Asymmetric synthesis of bis-tetrahydrofuran cores in annonaceous acetogenins† ‡

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The bis-THF cores of annonaceous acetogenins were synthesized using (3*R*,4*R*)-1,5-hexadiene-3,4-diol (1) as the sole source of carbon atoms. The methylene acetal function was applied as a new linker/tether to facilitate the ring-closing metathesis.

Annonaceous acetogenins are a large family—more than 430—of natural products isolated from tropical plants of *Annonaceae*.[1] These compounds are potent inhibitors of mitochondrial complex I and inducers of cell-apoptosis.[1] However, their detection in edible products and traditional medicines has also recently raised public health concerns.[2,3] Most of the known and potent acetogenins contain adjacent bis-tetrahydrofurans (THF) with various stereochemistries (Fig. 1).[1,4] The bis-THF core is considered the region for mitochondrial membrane recognition,[5] and recent structure–activity relationship studies support the supposition that the stereochemistry of the bis-THF core affects the cytotoxicity.[6]

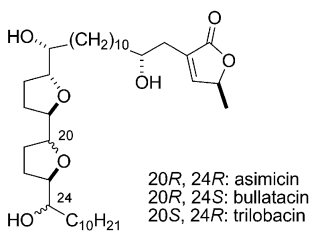
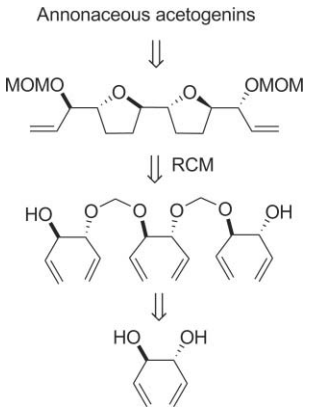


Fig. 1 Representative annonaceous acetogenins.

These interesting structural and biological properties of annonaceous acetogenins have attracted considerable attention in the synthetic community, and the construction of the bis-THF moiety remains as the main challenge in preparing these compounds.[4,7] Although many synthetic methodologies have been developed,[8] an appealing and potentially very efficient strategy to prepare the bis-THF core units of uvaricin and asimicin involves the use of C_2 symmetrical intermediates.[4a,9] Herein, we describe our synthesis of the bis-THF core from C_2 diene-diol **1**,[10] which provided the key carbon skeleton of the bis-THF core *via* ring-closing metathesis (Scheme 1).

Three units of the diene-diol **1** were linked as the methylene acetal **4**. The acetal was prepared by reaction of **1** with the bis-chloromethyl ether **3**, which was in turn prepared from the bis-methoxymethyl ether **2**, itself obtained from **1**.[11] Sharpless epoxidation allowed protection of the terminal olefins as dioxiranes **5**,[12] and subsequent ring-closing metathesis afforded **6**.[13] To our knowledge, this is the first example of using the methylene acetal moiety as a tether in RCM.[14–16] The S_N2 like, rather than acid catalysed, formation of the methylene acetal provided a controlled, clean way to connect three units of diene-diol **1**. To continue the synthesis, the alkenes were hydrogenated, and the epoxides were reduced to the bis-allylic alcohol **8**.[17] The hydroxyl functions were converted to the bis-benzyl ether **9**, this protecting group being selected because of its stability to the strongly acidic condition required for hydrolyzing the methylene acetals. The formation of the five-membered acetonide provided the desired diol **11**, in which the C_2 symmetrical hydroxyl groups are differentiated (Scheme 2).



Scheme 1 Retrosynthetic analysis.

Mesylation of **11** generated **12**, which was deprotected and then cyclised to form bis-THF derivative **13** having the stereochemistry *erythro*/*cis*/*threo*/*cis*/*erythro*. We found that the benzyl group could be readily removed using titanium chloride and then replaced with other protective groups such as the methoxymethyl group as in **14** (Scheme 3).[18]

The diol **11** could be used to prepare other diastereomers with bis-THF cores. For example, Mitsunobu reaction provided the diester **16** with the inverted stereocenters at C4 and C11.[19] Subsequent deprotection and cyclisation afforded the *threo*/*trans*/*threo*/*trans*/*threo* bis-THF **20**, the key intermediate in Marshall's synthesis of asimicin (Scheme 4).[8f]

In summary, we have developed a new strategy for preparing the bis-THF core of annonaceous acetogenins. This approach features use of the methylene acetal moiety as the tether for an RCM reaction, and of the C_2 diene-diol **1** as the only source of carbon atoms and of stereocenters. Moreover, **11** should be a key intermediate for the synthesis of various stereoisomers

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† Dedicated to Prof. John C. Gilbert on the occasion of his 70th birthday.

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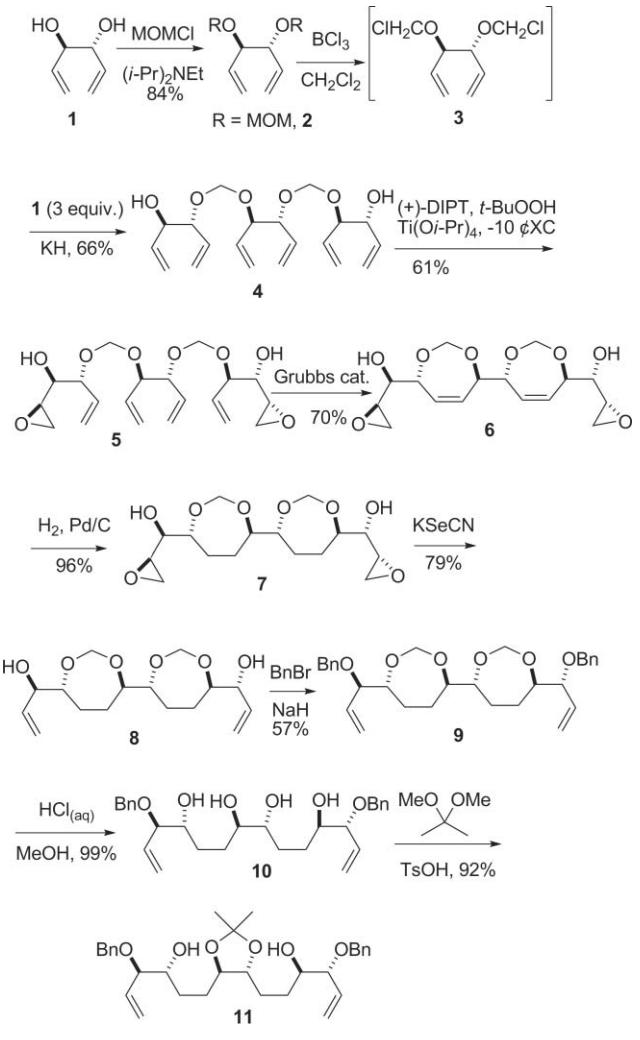
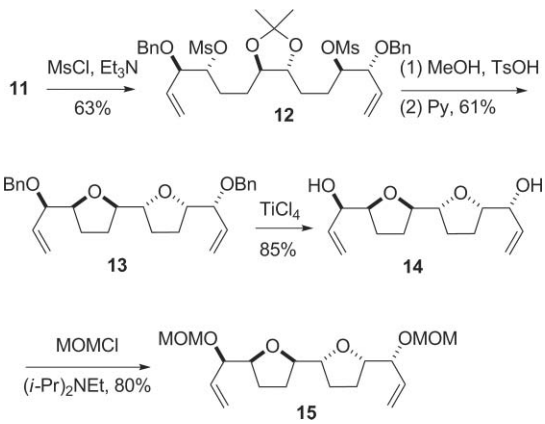


Scheme 2 Preparation of the C_2 diol **11**.



Scheme 3 Synthesis of *erythro*/*cis*/*threo*/*cis*/*erythro* bis-THF **15**.

of acetogenins with C_2 symmetry, such as squamocin-N[20] and asimicin.

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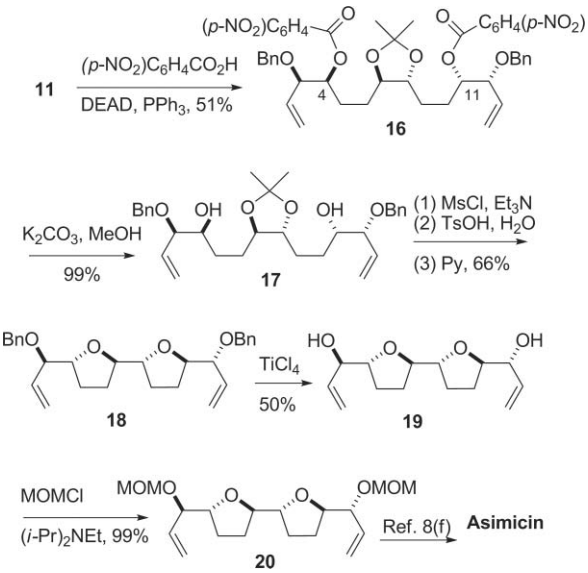

Scheme 4 Synthesis of *threo*/*trans*/*threo*/*trans*/*threo* bis-THF.

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