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Concise and Efficient Total Syntheses of (±)-Sarcophytols A and B, Two Antitumor Cembrane Diterpenoids, by An Intramolecular McMurry Olefination Strategy

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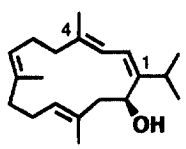
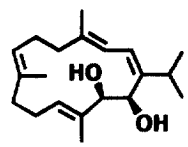
Abstract: *Efficient total syntheses of (±)-sarcophytol A and B, two antitumor cembrane diterpenoids isolated from marine soft corals, were presented by a low-valent titanium-mediated intramolecular McMurry olefination strategy starting from trans, trans-farnesol.*

Cembranoids, a large family of diterpenoid natural products characterized by the presence of a fourteen-membered ring, have been isolated from various marine sources as well as some terrestrial organisms since the 1960's.[1] These diterpenoids have become of great interest to synthetic chemists and biologists because of their unusual structural features and remarkably wide range of biological activities.[1] Although a number of synthetic strategies and methods for the construction of the 14-membered-ring system have appeared in the literature over the past two decades and notable progress has been made in this field, the lack of a general method for the preparation of 14-membered rings presents an ongoing challenge for total synthesis.[2]

Sarcophytols A (**1**) and B (**2**), two hydroxylated cembrenoids first isolated[3] from the Okinawan soft coral *Sarcophyton glaucum*, have been reported to show antitumor activity as well as potent inhibitory activities against various kinds of tumor promoters.[4] Particularly, extensive biological studies[5] have shown that **1** has therapeutic potential for cancer prevention with little toxicity. As a result, studies towards the total synthesis of sarcophytols have attracted a great deal of interest in recent years and several total syntheses of **1** have been reported.[6] The first total synthesis of (±)-**2** has aslo been achieved by McMurry *et al* using a low-valent titanium-induced intramolecular pinacol coupling.[7]



Sarcophytol-A (1)



Sarcophytol-B (2)

We report herein a general strategy leading to a concise and efficient total syntheses of both (±)-**1** and (±)-**2**, which is an extention of that previously employed[8] in the total synthesis of cembrene-C and (±)-isosarcophytol-A, two other cembrane diterpenes bearing the same carbon skeleton. The retrosynthesis, outlined in Scheme 1, was based on the application of low-valent titanium-mediated intramolecular dicarbonyl olefination (McMurry reaction)[9] as the key macrocyclization step in which the formation of the desired *Z* double bond is favoured. Preparation of keto aldehydes **3** and **4**, the macrocyclization precursors, involves a convergent coupling of C_{15} fragements derived from **5** with the C_5 unit **6** by alkylation and aldol condensation respectively, *via* the lithium enolate of α-silyloxyl ketone **6**.

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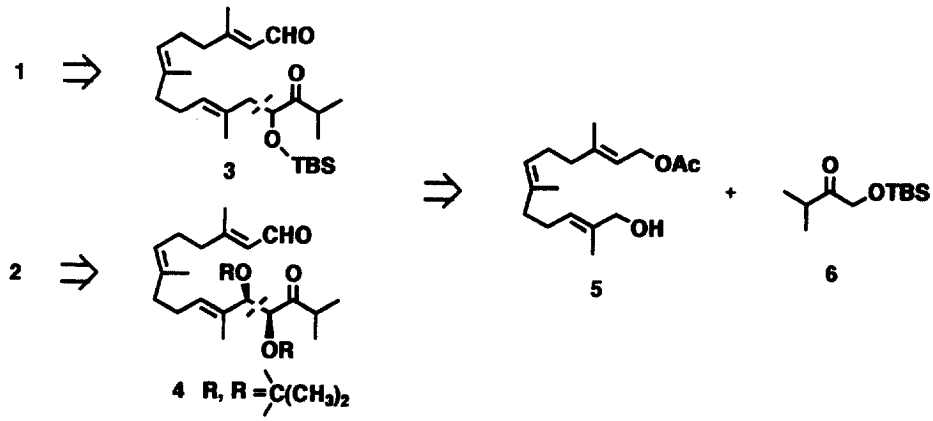
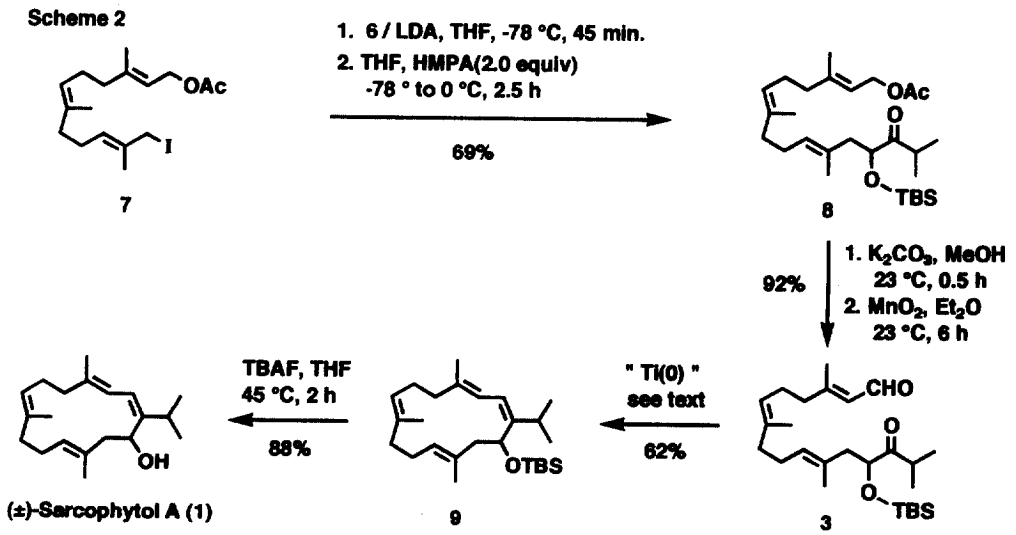


Scheme 1

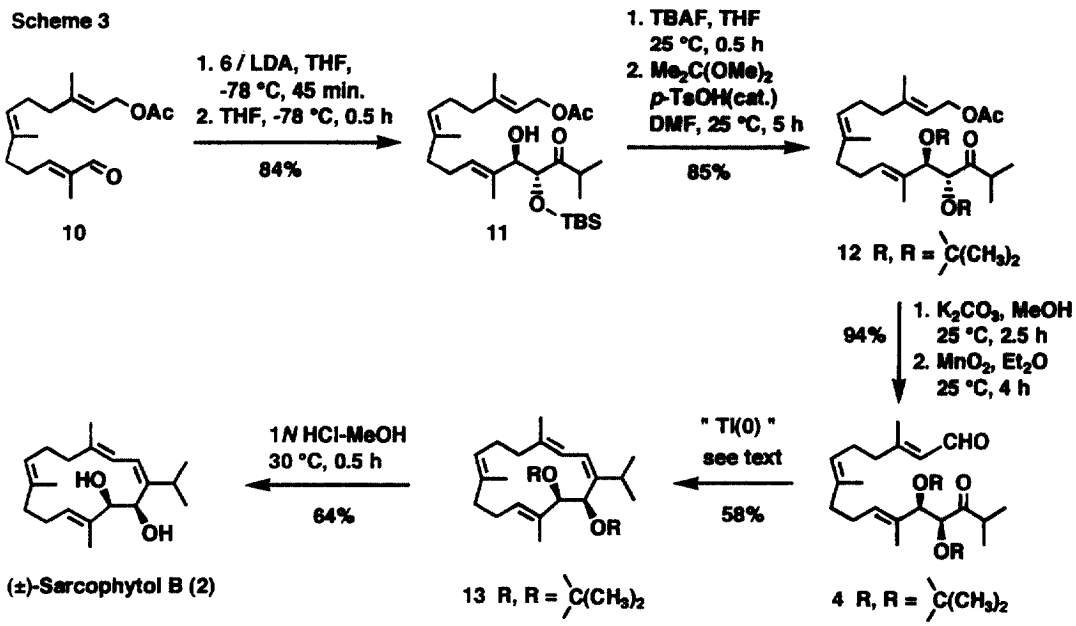
The total synthesis of (±)-sarcophytol-A (**1**) is detailed in Scheme 2. Allylic alcohol **5**,[10] readily available from *trans, trans*-farnesyl acetate by regioselective SeO_2 oxidation, was converted into the corresponding iodide **7** by a standard method[11] (Ph_3P, I_2, imidazole, 100%), and the iodide was subjected to alkylation using the lithium enolate of 1-*tert*-butyldimethylsilyloxyl-3-methyl-2-butanone (**6**)[12] (formed by treatment with LDA in THF at -78 °C) in the presence of hexamethylphosphoric triamide (HMPA) in THF to give keto acetate **8**[14] in 69% yield in which the whole carbon skeleton and three *trans* double bonds of **1** are assembled. The cyclization precursor, the keto aldehyde **3**, obtained by saponification of acetate **8** and subsequential MnO_2 oxidation (92%, two steps), was added slowly *via* a syringe pump to a suspension of low-valent titanium slurry (preformed[10] by the *in situ* reduction of $TiCl_4$ with two equivalents of Zn in the presence of a trace amount of pyridine) in THF under reflux over 20 h to afford the desired cyclized *tert*-butyldimethylsilyl (TBS) ether **9**[14] in 62% yield. Desilylation of **9** with tetra-*n*-butylammonium fluoride (TBAF) in THF gave (±)-**1** (88%), which showed spectroscopic properties identical with those of the natural product.[15]

Scheme 2



Outlined in Scheme 3 is the synthetic route to (±)-sarcophytol-B (**2**). Aldehyde **10**, prepared by MnO_2 oxidation of the allylic alcohol **5**, was subjected to an aldol condensation with the lithium enolate of **6** at -78 °C in THF to give *erythro* aldol **11**[16, 17] (84%) as the predominant diastereomer (> 95 : 5) after flash chromatography on silica gel.

Scheme 3



Aldol **11** was desilylated by treatment with TBAF in THF and the diol was transformed into the *erythro* acetonide **12**.[14, 16] Treatment of **12** with potassium carbonate in methanol at 25 °C for 2.5 h not only effected hydrolysis of the allylic acetate but also the epimerization[18] of the C-14 center of the acetonide α to the keto carbonyl to afford the desired *threo* acetonide **4**[14, 16] after MnO_2 oxidation. The macro-olefination of keto aldehyde **4** mediated by a low-valent titanium reagent was conducted in an analogous manner to the described above to give the desired cyclized acetonide **13** in 58% yield, which has showed identical spectral data with those previously reported.[19] (±)-Sarcophytol B (**2**) was obtained by treatment of the acetonide **13** with a warm 1*N* HCl in methanol, and showed identical spectroscopic properties with those of the natural product.[15]

In summary, efficient and convergent total syntheses of (±)-sarcophytols A and B have been accomplished *via* an *unified* macro-olefination strategy by using titanium-mediated McMurry couplings as the key reactions and the α-alkoxy ketone **6** and *trans, trans*-farnesol as buliding blocks.[20]

References and Notes

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