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First Total Synthesis of Natural 6-Epiplakortolide E

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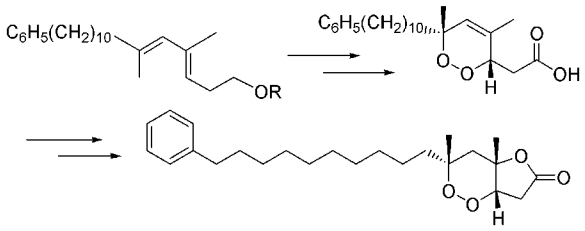
ABSTRACT

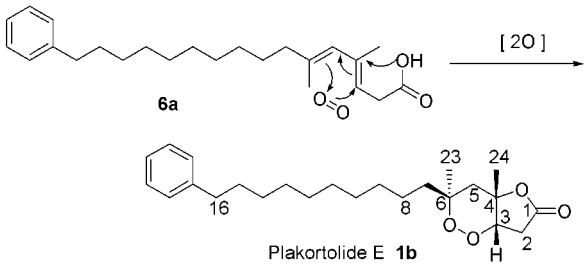


Natural 6-epiplakortolide E was first synthesized from readily available 1-bromo-10-phenyldecane in 10 steps by using singlet oxygen-mediated Diels−Alder reaction to form cyclic peroxide followed by a directed iodolactonization to give the peroxylactone core.

Plakortolide is a novel cyclic peroxylactone isolated in very low yield (0.0003% for 6-epiplakortolide E **1a**) from the marine sponge *Plakortis* sp.[1] Plakortolide E **1b** shows potent cytotoxicity against murine and human cancer cell lines[1f] and a derivative is active against the AIDS opportunistic parasite *Toxoplasma gondi*.[2] However, limited isolation of the peroxylactones was reported due to their instability.[1] Interestingly, these compounds hold a unique cyclic peroxylactone skeleton connected with long aliphatic side chains at C-6. Although the synthesis of some natural monocyclic peroxides due to their biological importance has already been reported,[3] no synthesis of any member of the scarce bicyclic plakortolide family of compounds has, heretofore, been achieved. In this letter, we wish to report our results on the preparation of natural (±)-6-epiplakortolide E **1a** as the first of its kind.

Considering that plakortolides are cyclic peroxylactones, a concise and simplified synthetic approach to their core skeleton should arise from the biosynthetic proposal in Scheme 1. This biosynthetic pathway involves singlet oxygen-mediated Diels−Alder cyclization of the plausible bioprecursor **6a**. Although rare, there are some instances where Diels−Alder processes have been found in nature and

Scheme 1. Plausible Biosynthetic Pathway for the Formation of Plakortolides from Precursor **6a** (Relative Stereochemistry Indicated)



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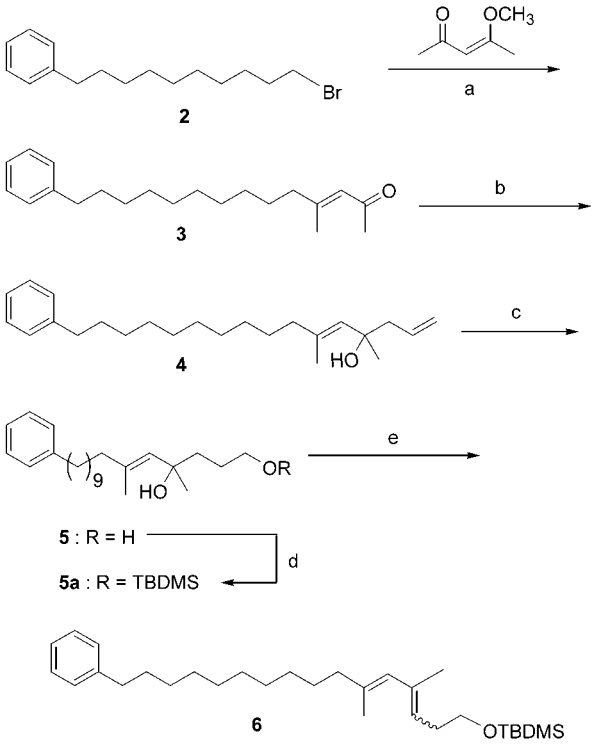
biologically catalyzed Diels−Alder reactions have been reported.[4] Subsequent lactonization of the cyclic peroxyacids, which are frequently isolated from marine sponges,[5,6] may afford plakortolide.

Starting from commercially available 1-bromo-10-phenyldecane **2**, the corresponding (3*E*)-α,*β*-unsaturated ketone **3** was readily obtained in 69% yield (Scheme 2).[7] Exclusive

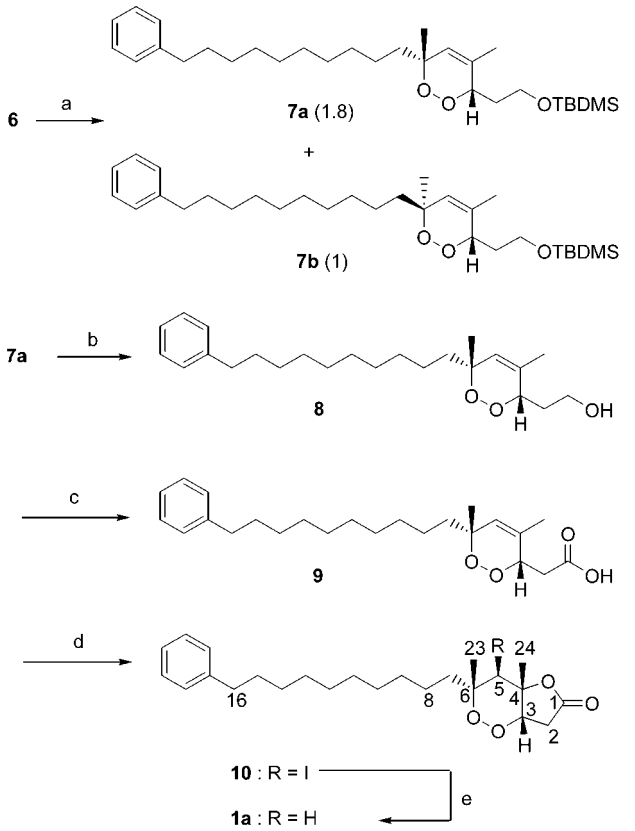
Scheme 2[a]



[a] Reaction conditions: (a) Mg/ether, room tmeperature, 2 h, 69%. (b) allylmagnesium bromide, ether, 0 °C, 1.5 h, 60%. (c) 9-BBN, room temperature, 3 N $NaOH/H_2O_2$, 2 h, 90%. (d) TBDMS-Cl, imidazole, DMF, room temperature, 4 h, 98%. (e) $TsOH/CaCl_2$, benzene, room temperature, 2 h, 80%.

1,2-addition of Grignard reagent, allylmagnesium bromide controlled by the steric factor of **3** resulted in the tertiary alcohol **4** (yield 60%). Subsequent hydroboration−oxidation of the terminal olefin of **4** with 9-BBN and 3 N $NaOH/H_2O_2$ afforded the diol **5** in 90% yield. Selective protection of the primary alcohol group of **5** with TBDMS-Cl and elimination of the tertiary alcohol group of **5a** gave the protected precursor **6** as regioisomers (3*E*, 5*E*/3*Z*, 5*E* in 1.8:1 ratio) in 83% yield. Diels−Alder cyclization of **6** with singlet oxygen generated by irradiation with a 500-W tungsten lamp in the presence of rose bengal in methylene chloride and 5% methanol at 0 °C for 4 h gave two cyclic peroxides **7a** and **7b** as diastereomers in 1.8:1 ratio in 45% yield (Scheme 3). Deprotection of the alcohol group of the isolated major

Scheme 3[a]



[a] Reaction conditions: (a) O_2, 500-W lamp, rose bengal, 0 °C, 6 h, CH_2Cl_2/MeOH (19:1), 45%. (b) 10% HCl, THF/MeOH, room temperature, 1 h, 87%. (c) Jones' reagent, acetone, room temperature, 1.5 h, 78%. (d) $NaHCO_3/I_2$, $CHCl_3/H_2O$, room temperature, 2 days, 55%. (e) AIBN/Bu_3SnH, benzene, 80 °C, 1 h, 68%.

isomer **7a** with 10% HCl without destruction of the cyclic peroxide to the cyclic peroxyalcohol **8** and subsequent Jones' oxidation of **8** in acetone afforded plakoric acid **9** in 78% yield. The α-face directed iodolactonization of **9** with $NaHCO_3/I_2$ produced 5*β*-iodo-6-*epi*-plakortolide E **10**, which is a cyclic peroxylactone in 55% yield. Subsequent reduction of **10** with Bu_3SnH (3.0 equiv) in the presence of AIBN (2.0 equiv) in benzene at 80 °C for 1 h finally provided the (±)-6-epiplakortolide E **1a** in natural configuration as a colorless oil in 68% yield. Interestingly, the cyclic peroxylactone remains untouched during the Bu_3SnH-mediated reduction of **10**, which is consistent with the selective reduction in the presence of the stable cyclic peroxide of artemisinin.[8,9] Their

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relative stereochemistry was unambiguously established as shown in the structures of **10** and **1a**, using the NOESY, ROESY, and TOCSY technique. All spectral data of synthetic **1a** are in agreement with the spectral data of natural 6-*epi*-plakortolide E reported in the literature.[1g] The same conversion of the **7b** followed by the α-face directed iodolactonization due to the already established chirality at C-3 will afford the plakortolide E **1b** in natural configuration. Thus, the first and concise total synthesis of natural 6-epi-plakortolide E was achieved by using an assembly process activated by singlet oxygen. This synthetic route finds some applications, since many analogues of plakortolide can be readily obtained by simply changing the long aliphatic side chain **2** during α,*β*-unsaturated ketone **3** formation. Thus, these scarce natural products can be provided in quantities suitable for more extensive biological evaluation.

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Supporting Information Available: Experimental procedures for the preparation of all compounds (**3**−**10** and **1a**) and spectral data of compounds **3**−**9** and those including NOESY, ROESY, and TOCSY of compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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