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Synthetic Strategy for Construction of the Furanohydrophenanthrene Ring System

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Abstract: An effective synthesis of furanohydrophenanthrene ring system, as an intermediate toward furanoid spongiaditerpenes syntheses, was accomplished using a furan ring transfer reaction, followed by bis-annulation with 1,7-octadien-3-one.

Of all invertebrates, sponges have yielded the largest number and greatest diversity of marine natural products.[1] A variety of spongiaditerpenoids with a ring D furan and functionalized ring A, *e.g.*, spongiadiosphenol,[2a] spongiadiol,[2b] and spongialactone[2c] have been isolated from sponges of the genus Spongia, order Dictyoceratida, collected from widely diverse geographical sites such as Australia, the Mediterranean, the Red Sea, and the Caribbean (Figure 1). Among them, many biologically active substances have been found, which exhibit species-specific toxicity against a wide range of organisms, including microorganisms, invertebrates, and vertebrates.

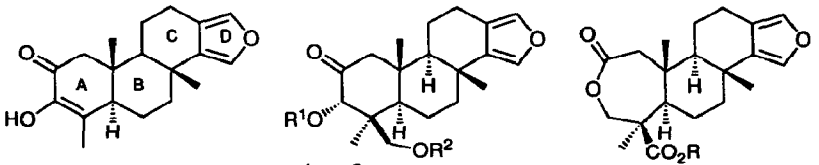
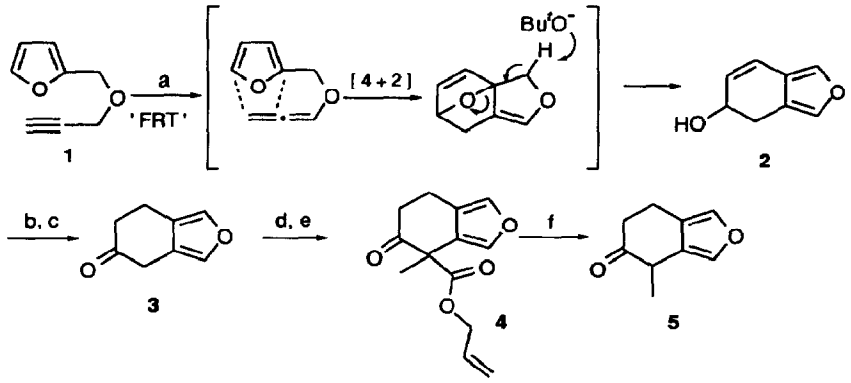


Figure 1. Furanoid Spongiaditerpenes.

In the stereoselective synthesis of furanoid spongiaditerpenes, it seems to be some troubles: i) the construction of 3,4-fused furan ring system needs for several steps, ii) the possession of acid- and photo-sensitive furan ring, iii) stereocontrolled synthesis of ABC ring system. In fact, to the best of our knowledge there is at present only one synthesis of furanoid spongiaditerpene by Nakano's group.[3] Recently, our interests have been focused on an allene moiety which has high reactivity as a dienophile. The greater facility

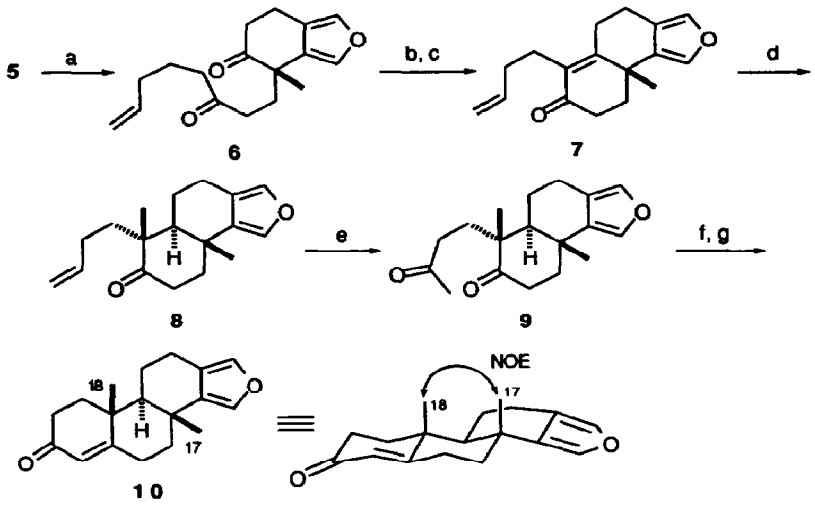
of the allene in the Diels-Alder reactions could be attributed to the favorable geometry in the transition state compared with vinyl or propargyl moiety.[4] From this point of view, we originally developed the efficient synthesis of 3,4-fused polycyclic furan ring systems, which proceed *via* the intramolecular Diels-Alder reaction of allenyl furfuryl ether, obtained by base-catalyzed isomerization of the initial propargyl ether, followed by the oxa ring cleavage of the resulting adduct (Scheme 1).[5] This ring transformation was named a furan ring transfer reaction (FRT reaction). In this paper, we describe an effective synthesis of the hydrophenanthrene ring system, which is a key intermediate for the synthesis of spongiaditerpenes, using the FRT reaction and the successive annulation as a key step.



Reagents and Conditions; (a) Bu^{t}OK(3eq.), Bu^{t}OH, 80 °C. (b) 5% Pd-C, H_2, EtOH, room temperature, 90% from 1. (c) DMSO, TFAA, CH_2Cl_2, -78 °C, 87%. (d) diallylcarbonate, NaH, benzene, 60 °C. (e) MeI, K_2CO_3, acetone, room temperature, 74% from 3. (f) 10 mol% $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, room temperature, 76%.

Scheme 1

As a precursor of FRT reaction, furfuryl propargyl ether **1** was employed, which is readily prepared from furfuryl alcohol by a conventional manner.[5] Treatment of the propargyl ether **1** with Bu^{t}OK (3 eq) in Bu^{t}OH at 80 °C resulted in a smooth FRT reaction to give the bicyclic allylic alcohol **2**. The allylic alcohol **2** is acid sensitive, because a dehydration easily proceeded into an unstable isobenzofuran. Therefore, **3** was hydrogenated immediately with Pd-C catalyst followed by Swern oxidation to afford the ketone **3**. Unfortunately, methylation of **3** with iodomethane under the various basic conditions gave *gem*-dimethylated product exclusively. So, we carried out mono-methylation of **3** according to Tsuji's protocol[6] as follows. The ketone **3** was converted to the allylic β-keto ester with diallyl carbonate in the presence of NaH at 60 °C, followed by the methylation with iodomethane in the presence of K_2CO_3 at 50 °C to afford **4** in 74% yield (two steps). Removal of the allyl ester by palladium-catalyzed reaction with ammonium formate under the mild conditions gave the desired monomethylated ketone **5** in 76 % yield.



Reagents and Conditions; (a) 1,7-octadien-3-one, DBU, THF, room temperature. (b) Bu^{t}OK, THF, room temperature. (c) KOH, MeOH, 60 °C, 33% from **5**. (d) Li, liq.NH_3, MeI, THF, -78 °C, 65%. (e) 10 mol% $PdCl_2$, 10 eq. CuCl, O2, DMF, 98%. (f) BuᵗOK, THF, room temperature, 59%. (g) *p*-TsOH, benzene, room temperature, 50%.

Scheme 2

The Michael addition of 1,7-octadien-3-one[7] to mono-methylated ketone **5** was carried out using DBU (1.5 eq) in THF solution at 0 °C to give the 1,5-diketone **6**(Scheme 2). The aldol condensation proceeded using Bu^{t}OK (1.5 eq) in THF solution at room temperature followed by dehydration with methanolic KOH solution at 60 °C to give the desired tricyclic enone **7** in 33% yield from **5**. Introduction of methyl group to the enone **7** was carried out by the reductive alkylation with iodomethane in lithium-liquid ammonia solution at -78 °C to afford **8** as a single isomer in 65% yield. In this stage, the stereochemistry of **8** could not be determined. The terminal double bond of **8** was oxidized successfully by Wacker oxidation using excess CuCl to supress an acidic condition and the diketone **9** was obtained in 98% yield. The aldol condensation of **9** was carried out with Bu^{t}OK in THF solution at room temperature to afford β-hydroxy ketone in 59% yield, followed by dehydration with *p*-toluenesulfonic acid gave the desired tetracyclic compound **10** in 50% yield. The stereochemistry of **10** was determined by a 2D ^{1}H NOESY experiment between the C-17 and C-18 protons.

Thus, we have developed a new synthetic strategy for the synthesis of substituted spongiaditerpenes *via* a furan ring transfer reaction and bis-annulation sequence which permitted the construction of the tetracyclic intermediate **10**. Efforts toward functionalization of ring A of **10** are currently in progress.

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