 47.22, 44.35, 41.65, 41.34, 39.73, 38.91, 38.81, 36.61, 35.60, 29.97, 29.69, 28.33, 25.73, 24.69, 23.73, 22.96, 21.85, 21.26, 18.48, 18.22, −4.04, −4.17 ppm; IR (film): $\tilde{\nu} = 2957$, 2930, 2860, 1714, 1577, 1459, 1362, 1304, 1191, 1075, 1061, 836 cm^{-1}; HRMS (FD): m/z: calcd for $C_{35}H_{51}NO_5Si$: 593.3537; found: 593.3526 $[M]^+$.

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[28] As the compounds **29** and **30** were labile on silica gel, the crude products were directly used in the next reactions.

[29] The use of an excess amount of LDA resulted in the formation of a C19-dimethylated compound as the major product, along with **32**.

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

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