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AN EFFICIENT TOTAL SYNTHESIS OF (±)-ISOSARCOPHYTOL-A

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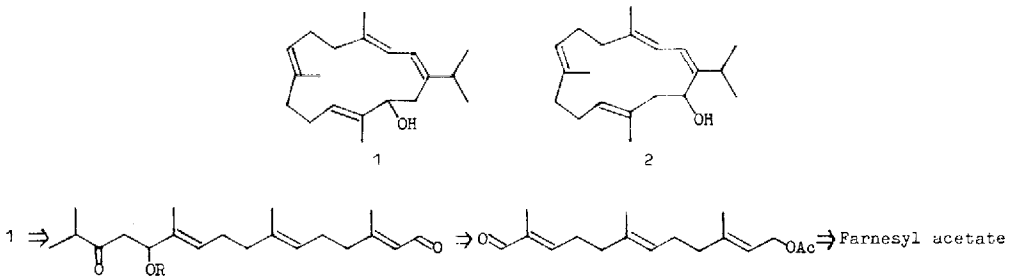
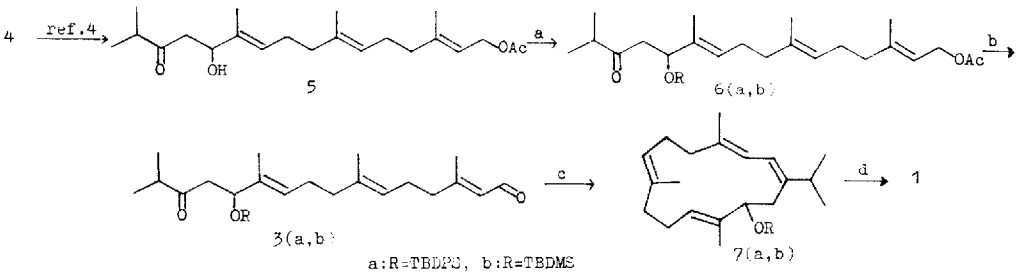
Summary: The first total synthesis of (±)-isosarcophytol-A, a marine cembranoid, was achieved *via* seven steps from *E,E*-farnesyl acetate.

Isosarcophytol-A(**1**) [1], a cembrane-type diterpenoid, was first isolated from Australian soft coral *(Nephthea brassica)* in 1982, and its structure was established as (1,3,7,11-all *E*,13*S*)-cembra-1,3,7,11-tetraen-13-ol, an isomer of sarcophytol-A(**2**) [2] which exhibits potent antitumor activity [3]. As far as we know, the bioactive test and total synthesis of **1** have not been reported yet. In previous work, we have reported the synthesis of isosarcophytol-A precursor [4]. Herein we wish to describe the total synthesis of (±)-isosarcophytol-A(**1**).



Scheme 1

The synthetic strategy from available *E,E*-farnesyl acetate was outlined in Scheme 1. The crucial steps are the synthesis of dicarbonyl precursor **3** employing Heathcock's aldol condensation and the macrocyclization of **3** induced by low valent titanium reagent ($TiCl_4$ / Zn). The synthetic route was showed in Scheme 2.



Scheme 2. Reagents and conditions: a) TBDPSCl or TBDMSCl / imidazole or DMAP–TEA, DMF, r.t.(90%); b) 1.K_2CO_3 / MeOH, 0℃; 2. MnO_2 / Na_2CO_3, CH_2Cl_2, r.t.(81%); c) $TiCl_4$ / Zn, Py, THF, reflux, 36h(78%); d)*n*–$Bu_4N^+F^-$, THF, 0℃(100%).

The ketone **5** [4] was protected [5] as its *tert*–butyldiphenylsilyl ether **6a** or *tert*–butyldimethylsilyl ether **6b**, which was subjected to mild hydrolysis (K_2CO_3 / MeOH, 0℃) and followed by oxidation [6] (MnO_2 / Na_2CO_3) to give the dicarbonyl precursor **3a** [4] or **3b** [7]. It is noteworthy that the tetrahydropyranyl ether yielded the unexpected *trans* eliminated hydrolytic product [8] (J=16Hz) in high yield even using more gentle condition (K_2CO_3 / MeOH, –20℃).

The macrocyclization of **3a** and **3b** was conducted by syringing its dilute solution (0.005M) in THF slowly to the refluxing low valent titanium reagent ($TiCl_4$ / Zn) in the presence of pyridine [9]. The desired cyclized product **7a** or **7b** [7] was obtained in 78% yield after careful column chromatographic purification, which was deprotected [5] using *n*–$Bu_4N^+F^-$ to give the sole oilly product **1** quantitatively. The spectral data of **1** agreed with that of literatures [10]. The bioactive test and the enantioselective convertion to enantiomerically pure isosarcophytol–A are in progress.

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References and Notes

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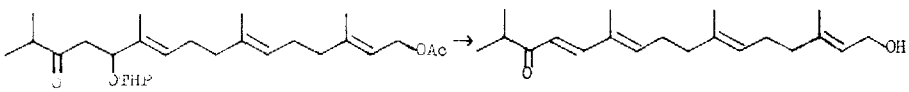
7. The spectral data: **3b**:υ_{max}: 1713(s,C=O), 1676(s,C=O)cm^{-1}; δ_H(80MHz, $CDCl_3$): 0.06(s, 6H), 0.95(d, 6H, J=7.1Hz), 1.04(s, 9H), 1.53、1.67(2s, 9H), 1.85~2.20(m, 8H),2.40~2.75(m, 3H), 4.55(t, 1H, J=7.3Hz), 5.00~5.25(m, 2H), 5.86(d, 1H, J=8.5Hz), 10.00(d, 1H, J=8.5Hz)ppm; *m / z* (EI, 70ev): 419(M^+–15, 1%),377(M^+–57, 20), 171(18), 143(31), 75(100); **9a**: υ_{max}: 3049, 1653(C=C), 1359, 1109, 1051, 703 cm^{-1}; δ_H(80MHz, $CDCl_3$): 1.04(d, 6H, J=7.2Hz), 1.08(s, 9H), 1.49、1.60、1.67(3s, 9H), 1.90~2.24(m, 8H), 2.25~2.73(m, 1H), 2.70(dd, 1H, J=7.8、13.2Hz), 2.79(sept, 1H, J=6.8Hz), 4.00(dd, 1H, J=3.7、7.7Hz), 4.90(m ,1H), 5.03(t, 1H, J=6.5Hz), 5.73(d, 1H, J=11.4Hz), 5.91(d, 1H, J=11.3Hz), 7.27~7.75(m, 5H)ppm; *m / z*(EI, 70ev): 526(M^+, 29%), 469(M^+–57, 14), 389(13), 265(51), 199(100), 135(65), 57(33)
8. Its structure was confirmed by spectral data of IR、^{1}HNMR and MS. The reaction was expressed in following equation:



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10. Standard sample of natural isosarcophytol–A for direct comparison was not available.

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