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Synthetic studies of zoanthamine alkaloids. Stereoselective synthesis of the ABC ring system of norzoanthamine by an intramolecular Diels–Alder reaction

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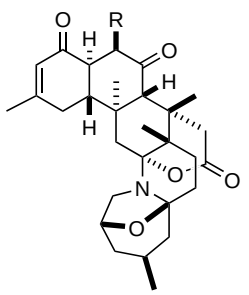
Abstract—Stereoselective synthesis of the ABC ring system of norzoanthamine having five asymmetric centers including two quaternary carbon atoms has been successfully accomplished by an intramolecular Diels–Alder reaction. A key intermediate for the Diels–Alder reaction was efficiently and stereoselectively synthesized by a tandem conjugate addition–aldol strategy and subsequent photosensitized oxidation of a furan derivative. © 2002 Elsevier Science Ltd. All rights reserved.

The zoanthamine alkaloids, a family of marine metabolites, not only have a unique array of structural and stereochemical complexity but also display, inter alia, zoanthamine (**1**, Fig. 1), potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects.[1,2] Recently, norzoanthamine (**2**) isolated from the colonial zoanthid *Zoanthus* sp.[3,4] has been shown to suppress the loss of bone weight and strength in ovariectomized mice.[3] Interestingly, a polyketide biogenetic pathway involving the intramolecular Diels–Alder reaction has been proposed for the zoanthamine alkaloids by Uemura et al., although these compounds are regarded as terpenoids.[3] Their unique structures as well as significant biological activities have elicited much attention from synthetic organic chemists.[5,6] So far, however, work on the synthesis of the functionalized ABC ring system of the zoanthamine alkaloids by the biomimetic Diels–Alder strategy towards their total synthesis has been quite limited.[5] We describe herein the stereoselective synthesis of the functionalized ABC ring system having five asymmetric centers including two quaternary carbon atoms by an intramolecular Diels–Alder reaction.



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

Figure 1.

The key intermediate (**13**) for the Diels–Alder reaction was efficiently and stereoselectively synthesized as shown in Scheme 1. Conjugate addition of di[(*E*)-4-(triisopropylsilyl)oxy-2-butenyl]cupurate[7] to cyclohexenone (**3**) cleanly occurred in the presence of TMSCl[8] in THF at −78°C to give the TMS enol ether **4** in 94% yield. The zinc enolate generated from **4** was reacted with a furaldehyde derivative **5**, which was prepared from commercially available ketone **14** as shown in Scheme 2,[9] to provide the aldol **6** as a 1:1 epimeric mixture in excellent yield. The aldol mixture **6** was then converted to the enone **7** by acetylation followed by treatment with DBU, wherein the enol acetate of **7** was formed to some extent; therefore, the crude product was treated with K_2CO_3 resulting in formation of the desired enone **7** in quantitative yield. Reduction of the enone moiety of **7** was efficiently performed by using triethylsilane in the presence of Wilkinson's catalyst[10] in THF at 70°C followed by treatment of the resulting enol silyl ether with K_2CO_3 in MeOH. The ketone **8** thus obtained was transformed into the acetate **9** in two steps, in which reduction of **8** with K-Selectride afforded the β-alcohol as the sole product. The acetate **9** was routinely converted to the methyl ketone **11** by a four-step reaction sequence in 70% overall yield: (1) desilylation; (2) oxidation of the

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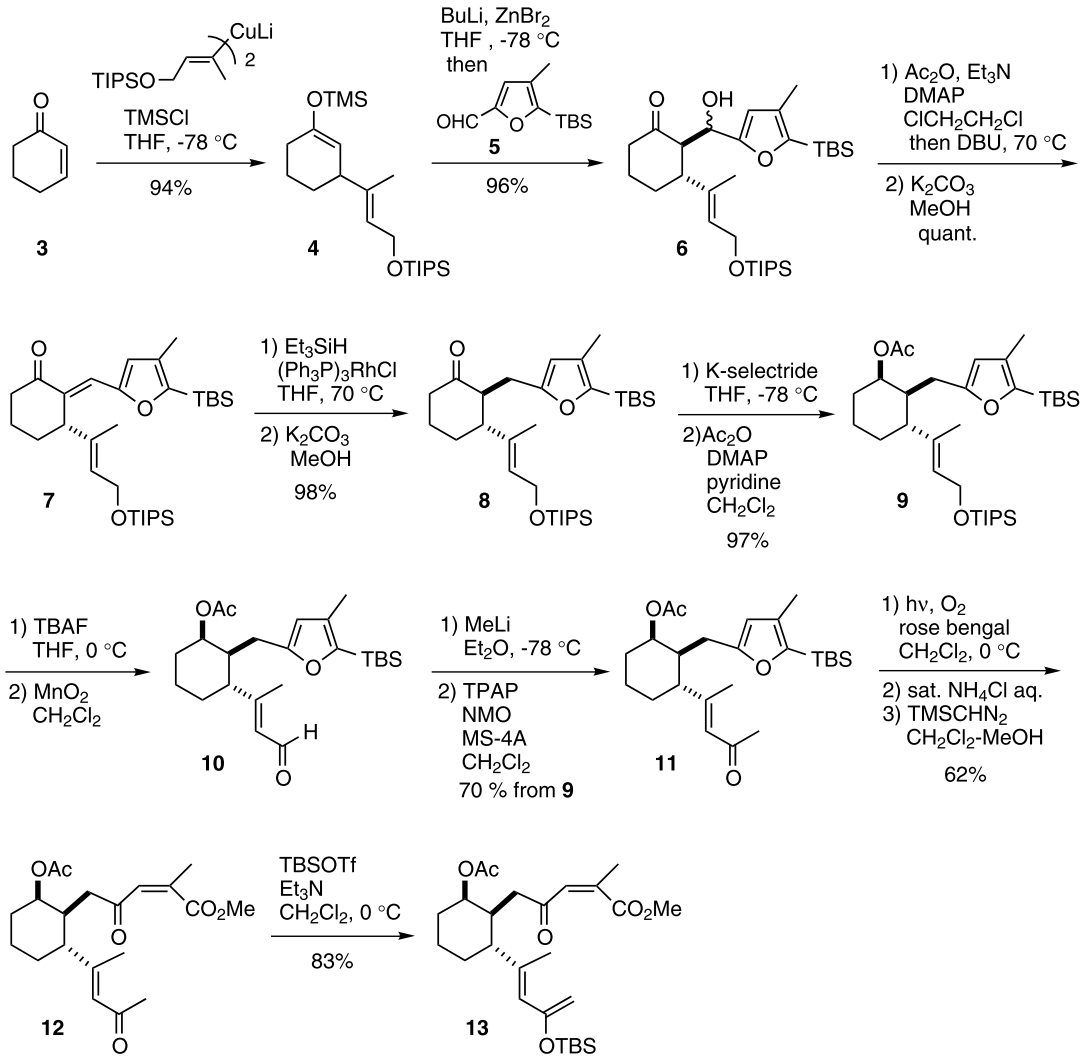
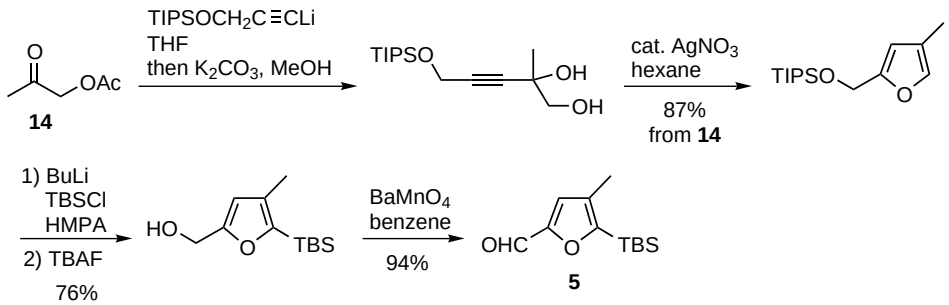


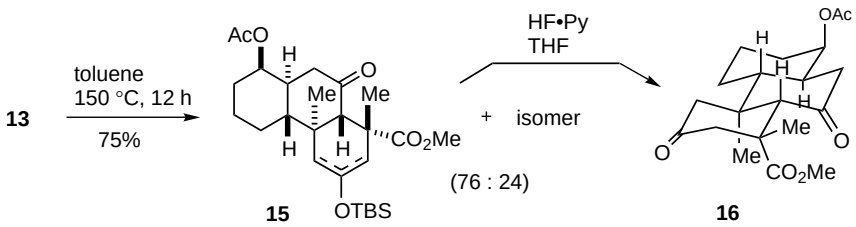
Scheme 1.



Scheme 2.

allylic alcohol; (3) methylation; (4) oxidation of the secondary alcohol. The crucial photosensitized oxidation of the furan **11** was successfully performed using a halogen lamp in the presence of rose bengal in CH_2Cl_2 at 0°C according to Katsumura's protocol.[11] The crude TBS ester was hydrolyzed by a saturated NH_4Cl solution, and the resulting carboxylic acid was esterified with (trimethylsilyl)diazomethane[12] giving rise to the (*Z*)-γ-keto unsaturated ester **12**, the key intermediate in the present synthesis, in 62% yield. Then, **12** was transformed into the diene **13**, the crucial intermediate for the Diels–Alder reaction, by treatment with TBSOTf and Et_3N.

The key intramolecular Diels–Alder reaction of **13** was carried out in toluene at 150°C using a sealed tube (Scheme 3). As a result, three products were obtained in 75% combined yield (85% yield based on the consumed



Scheme 3.

starting material), two of which were found to be regioisomers of the enol silyl ethers **15**. The stereostructure of the major product has been unambiguously established by X-ray crystallographic analysis[13] of the keto ester **16**[14] (Fig. 2) derived from **15**, while the structure of the minor stereoisomer is not determined at present. These results demonstrate that the Diels–Alder reaction of **13** preferentially occurred via an *exo* transition state rather than an alternative *endo* transition state (Fig. 3) as anticipated. We are further examining the optimum conditions for the Diels–Alder reaction including stereoselectivity.

In conclusion, we have achieved the stereoselective synthesis of the ABC ring system of the zoanthamine alkaloids bearing five asymmetric centers including two quaternary carbon atoms by employing an intramolecular Diels–Alder reaction as the key step. Further studies toward total synthesis of the zoanthamine alkaloids are in progress in our laboratory.

Acknowledgements

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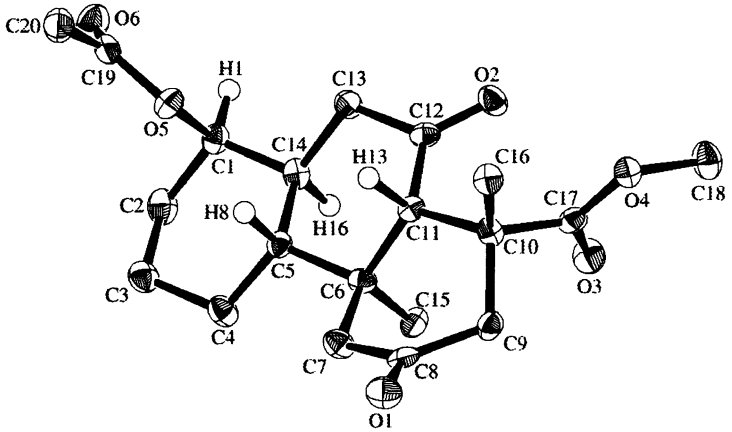

Figure 2. X-Ray structure of compound **16**.

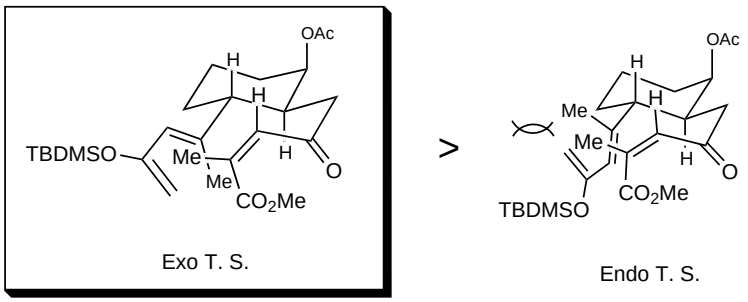

Figure 3.

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13. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary CCDC 174196.
14. Data for compound **16**: mp 182–183°C; IR ($CHCl_3$): 1720, 1213, 1045 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.03 (s, 3 H), 1.06–1.76 (m, 8 H including a singlet at 1.37), 1.85–2.04 (m, 3 H), 2.13 (s, 3 H), 2.22–2.33 (m, 4 H), 2.52 (dd, $J=1.6$, 14.5 Hz, 1 H), 2.70 (dd, $J=1.5$, 14.5 Hz, 1 H), 2.73 (s, 1 H), 3.70 (s, 3 H), 4.90–4.93 (bq, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 16.26, 20.03, 21.36, 25.00, 28.74, 29.77, 29.98, 40.69, 44.57, 45.32, 49.07, 50.66, 52.17, 52.51, 66.53, 72.00, 170.19, 174.97, 206.22, 206.83. HRMS calcd for $C_{20}H_{28}O_6$: 364.1886; found: 364.1906.