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The first synthesis of marine sesterterpene (+)-scalarolide

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Dedicated to Professor Li-Xin Dai (Shanghai Institute of Organic Chemistry) on the occasion of his 85th birthday

ABSTRACT

The synthesis of the first example of C12 oxygenated marine scalaranic sesterterpenes (+)-scalarolide was achieved through three key steps including the ring-opening rearrangement of epoxide, stereoselective Diels–Alder addition and one-pot γ-butenolide formation process, and the absolute configuration of natural scalarolide was confirmed.

An increasing number of compounds of the scalarane sesterterpenoids,[1] which display a variety of biological activities such as cytotoxic,[2] antifeedant,[3] anti-inflammatory[4] and platelet-aggregation inhibitory effects[5] have been isolated from different marine organisms during the past three decades. Many members of this group of scalaranic sesterpenes possess an ABCDE pentacyclic-fused ring skeleton, which contains a γ-butenolide or furan as ring E moiety, as well as a C12 oxygenated functional group as common structural features. Some representative compounds are depicted in Figure 1, such as scalarolide (**1**),[2b,3a] sesterstatin 7 (**2**),[6] sesterstatin 6 (**3**),[7] 12-epi-acetylscalarolide (**4**),[2a] hyatolide E (**5a–b**),[2c] heteronemin (**6**),[8] sesterstatins 4 and 5 (**7a–b**)[9], and scalarafuran (**8**).[3a]

Due to their important ecological roles,[3a] interesting biological properties, and unique structural skeleton, many efforts have been made toward the total synthesis of these marine scalarane sesterterpenes.[10,11] A variety of strategies have been developed to construct the scalarane framework such as the electrophilic cyclization of bicyclic (AB ring) substrate forming the CD fused ring,[12] the biomimetic-like electrophilic cyclization[13] of C25 aliphatic substrates providing ABCD tetracyclic ring in one step, as well as the Diels–Alder addition[14] constructing the D ring from an ABC tricyclic ring precursor. However, to the best of our knowledge, in most cases, the above mentioned synthetic routes end up with the construction of the tetracyclic ring skeleton, none of them has been successfully utilized to produce the scalarane sesterterpenes containing C12 oxygenated group, which is supposed to be a prerequisite maintaining the biological activity. As Ungur once pointed,[10] new efficient synthetic paths toward scalaranic sesterterpenes possessing the unique C12 oxygenated function are still a real challenge to synthetic organic chemists today.

For our continuing interest in developing simple and versatile synthetic routes for the total synthesis of terpenoids from readily available chiral starting materials,[15] we are intrigued by the fact that not a single successful report on the synthesis of naturally occurring scalaranes functionalized at position 12 has been published so far. The key strategy involved in our synthesis is the Diels–Alder addition of tricyclic diene with DMAD, which provides the D ring. It should be noted that this Diels–Alder addition method[14b] has been proved a failure to construct the scalarane skeleton with right stereochemistry in the synthesis of natural scalaranic sesterterpenes without C12 oxygenated function. In view of the above reported stereochemical outcome, we envisioned that the introduction of C12 functional group might be an option potentially capable of altering the stereochemistry of the Diels–Alder addition. Herein, we would like to present the preliminary results on the first stereoselective synthesis of marine sesterterpene scalarolide **1**. As far as we know, this is also the first successful example of synthetic approach to the C12 oxygen-functionalized scalaranic sesterterpenoids since their first isolation in 1972.[16]

Our approach commences with the preparation of the tricyclic intermediate **10** (50% yield over 8 steps) by a published procedure[12b,14a,17] from readily available sclareol **9** as starting material (Scheme 1). Epoxidation of **10** using *m*-CPBA gave epoxide **11** in 78% yield. Subsequent ring-opening rearrangement of **11** to α,β-unsaturated ester **12** under basic condition, being our initial strategy to introduce the C12 hydroxy group, turned out to be completely a failure. This is probably one of the main reasons most synthetic methods failed in the incorporation of the oxygenated function at the C12 position of scalaranes to date.

Alternatively (Scheme 2), epoxidation of aldehyde **14**, which was prepared from **10** through LAH reduction and swern oxidation, furnished the epoxide **16** as a major product in 70% yield, accom-

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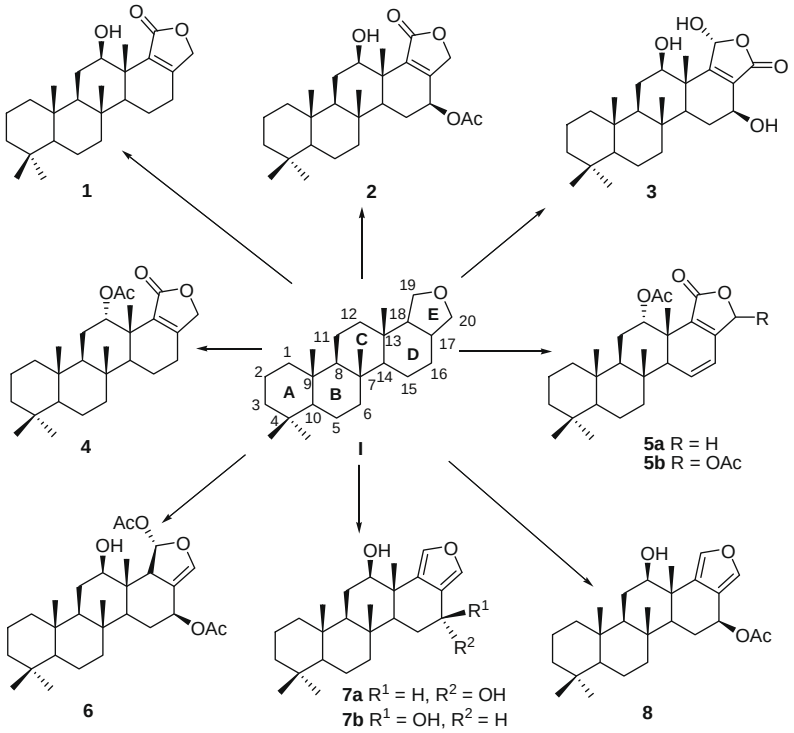
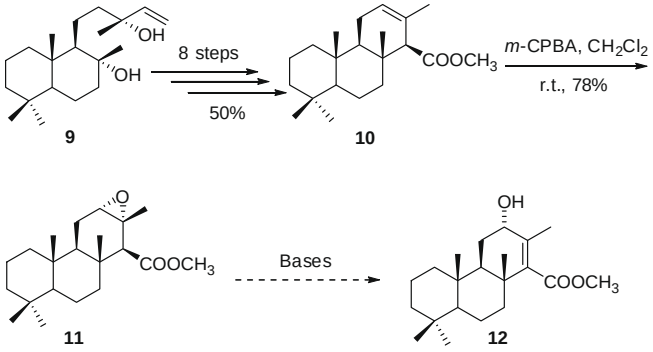


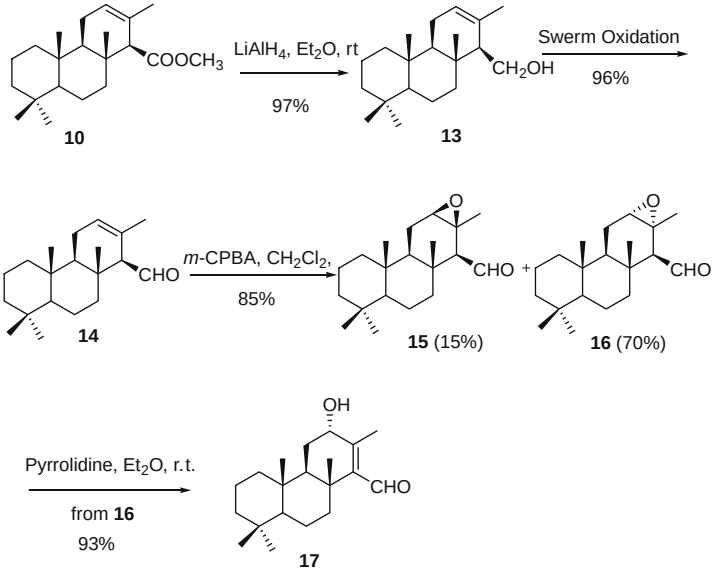
Figure 1.



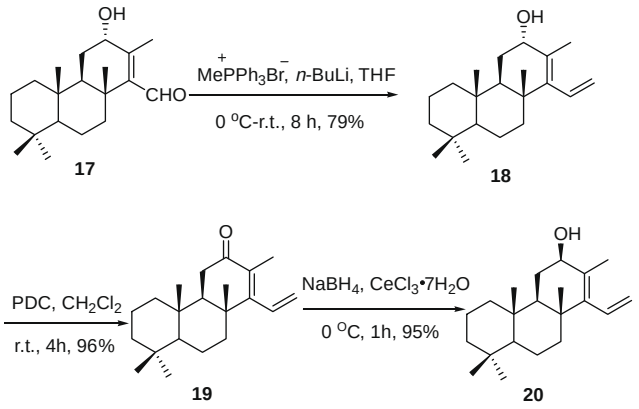
Scheme 1.

panied with diastereoisomer **15** as minor product. To our amazement, the treatment of epoxide **16** with pyrrolidine as base in ether at room temperature, in this case, underwent the ring-opening rearrangement with 12α-OH-α,β-unsaturated aldehyde **17** in 93% yield. With the success of the establishment of C12 hydroxy group on the tricyclic ring skeleton, we then focused on the stereoselective Diels–Alder addition. Wittig olefination of enal **17** provided the 12α-OH diene **18** in 79% yield, followed by a consecutive oxidation with PDC and stereoselective reduction to produce the 12-epimer of **18**, 12β-OH diene **20** in excellent yield (Scheme 3).

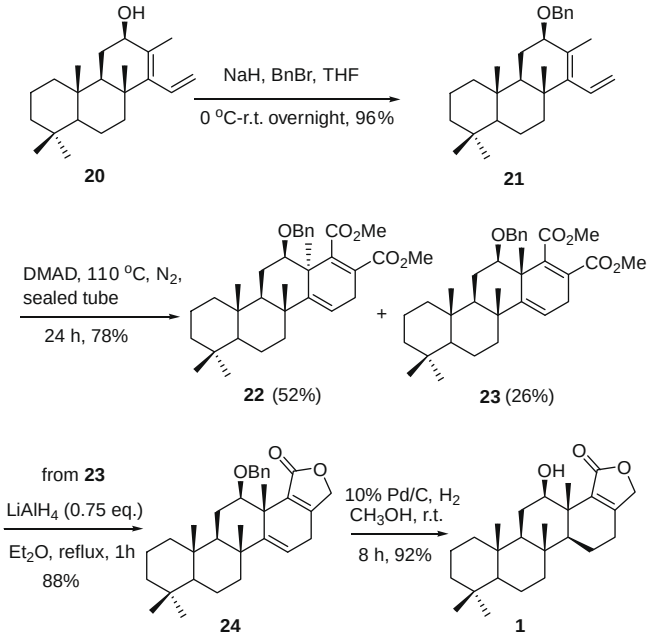
As depicted in Scheme 4, the benzyl protection of 12β-OH of **20** with benzyl bromide gave diene **21** (96% yield), which was then subjected to Diels–Alder addition with DMAD in sealed tube at 110 °C. As expected, the Diels–Alder addition afforded undesired



Scheme 2.



Scheme 3.



Scheme 4.

22 in 52% yield and desired **23** in 26% yield. The 2D NOESY spectra of **22** and **23** established the above stereochemical assignment due to an obvious crosspeak between newly formed angular methyl group and the axial proton at C12 for **22,** while the absence of such a crosspeak for **23**. This stereochemical result is different from that of previous report.[14b] LAH (0.75 equiv) reduction of adduct **23** in ether at reflux temperature resulted in highly regioselective reduction of less hindered methyl ester group, and spontaneous lactonization smoothly afforded γ-butenolide **24** in 88% yield. This one-pot process of regioselective construction of γ-butenolide moiety is superior to that of previously reported synthetic route of (+)-12-deoxyscalarolide.[18] Further hydrogenation of **24** using 10% Pd/C accomplished the synthesis of scalarolide **1** in 92% yield. Comparisons of specific optical rotation ($[\alpha]_D^{18}$ +23.6, *c* 0.13, CH_2Cl_2 versus ($[\alpha]_D^{25}$ +24.9, *c* 0.15, CH_2Cl_2 of lit.[2b]), ^1H NMR, ^{13}C NMR and HRMS data of our synthetic **1** established the structural identity with the natural (+)-scalarolide isolated by Youssef[2b] and Faulkner[3a] reported to be structure **1**.

In summary, we have finished the first synthesis of marine (+)-scalarolide **1** in 19 steps of reaction in an overall of 4.4% yield.[19] Taking into account the convenient chemical transformation of Diels–Alder adduct **23** and γ-butenolide moiety,[3a] we believe that our method would be of great benefit to the synthesis of other naturally occurring C12 oxygenated scalaranes, such as sesterstatins, hyatolides, heteronemins, and scalarafurans, which have hitherto been beyond the reach of chemical synthesis. Investigation is currently to further improve the stereoselectivity of Diels–Alder addition, and to elaborate the attractive intermediate **23** toward scalarafurans and other biologically active compounds in our laboratory.

Acknowledgments

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Supplementary data

The copies of ^1H, ^{13}C NMR spectra of key intermediates **22** and **23**, final product **1** and authentic natural scalarolide.[2b] Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.064.

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19. *Data for* **1**: white solid, mp >300 °C; $[\alpha]_D^{18}$ +23.6 (*c* 0.13, CH_2Cl_2); IR (KBr, *v*, cm^{-1}): 3393.0, 2928.7, 1711.3, 1442.2, 1387.3, 1060.8; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.75–4.65 (m, 2H), 3.67 (dd, *J* = 5.2, 10.9, 1H), 2.48–2.18 (m, 2H), 1.97–1.25 (m, 12H), 1.13 (s, 3H), 1.12–1.05 (m, 2H), 0.90 (s, 3H), 0.86 (s, 6H), 0.82 (s, 3H), 0.95–0.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 162.1, 135.9, 75.6, 72.1, 58.0, 56.7, 55.2, 42.2, 42.1, 41.7, 39.7, 37.4, 37.3, 33.3, 31.0, 25.8, 25.3, 21.3, 18.6, 18.3, 17.2, 16.8, 16.5, 16.0; HRMS (ESI) calcd for $C_{25}H_{39}O_3^+$ $[M+H]^+$ 387.2899, found 387.2896.