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First Total Syntheses of (±)-Annuionone B and (±)-Tanarifuranonol

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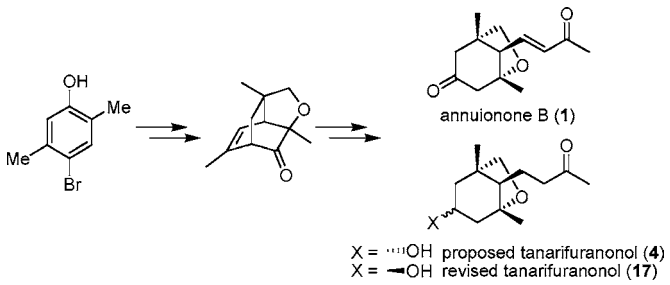
ABSTRACT



The intramolecular Diels–Alder reaction of *o*-quinol allyl ether was accomplished and subsequently applied to the first total syntheses of natural products annuionone B (1) and both the proposed and revised structure of tanarifuranonol, 4 and 17.

6-Oxabicyclo[3.2.1]octane is an important skeleton found in a variety of natural products, exhibiting a broad range of biological activities[1] (Figure 1). Grubbs and co-workers[2] in 1971 first constructed the 6-oxabicyclo[3.2.1]octane skeleton by using the intramolecular oxymercuration protocol of 4,4-bis(hydroxymethyl)-1-cyclohexene. Subsequently, the key transformation of cyclic ether was also accomplished either by means of intramolecular iodine-induced cyclization[3] and epoxidation[3] or by means of acid-catalyzed rearrangement of epoxide[4a] and diene.[4b] Takikawa[5] achieved the first total synthesis of annuionone A (**2**) in 2005; an intramolecular oxy-Michael addition was applied as a key step to acquire

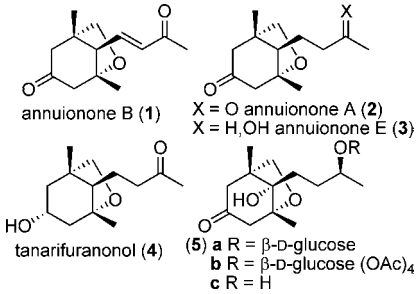


Figure 1. Natural products having a 6-oxabicyclo[3.2.1]octane skeleton.

the 6-oxabicyclo[3.2.1]octane skeleton. Apart from the usual intramolecular cyclizations from the cyclohexene system to the 6-oxabicyclo[3.2.1]octane system, new synthetic meth-

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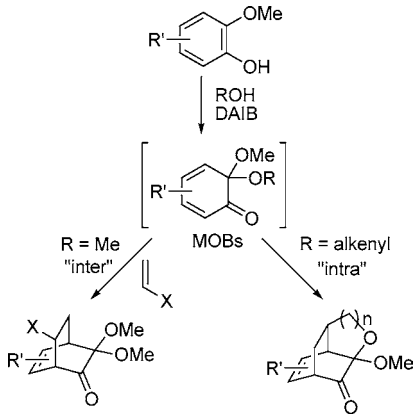
odologies encompassing further synthetic diversity and functionality are needed.

We have previously developed convenient and general approaches via the inter- or intramolecular Diels−Alder reaction of masked *o*-benzoquinones (MOBs)[6] (Scheme 1)

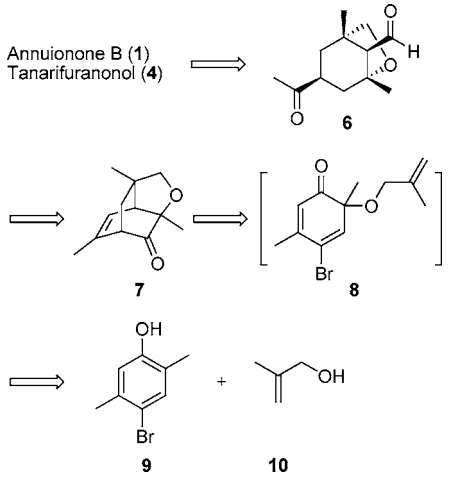
Scheme 1. Generation of MOBs and Its Diels−Alder Reactions



to obtain diverse structural frameworks including *cis*-decalin systems, highly substituted cyclohexenes, diquinanes, and triquinanes. Further, these strategies were successfully employed for the synthesis of natural products such as magellanine,[7] bilosespenes A and B,[8] penicillones A and B,[9] and pallescensin B.[10] The Diels−Alder reactions of MOBs could easily provide multifarious functionalized bicyclo-[2.2.2]octenone cores. Therefore, we decided to extend the strategy to construct a 6-oxabicyclo[3.2.1]octane skeleton starting from the bicyclo[2.2.2]octenone structure generated via the intramolecular Diels−Alder reaction of *o*-quinol allyl ether. *o*-Quinol alkyl ethers,[11] like MOBs, were generally obtained by using lead tetraacetate,[11c−f] sodium periodate,[11g] or diacetoxyiodobenzene (DAIB)[11h] as oxidants. Furthermore, the preparation of *o*-quinol allyl ether was only reported in situ by thermal pyrolysis by Singh and coworkers.[12] In this communication, we describe a direct and novel strategy to synthesize *o*-quinol allyl ether and its application to the total syntheses of annuionone B (**1**) and tanarifuranonol (**4**).

Annuionone B (**1**), like annuionone A (**2**), was first isolated from *Helianthus annuus* (sunflower) as an allelopathic agent in 1998,[13] and its structure was revised from the originally proposed *exo*-epoxide arrangement to the 6-oxabicyclo[3.2.1]-octane structure in 2004.[1a] Tanarifuranonol (**4**) was first obtained from the plant extracts of *Macaranga tanarius* in 2005.[1b] On a closer look at the structures of annuionone B (**1**) and tanarifuranonol (**4**), it occurred to us that both natural products can be obtained from oxabicyclic derivative **6**, which has the structural framework of 6-oxabicyclo[3.2.1]-octane (Scheme 2). Furthermore, oxabicyclic **6** can be

Scheme 2. Retrosynthetic Analysis



prepared from intramolecular Diels−Alder adduct **7** via ozonolysis. Most importantly, the rationale of the intramolecular Diels−Alder reaction will be achieved through *o*-quinol allyl ether **8** prepared in situ from 2-methylphenol **9** and isobutenol **10** via DAIB-mediated oxidation addition.

To start, phenol **9** with bromo substitution[14] in the presence of DAIB and methallyl alcohol **10** as solvent underwent oxidative followed by an intramolecular Diels−Alder reaction to provide tricyclic compound **12 (**Scheme 3). Since the bromo substitution acted as a traceless protecting group to block the oxidation of phenol at the para position, a similar detour method comprising sequential bromination, tandem oxidation/Diels−Alder reaction, and debromination has been developed by us.[15] The yield of product **12** is moderate, mainly because of the poor electron-donating effect of the methyl group next to phenol and the mild nucleophilicity of allylic alcohol **10**. It is worth noting that the tricyclic core

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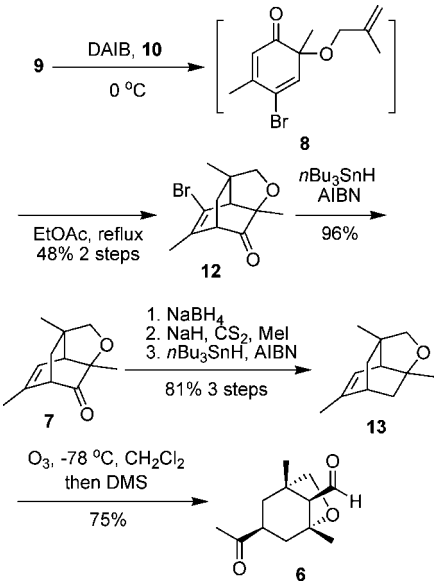
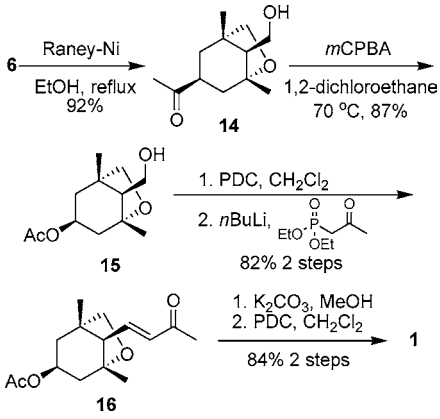
Scheme 3. Synthesis of Key Intermediate **6**



Scheme 4. Total Synthesis of Annuionone B (**1**)

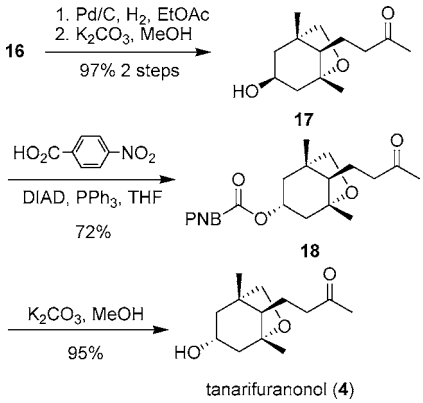


obtained via a two-step synthesis has all the functionalities required for the carbon framework of natural products **1** and **4**.

Debromination was performed utilizing AIBN as a radical initiator and nBu$_3$SnH as a hydrogen atom donor to provide compound **7** in 96% yield. After several attempts of deoxygenation methods such as Wolf−Kishner reduction, dithioketal reduction, tosylhydrazones with sodium borohydride−acetic acid, and tosylate reduction by LiAlH$_4$, a three-step Barton-McCombie deoxygenation procedure[16] successfully gave the desired compound **13** in 81% yield. Ozonolysis of **13** furnished oxabicyclic compound **6**, which possesses the core structure of annuionone B and tanarifuranonol having both the ketone and aldehyde functionalities as required. Selective carbonyl reduction with Raney-Ni[17] delivered the corresponding primary alcohol **14** (Scheme 4), whereas a general hydride source, such as LiAlH$_4$, NaBH$_4$, and NaBH$_3$CN, failed to give **14**. Furthermore, to introduce a key secondary hydroxyl group of the cyclohexane ring, Baeyer−Villiger oxidation[18] of methyl ketone **14** offered the corresponding acetate **15** in an excellent yield. Oxidation of primary alcohol in **15** with pyridinium dichromate (PDC) followed by a Horner−Emmons olefination[19] with diethyl (2-oxopropyl)phosphonate provided the Wittig product **16** in 84% overall yield for the two steps. Finally, annuionone B was obtained via deprotection of acetate in **16** followed by PDC oxidation. Overall, the total synthesis of natural product annuionone B was achieved in 13 steps with 15% overall yield from the phenol **9**.

Compound **16**, which acted also as a potential precursor for the synthesis of tanarifuranonol (**4**), was reduced under Pd−C/H$_2$ conditions followed by base-catalyzed deprotection to get the desired hydroxyl methylketone **17** (Scheme 5). In

Scheme 5. Total Synthesis of Tanarifuranonol (**4**)



order to inverse the stereochemistry of the secondary hydroxyl group, Mitsunobu procedure[20] was applied to obtain the corresponding benzoate **18**, which was hydrolyzed to furnish the proposed structure **4** of tanarifuranonol in two steps. Thus, the proposed structure **4** of tanarifuranonol was accomplished in 15 steps and 12% overall yield.

Surprisingly, the ^{1}H and ^{13}C NMR data of our synthetic tanarifuranonol (**4**) did not match with those of the reported natural compounds (see the Supporting Information). However, compound **17** had ^{1}H and ^{13}C NMR data comparable with those of the reported natural product.[1b] In order to confirm the relative stereochemistry of synthetic natural product, NOE correlation studies of **4**, **17**, and **18** were performed (see the Supporting Information). Moreover, Mitsunobu product **18** was transformed to the crystalline

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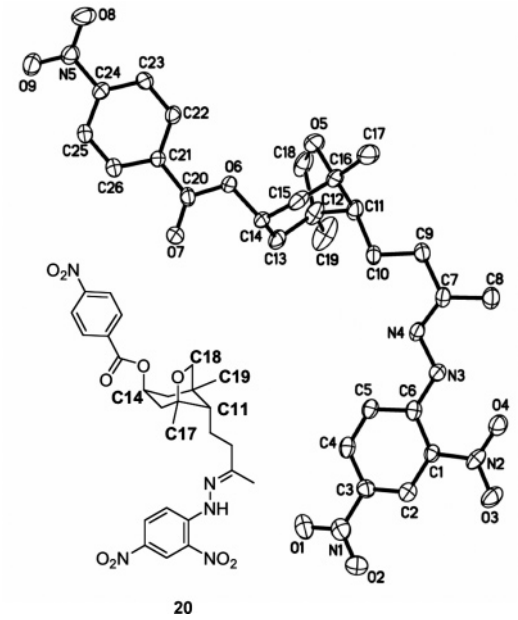

Figure 2. ORTEP drawing of hydrazone derivative **20**.

hydrazone derivative **20**. Single-crystal X-ray diffraction analysis of **20** unambiguously proved that a side chain with hydrazone is opposite to the benzoate group (Figure 2). Hence, to the best of our knowledge, after comparison of all spectral data, we propose compound **17**, which is an epimer of **4** and has a different configuration at the chiral center bearing a hydroxyl functional group, to be the structure of the isolated natural product.

In conclusion, an intramolecular Diels−Alder reaction of *o*-quinol allyl ether was demonstrated to lead to the convenient construction of the 6-oxabicyclo[3.2.1]octane skeleton. This methodology was then successfully applied to the first total syntheses of racemic annuionone B (**1**) in 15% overall yield and the proposed and revised structures of tanarifuranonol, **4** and **17**, in 12 and 18% overall yield, respectively.

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Supporting Information Available: General experimental procedures, NMR spectra of all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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