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Recent progress in the synthesis of bioactive polycyclic natural products*

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Abstract: The zoanthamine alkaloids, a type of heptacyclic marine alkaloid isolated from colonial zoanthids of the genus *Zoanthus* sp., have distinctive biological and pharmacological properties as well as their unique chemical structures with stereochemical complexity. Namely, norzoanthamine can suppress the loss of bone weight and strength in ovariectomized mice and has been considered a promising candidate for an antiosteoporotic drug, whereas zoanthamine has exhibited potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects. Recently, norzoanthamine derivatives were demonstrated to inhibit strongly the growth of P-388 murine leukemia cell lines, in addition to their potent antiplatelet activities on human platelet aggregation. These distinctive biological properties, combined with novel chemical structures, make this family of alkaloids extremely attractive targets for chemical synthesis. However, the chemical synthesis of the zoanthamine alkaloids has been impeded owing to their densely fuctionalized complex stereostructures. We report here the first and highly stereoselective total syntheses of norzoanthamine and zoanthamine, which involves stereoselective synthesis of the requisite triene for intramolecular Diels–Alder reaction via three-component coupling reactions, a key intramolecular Diels–Alder reaction, and subsequent crucial bis-aminoacetalization as the key steps.

Keywords: norzoanthamine; zoanthamine; marine alkaloids; total synthesis; antiosteoporotic drug.

SYNTHETIC STUDIES OF THE ZOANTHAMINE ALKALOIDS

The zoanthamine alkaloids are a type of heptacyclic marine alkaloid isolated from the genus *Zoanthus* sp. [1–11]. Because they possess distinctive biological and pharmacological properties and have significant stereochemical complexity, zoanthamine alkaloids have attracted much attention across a broad range of fields, including medicinal chemistry, pharmacology, natural product chemistry, and synthetic organic chemistry. For example, norzoanthamine (**1**) (Fig. 1), isolated by Uemura et al. in 1995 [1–3], can suppress the loss of bone weight and strength in ovariectomized mice, and has been considered a promising candidate for an antiosteoporotic drug [3,12]. On the other hand, zoanthamine (**2**), isolated by Rao and Faulkner [4,5], has exhibited potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects [5,6]. Norzoanthamine (**1**) and zoanthamine (**2**) have the same chemical structure, with the exception of the methyl group at the C-19 position. Very re-

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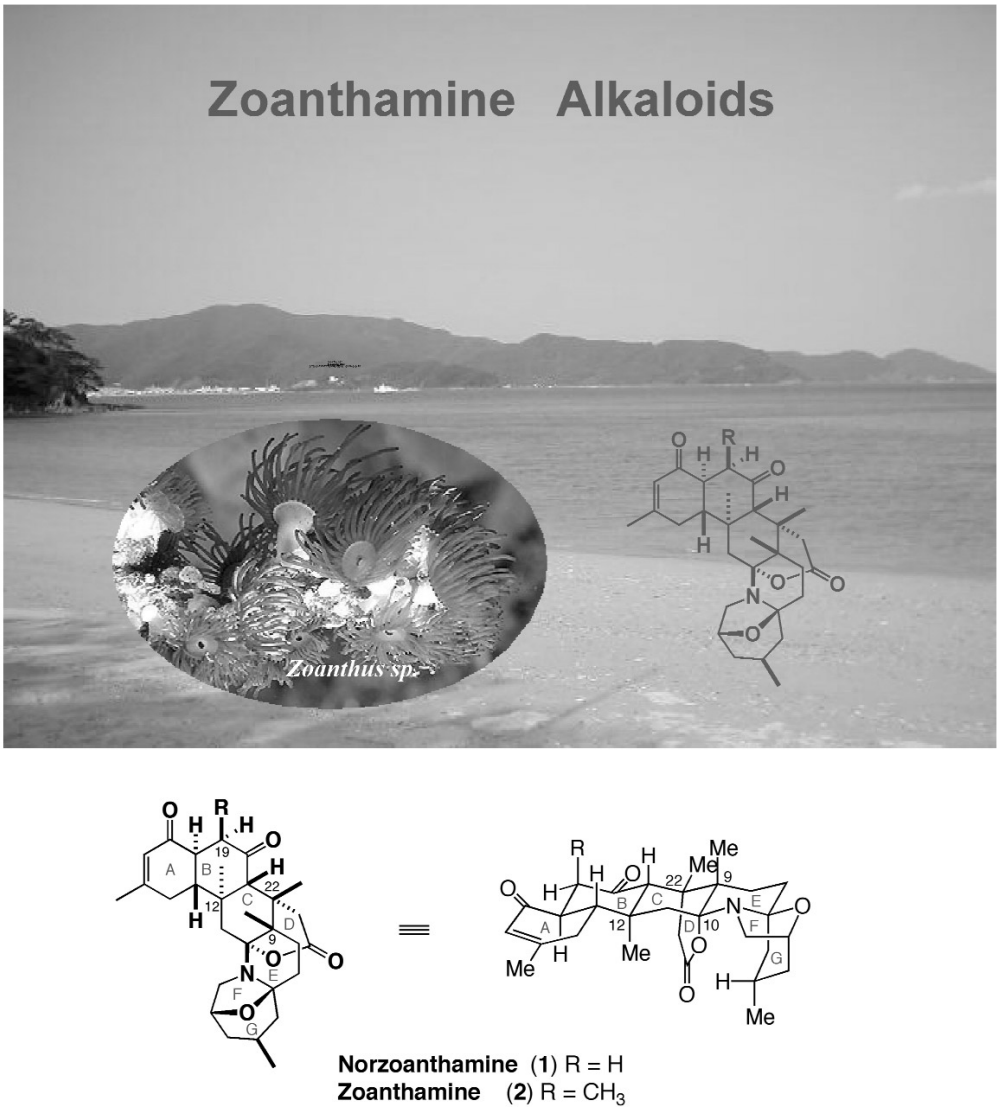

Fig. 1 Molecular structures of norzoanthamine (**1**) and zoanthamine (**2**).

cently, norzoanthamine derivatives were demonstrated to strongly inhibit the growth of P-388 murine leukemia cell lines, in addition to their potent antiplatelet activities on human platelet aggregation [13]. Thus, norzoanthamine (**1**) has been studied with keen interest, particularly in relation to the development of a new type of antiosteoporotic drug for use in those advanced in age [3,12].

These distinctive biological properties and novel chemical structures of this family of alkaloids make them extremely attractive targets for chemical synthesis [14–31]. However, the chemical synthesis of zoanthamine alkaloids has been impeded due to their densely functionalized, complex stereostructures. The synthetic challenges posed by these alkaloids include construction of the stereochemically dense C-ring-bearing four adjacent quaternary asymmetric carbon atoms at the C-9, C-10, C-12, and C-22 positions (Fig. 1); stereoselective synthesis of the ABC carbon framework consisting of the *trans-anti-trans*-fused perhydrophenanthrene skeleton; and stereoselective construction of two novel aminoacetal structures, including a bridging δ-lactone. Particular issues in the synthesis of the

zoanthamine alkaloids are stereoselective synthesis of the ABC ring system and construction of the two novel aminoacetal structures with overcoming severe steric repulsion between the methyl group at the C-12 position and the bridging lactone and that between the lactone and the G-ring, respectively.

TOTAL SYNTHESIS OF NORZOANTHAMINE

We set about synthetic studies of norzoanthamine (**1**) that aimed at developing an efficient synthetic route flexible enough to provide access to several members of the zoanthamine alkaloids [25]. Our synthetic strategy is shown in Fig. 2 [25,32]. The DEFG ring system, including the distinctive aminoacetal structures, were to be constructed from the precursor keto acid (**A**) bearing an amino alcohol side chain by bis-aminoacetalization. In order to construct the ABC carbon framework stereoselectively, we de-

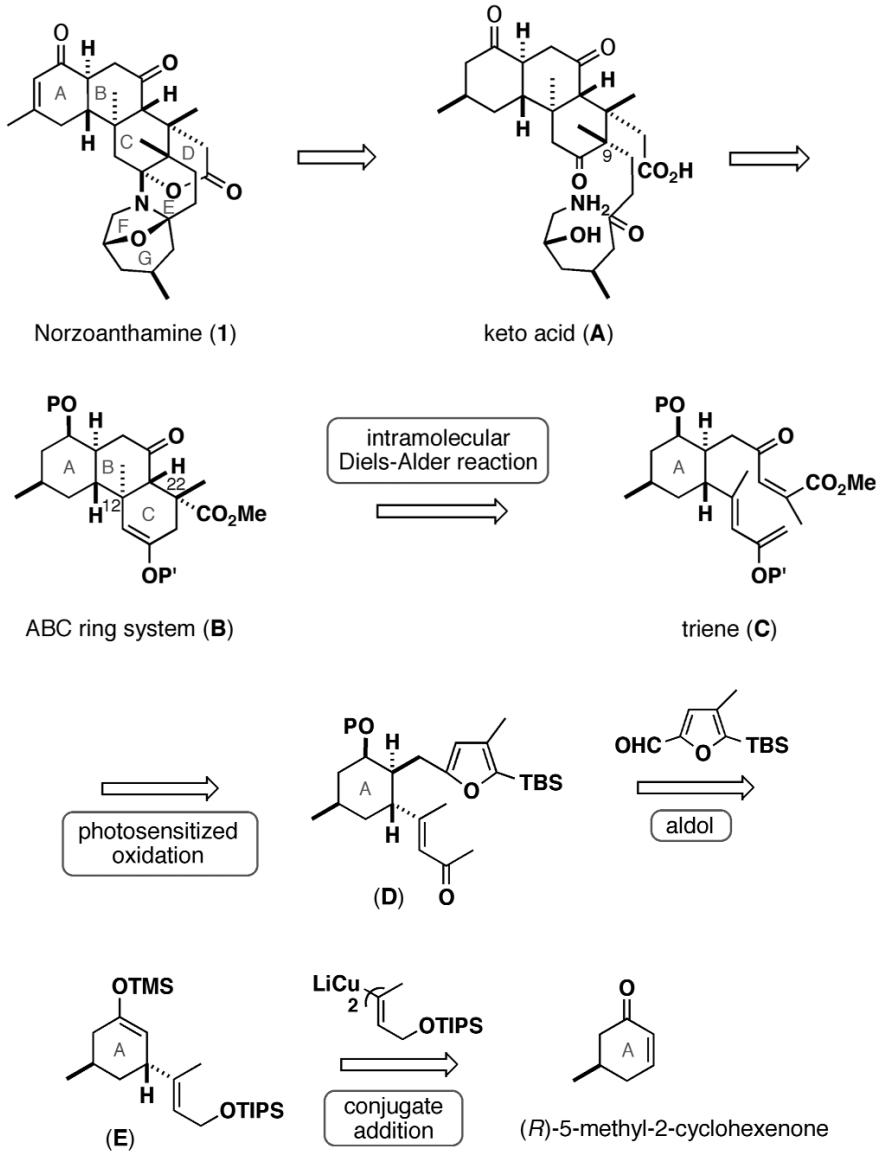

Fig. 2 Retrosynthesis of norzoanthamine (**1**).

signed a synthetic route involving an intramolecular Diels–Alder reaction of a triene (**C**) with a doubly activated dienophile moiety. If the key intramolecular Diels–Alder reaction were to occur via the exo-transition state, as we expected, the ABC carbon framework (**B**) having two quaternary asymmetric carbon atoms at the C-12 and C-22 positions would be obtainable in one step. To synthesize the requisite triene (**C**) stereoselectively, we also designed a synthetic route based on three-component coupling reactions, involving conjugate addition of a vinylcupurate reagent to (*R*)-5-methyl-2-cyclohexenone followed by an aldol reaction of the resulting silyl enol ether (**E**) with a furaldehyde and subsequent photosensitized oxidation of the furan derivative (**D**).

Initially, we focused on the synthesis of the key precursor triene (**C**) by the three-component coupling reactions. Conjugate addition of the vinylcuprate [25] to the optically active (*R*)-5-methyl-2-cyclohexenone (**3**) [33] in the presence of trimethylsilyl (TMS) chloride [34] followed by aldol reaction of the resultant silyl enol ether **4** with the functionalized furaldehyde [25] by means of the zinc enolate gave the desired aldol **5** as a diastereomeric mixture in 84 % yield (Fig. 3). As we expected, the conjugate addition of the vinylcuprate exclusively occurred from the opposite side of the secondary methyl group on the cyclohexene ring. After dehydration of the aldol products **5**, the resulting enones **6** were

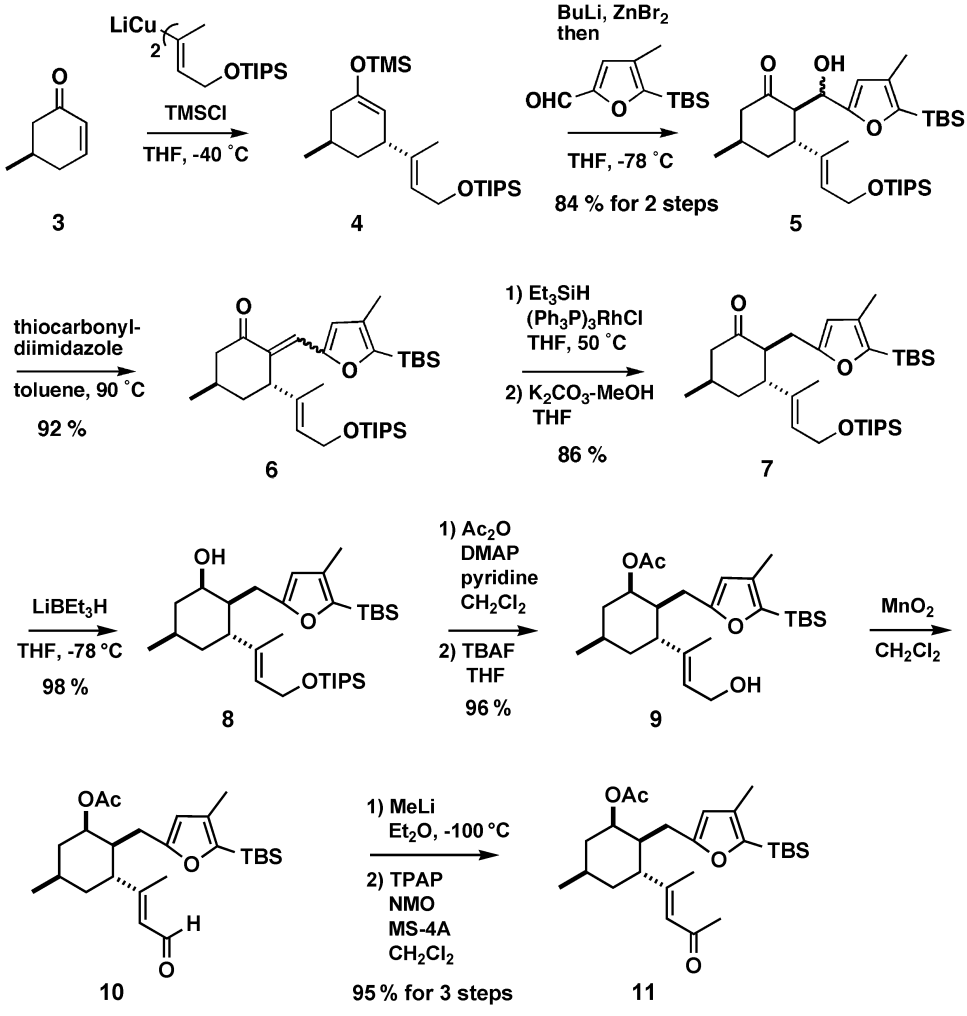

Fig. 3 Synthesis of methyl ketone **11**.

subjected to the hydrosilylation reaction and subsequent treatment of the silyl enol ether with K_2CO_3 in MeOH furnished the trisubstituted cyclohexanone **7** with the desired stereochemistry in high yield. Reduction of **7** with Super-Hydride® afforded the single β-alcohol **8** quantitatively, which was converted to methyl ketone **11** by a routine five-step reaction sequence, involving acetylation, removal of the triisopropylsilane (TIPS) group with tetrabutylammonium fluoride (TBAF), oxidation of the primary alcohol to aldehyde **10**, addition of methyllithium followed by oxidation of the secondary alcohol with tetrapropylammonium perruthenate (TPAP) [35] in remarkably high yield. The yield of each step was over 95 % (Fig. 3).

The next crucial photosensitized oxidation of the furan **11** was successfully performed according to the Katsumura protocol [36] with a halogen lamp and rose bengal, to afford *Z*-γ-keto-unsaturated silyl ester **12** quantitatively (Fig. 4). Since the product **12** was unstable, it was immediately converted to the stable methyl ester **13** using TBAF and MeI [37]. The requisite triene **14** was synthesized by treatment of **13** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and *N*,*N*-dimethylethylamine in 90 % yield. Thus, the important precursor triene **14** was synthesized efficiently and highly stereoselectively via the three-component coupling reactions and subsequent photosensitized oxidation of the furan (Fig. 4).

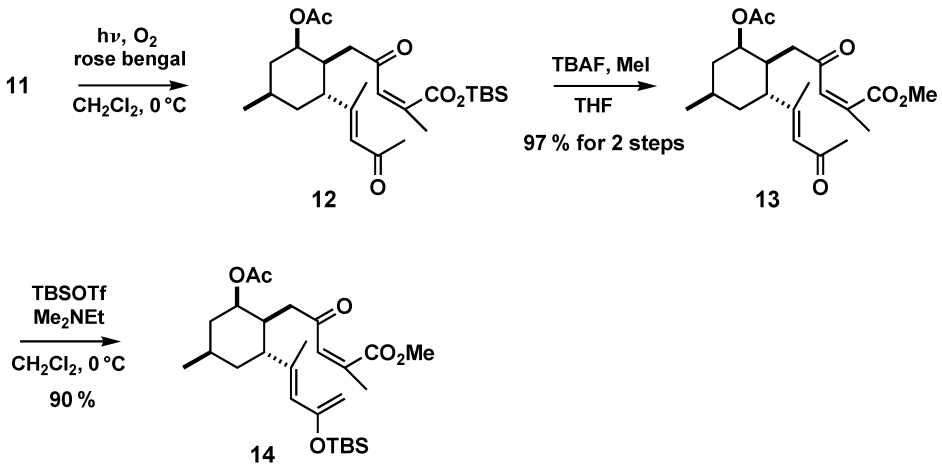

Fig. 4 Synthesis of the triene **14**.

THE KEY INTRAMOLECULAR DIELS–ALDER REACTION

The next step involves the key intramolecular Diels–Alder reaction. We presumed that the Diels–Alder reaction of the triene **14** would occur via the chair conformation on the B-ring, and if so, two transition states are feasible: the exo and the endo transition states, as shown in Fig. 5. The exo transition state was thought to be preferable to the endo transition state because of the steric repulsion between 1,3-diaxial methyl groups in the endo transition state. If the Diels–Alder reaction occurred as expected, the ABC ring system bearing two quaternary asymmetric carbon atoms at the C-12 and C-22 positions would be constructed in one step.

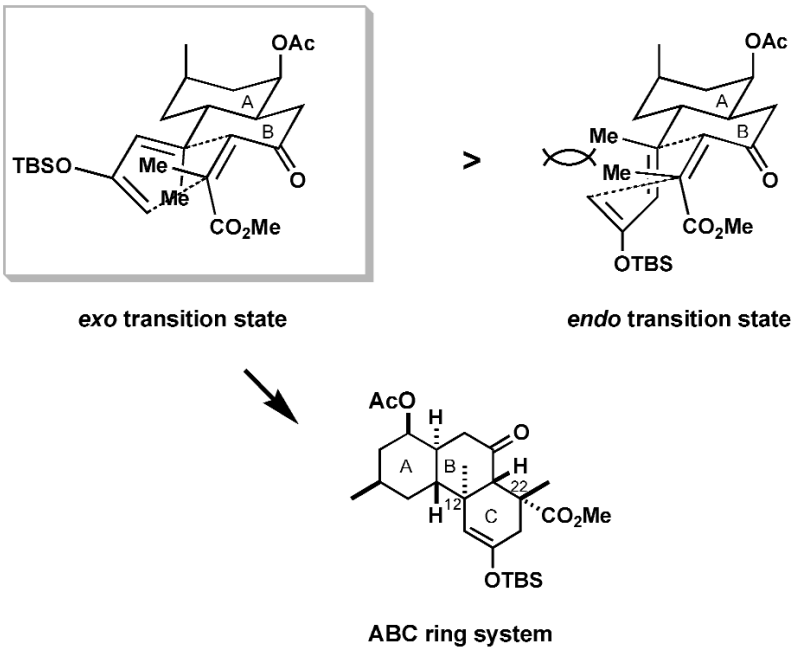

Fig. 5 Transition states of the intramolecular Diels–Alder reaction of **14**.

As shown in Fig. 6, the key Diels–Alder reaction proceeded with high efficiency by adding dropwise a solution of **14** in 1,2,4-trichlorobenzene into the same solvent heated at 240 °C, which gave rise to a 72:28 mixture of the exo and the endo adducts, respectively, in 98 % combined yield. When the adducts were treated with HF-pyridine, the major crystalline compound **16** was readily obtainable by simple crystallization in 51 % isolated yield. The stereostructures of the major and the minor products were unambiguously confirmed by X-ray crystallographic analyses (Fig. 7) and determined to be those of the exo adduct **16** and the endo adduct **17**, respectively. Thus, the intramolecular Diels–Alder reaction of **14** occurred stereoselectively through the exo transition state, as we expected, to give rise to the ABC ring system **16** with two quaternary asymmetric carbon atoms at the C-12 and C-22 positions. At this stage, the total yield of the exo adduct **16** from 5-methyl-2-cyclohexenone (**3**) was remarkably high, 29 % in 16 steps.

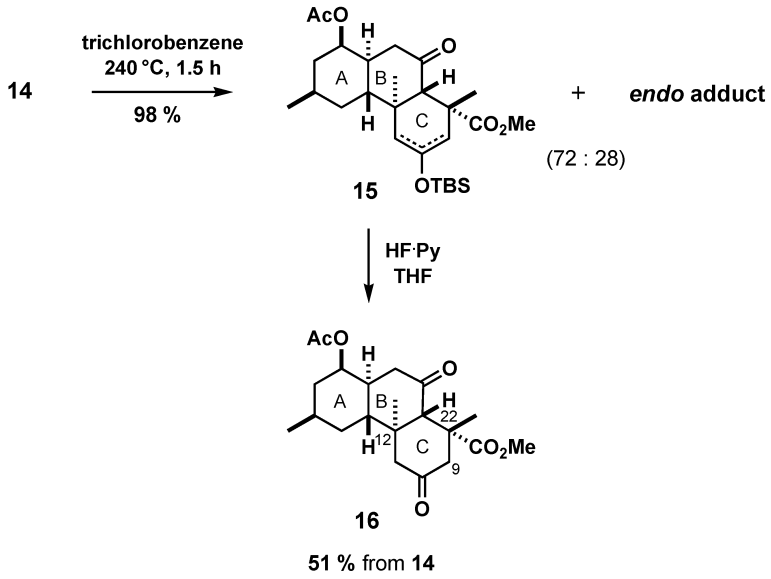

Fig. 6 Intramolecular Diels–Alder reaction.

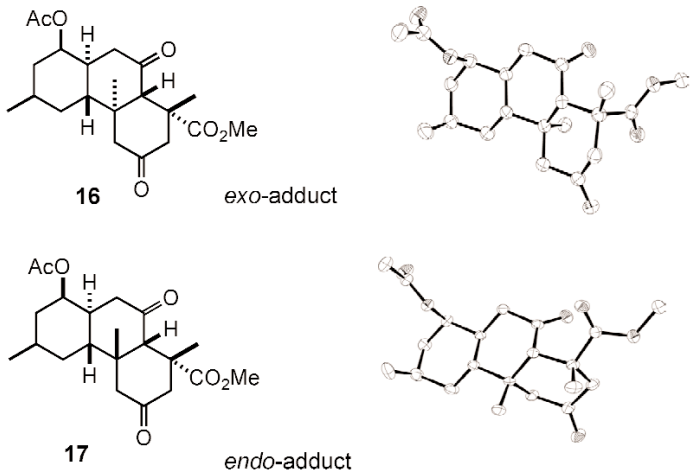

Fig. 7 X-ray crystallographic analyses of the major and the minor products.

We focused next on construction of another quaternary asymmetric carbon center at the C-9 position. To this end, when the diketo ester **16** was reduced with K-Selectride at –78 °C, the sterically less hindered ketone at C-10 was selectively reduced to form lactone **18** in situ (Fig. 8). On warming the reaction mixture to –10 °C, another ketone at C-20 was reduced to afford hydroxy lactone **19** in a highly stereoselective manner. Thus, reduction of the two ketone functions occurred exclusively from the β-face. After protection of the secondary alcohol in **19** with a TBS group, the acetate was replaced with a TES group in two steps in 90 % yield. Lactone **21** was then converted to the crucial precursor keto alcohol **25** in four steps, involving reduction of **21** with diisobutylaluminum hydride (DIBAH) followed by a Wittig reaction of the resultant lactol **22**, hydroboration with 9-BBN, which gave diol **24**, and chemoselective oxidation of the secondary alcohol by the Trost protocol [38], using ammonium molybdate, in 90 % overall yield (Fig. 8).

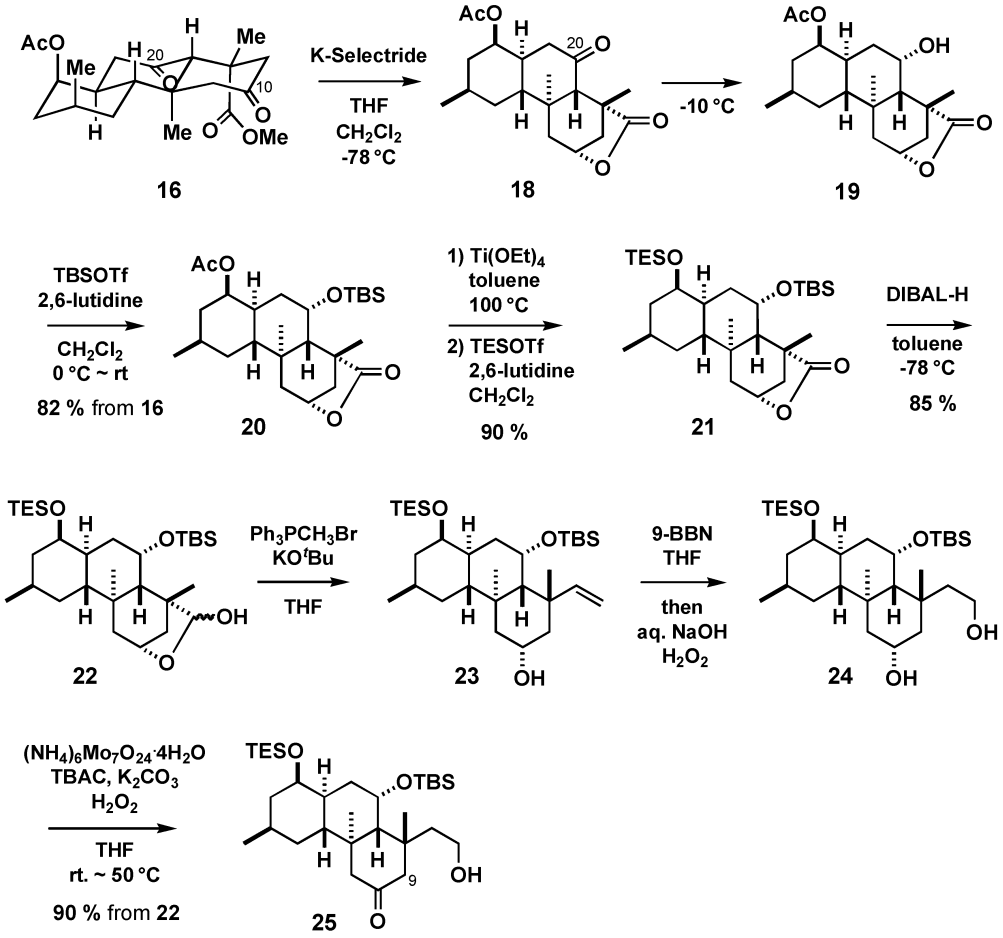

Fig. 8 Synthesis of keto alcohol **25**.

With the keto alcohol **25** in hand, we focused on the stereoselective construction of the quaternary asymmetric carbon center at the C-9 position. The key conversion was realized as follows. Upon treatment of **25** with dimethyl carbonate and Li*O*t*Bu* in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA), formation of carbonate **26** and subsequent intramolecular acylation reaction smoothly occurred to form the lithium enolate of the β-keto lactone, which was reacted with MeI to give methyl enol ether **27** as a single product in 92 % yield (Fig. 9). Further treatment of **27** with lithium hexamethyldisilazide (LHMDS) in THF and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), followed by an addition of MeI, produced the targeted compound **29** as a single stereoisomer in 83 % yield, in which a new methyl group was highly stereoselectively introduced from the β side at the C-9 position, presumably via the conformation **28** (Fig. 9). Thus, construction of the quaternary asymmetric carbon center at the C-9 position was achieved with complete stereoselectivity.

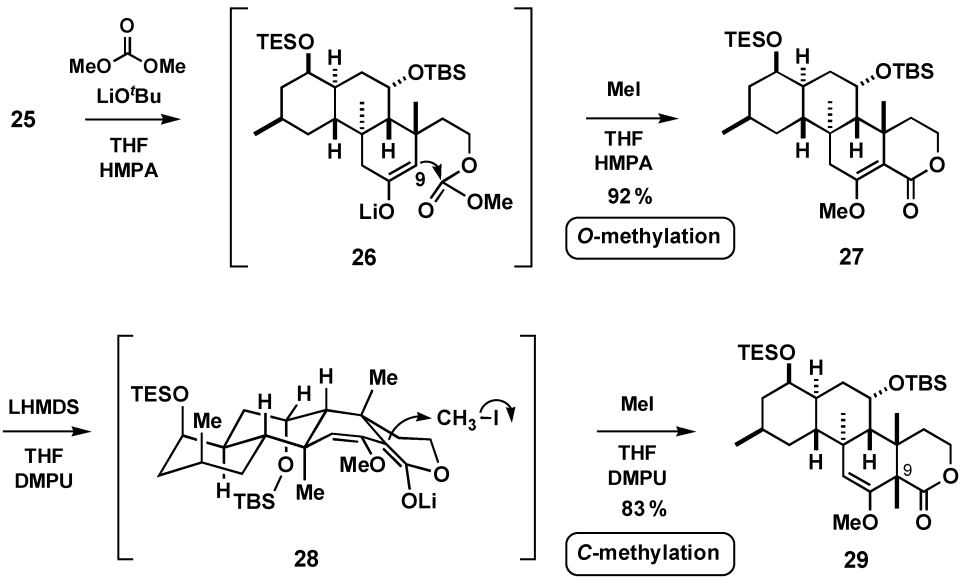

Fig. 9 Construction of the C-9 quaternary asymmetric carbon center.

Consideration of a coupling reaction with the amino-alcohol segment led us to target synthesis of the key alkyne segment **31** shown in Fig. 10. The crucial alkyne **31** was derived from **29** by a three-step reaction sequence: addition of MeLi, protection of the resulting primary alcohol with a TBS group leading to methyl ketone **30**, and formation of enol triflate and subsequent elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Although the desired product was obtained in 66 % yield by this reaction sequence, a considerable amount of the unexpected vinyl ether **32** was also formed in 30 % yield (Fig. 10).

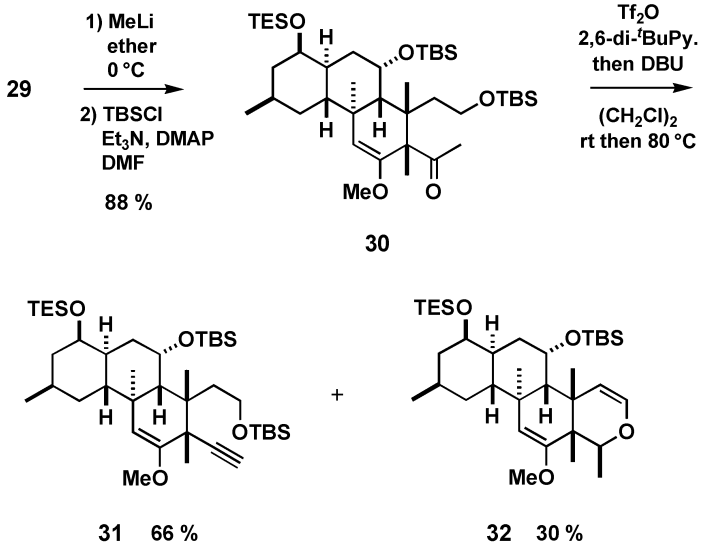

Fig. 10 Synthesis of the crucial alkyne segment **31**.

Formation of **32** was rationalized as follows. Namely, treatment of **30** with Tf_2O produces the corresponding enol triflate **33**, which is smoothly converted to the alkyne **31** upon treatment with DBU (Fig. 11). An alternative route involving a 1,5-hydride shift from the methylene adjacent to the TBS ether to the carbonyl group is also conceivable. In this case, aldehyde **34** generated in situ probably undergoes a smooth cyclization via an enolate to afford the by-product vinyl ether **32**. The mechanistic analysis prompted us to utilize a deuterium kinetic isotope effect. Namely, we anticipated that deuterium isotope effects would probably suppress the 1,5-hydride shift, consequently, formation of the by-product **32**. Based on this hypothesis, methyl ketone **36** bearing two deuterium atoms was prepared using commercially available deuterated Wittig reagent and a similar reaction sequence to that described in high overall yield (Fig. 12). When the deuterium-incorporated methyl ketone **36** was subjected to the alkynylation reaction, the desired product **37** was obtained in 81 % yield, and formation of vinyl ether **38** was suppressed down to 9 %. Thus, the crucial alkyne segment **37** was efficiently synthesized by exploiting a deuterium kinetic isotope effect [39].

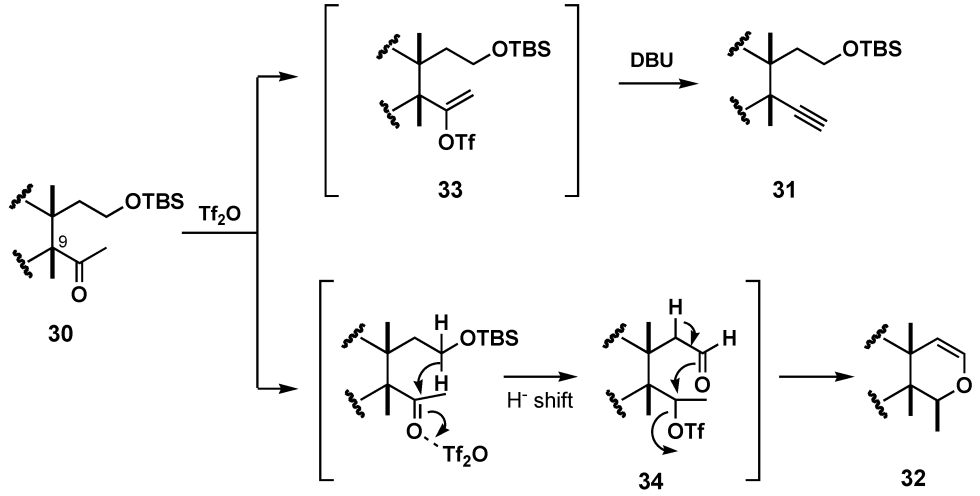

Fig. 11 Mechanism of the formation of **31** and **32**.

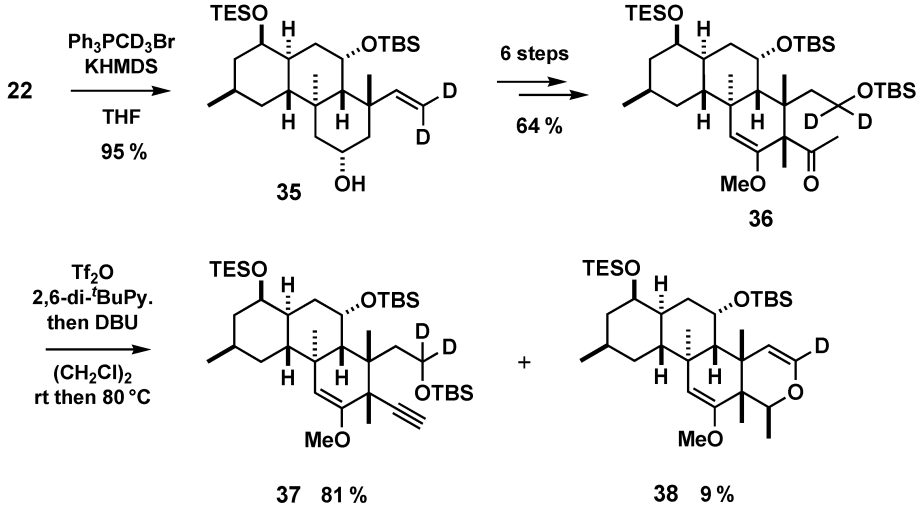

Fig. 12 Deuterium kinetic isotope effect in the synthesis of the alkyne segment.

On the other hand, the amino-alcohol fragment **43** was synthesized starting from (*R*)-citronellal **39** by means of the Jacobsen kinetic resolution protocol [40] using chromium salen complex, as shown in Fig. 13.

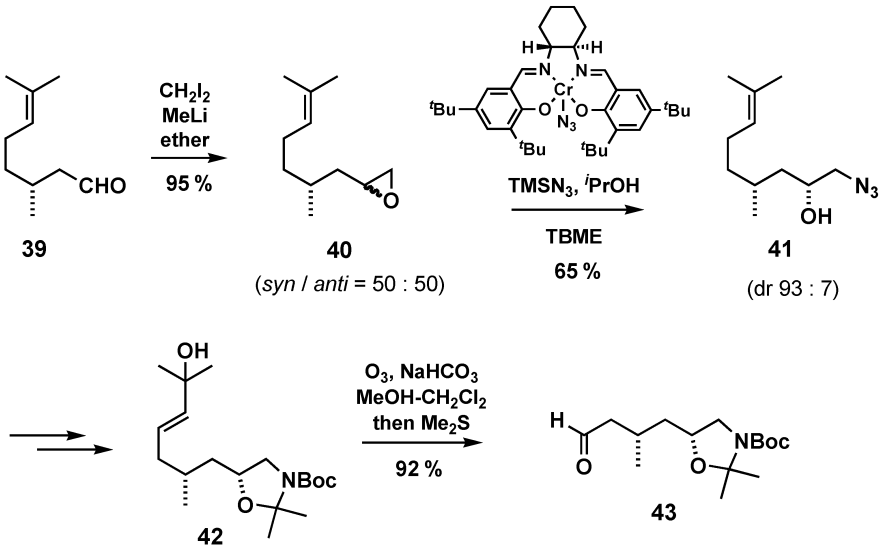

Fig. 13 Synthesis of the amino-alcohol fragment **43**.

With the key alkyne segment **37** and the amino-alcohol segment **43** in hand, we then needed to couple the two segments, install a double bond into the A-ring, and perform the final bis-amino-acetalization to form the DEFG ring system. The coupling reaction of **37** and **43** with BuLi in THF, followed by oxidation of the adducts **44** with Dess–Martin periodinane [41], afforded **45** in 82 % yield (Fig. 14). Alkynyl ketone **45** was then converted to the crucial keto acid **48** by the following reaction sequence: (i) hydrogenation of the triple bond; (ii) treatment with aqueous AcOH at 50 °C leading to aminoacetal **46**; (iii) removal of the two TBS groups with TBAF; (iv) selective oxidation of secondary hydroxyl groups with ammonium molybdate to derive **47**; (v) oxidation of the primary alcohol to aldehyde with TPAP; and (vi) sodium chlorite oxidation of the aldehyde to the carboxylic acid **48**.

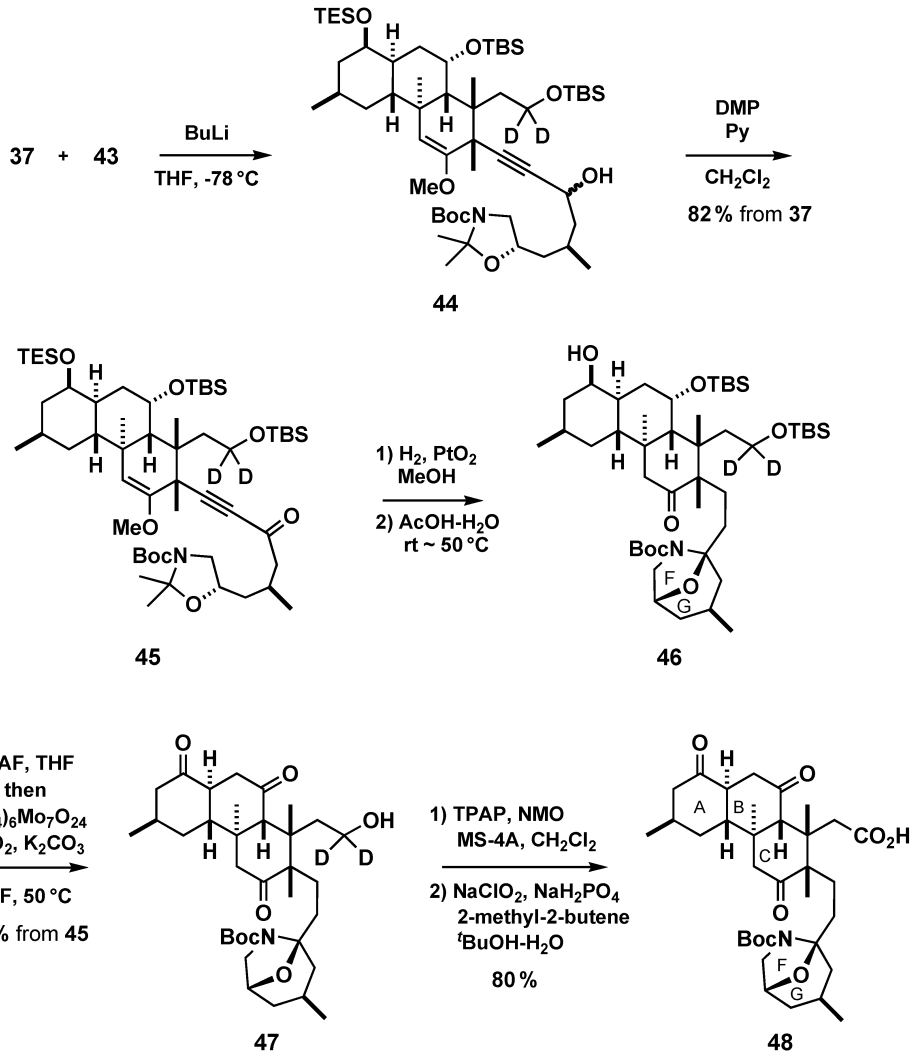

Fig. 14 Synthesis of the crucial precursor keto acid **48**.

Regioselective introduction of a double bond into the A-ring was successfully performed by using the Ito–Saegusa method [42]. Esterification of **48** with $TMSCHN_2$ in CH_2Cl_2, followed by treatment with TMSCl and LHMDS in THF, solely produced TMS enol ether of the ketone in the A ring (Fig. 15). Reaction with $Pd(OAc)_2$ in CH_3CN furnished the desired enone **50** in 96 % yield for the three steps.

The final critical bis-aminoacetalization, i.e., the construction of the DEFG rings culminating in the total synthesis of norzoanthamine (**1**), was achieved by initial treatment of **50** with aqueous AcOH at 100 °C followed by treatment of the resulting iminium salt **51** with aqueous TFA at 110 °C to produce the ammonium salts of norzoanthamine **52**. Finally, desalination of **52** with basic alumina in MeOH furnished norzoanthamine (**1**) in 81 % yield (three steps). The synthetic compound was identical in all respects with naturally occurring norzoanthamine, including spectroscopic characteristics (^{1}H and ^{13}C NMR spectra, infrared spectroscopy, and mass spectra), circular dichroism (CD), and optical rotation ($[\alpha]^{24}_D$ –6.0 (*c* 0.23, $CHCl_3$); natural norzoanthamine: $[\alpha]^{24}_D$ –6.2 (*c* 0.23, $CHCl_3$)) [43,44]. The total yield of synthetic norzoanthamine was 3.5 % in 41 steps starting from **3**.

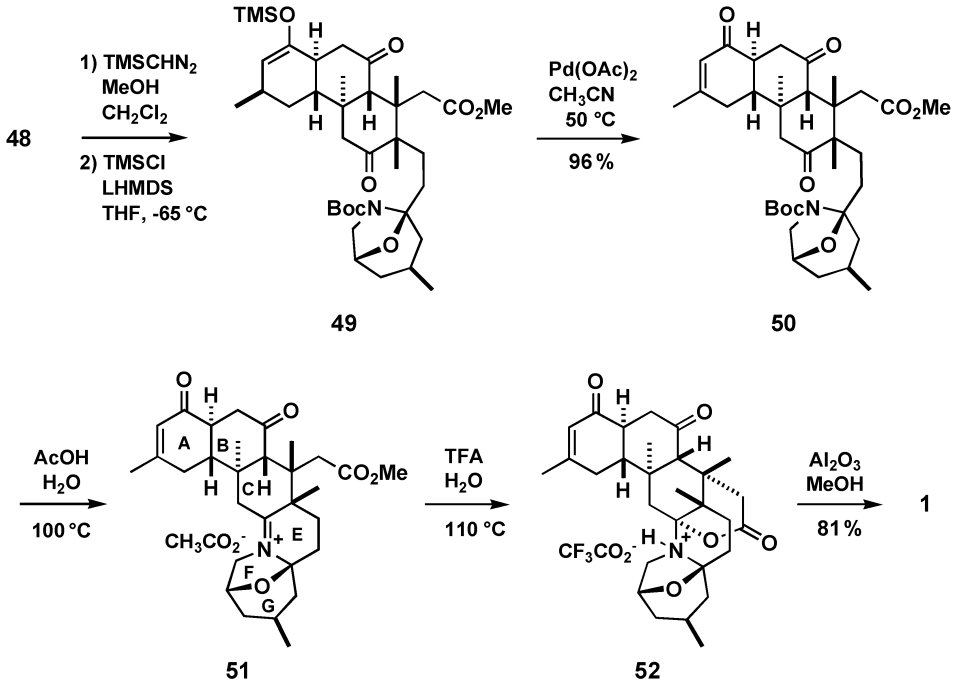

Fig. 15 Completion of the total synthesis of norzoanthamine (**1**).

TOTAL SYNTHESIS OF ZOANTHAMINE

We have also studied the total synthesis of zoanthamine (**2**). It is necessary to introduce another methyl group at the C-19 position for the synthesis of zoanthamine. Fortunately, we recently achieved the first total synthesis of zoanthamine (**2**) by the following reaction sequence (Fig. 16). Thus, treatment of the previous triketo ester with LHMDS and TESCl produced the TES enol ether of the ketone in the A-ring regioselectively, which was subjected to a methylation reaction with LHMDS and MeI, whereupon a methyl group was regio- and stereoselectively introduced at the C-19 position to give rise to **53** (Fig. 16). Subsequent Ito–Saegusa reaction furnished the desired enone **54** in 41 % yield for the four steps. The enone **54** was successfully converted to zoanthamine (**2**) using similar bis-aminoacetalization to that described. The synthetic compound was identical in all respects to naturally occurring zoanthamine, including ^{1}H and ^{13}C NMR spectra, IR, and mass spectra.

The absolute structures of norzoanthamine (**1**) and zoanthamine (**2**) were rigorously verified by the present total syntheses. The chemistry described here not only offers a solution to formidable synthetic challenges but also opens a completely chemical avenue to norzoanthamine (**1**), zoanthamine (**2**), other naturally occurring zoanthamine alkaloids, and their synthetic derivatives.

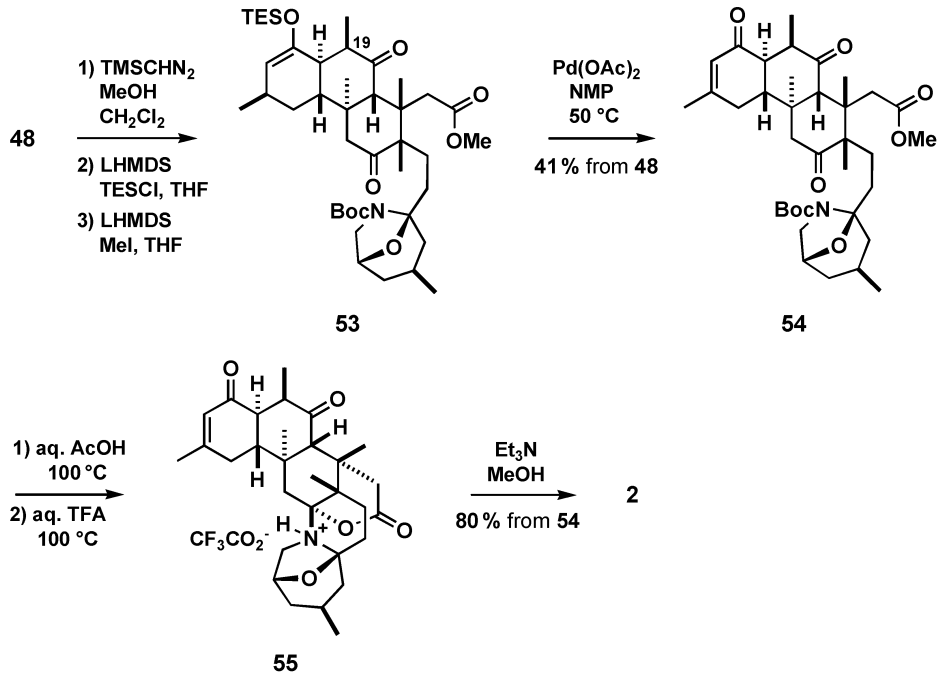

Fig. 16 Completion of the total synthesis of zoanthamine (**2**).

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