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Synthesis of Nonadjacently Linked Tetrahydrofurans: An Iodoetherification and Olefin Metathesis Approach

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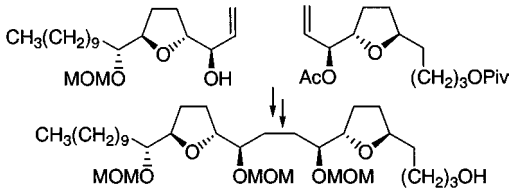
ABSTRACT



A convergent approach to the synthesis of the bis-tetrahydrofuran (THF) components of the nonadjacently linked THF-containing acetogenins is illustrated in the synthesis of 2, a potential intermediate for the antitumor agent bullatanocin (squamostatin C). The plan centers on the olefin cross-metathesis of THF allylic alcohol derivatives 3 and 4 as the key segment coupling step and the assembly of 3 and 4 through the iodoetherification of 1,2-*O*-isopropylidene-5-alkene precursors.

Tetrahydrofuran (THF)-containing acetogenins have attracted interest because of their potent antitumor activities.[1] There are three main structural types, classified according to the THF substructure: mono-THFs, adjacently linked bis-THFs, and nonadjacently linked bis-THFs. While there are several total syntheses in the first two groups,[2] nonadjacently linked structures are relatively unexplored.[3,4] Approaches to these structures are, in general, limited by very lengthy linear sequences. Herein we illustrate in the synthesis of **2** the bis-THF core of bullatanocin (squamostatin C) **1**,[5] a convergent strategy for nonadjacently linked THF-containing acetogenins (Scheme 1). Bullatanocin shows ED_{50} of less than 10^{-8} μg/mL against the colon cell line HT-29 and the lung cell line A-549, which is over 10 000 times the activity of adriamycin. Typical of the nonadjacently linked THFs, bullatanocin contains two THF rings connected by a 1,4-dihydroxybutyl linker. Our synthetic plan centers on the construction of this bis-THF-diol segment via an olefin cross-metathesis (CM) of THF-allylic alcohol components **3** and **4**.[6,7] An attractive aspect of this strategy is the convergent assembly of the bis-THF from two relatively simple mono-

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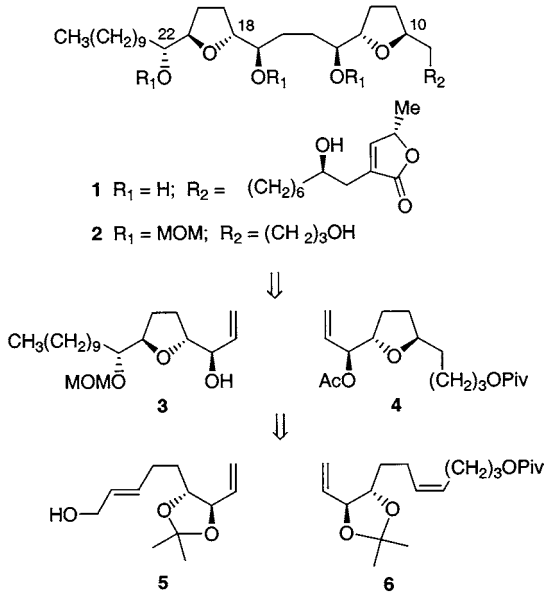
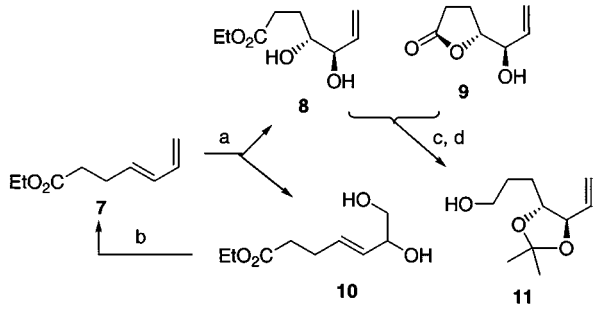
Scheme 1



THF components. We envisaged that the latter would be accessible via application of our iodoetherification methodology on the 1,2-*O*-isopropylidene-5-alkene precursors **5** and **6**, respectively.[8] The pseudo-antipodal relationship between **5** and **6** suggested the possibility for enantiodivergent syntheses of these materials.

Synthesis of 1,2-*O*-Isopropylidene Alkenes 5 and 6. The synthesis of **11** and *ent*-**11**, the precursors for **5** and **6**, respectively, started from the asymmetric dihydroxylation of ethyl (*E*)-4,6-heptadienoate[9] (Scheme 2). For **11**, the AD-

Scheme 2 [a]

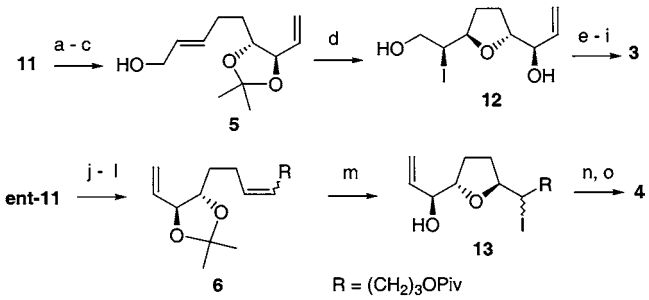


[a] Reaction conditions: (a) AD-mix-β, *t*-BuOH−H_2O, $MeSONH_2$, **8**/**9** (47%), **10** (51%); (b) Ph_3P, I_2, Imidazole, CH_2Cl_2, 71%; (c) DIBALH, THF, −78 °C; (d) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, 87%, two steps.

mix-β-mediated dihydroxylation of the 1,3 diene **7**[10,11] provided an approximately 1:1 ratio of products resulting from dihydroxylation of the E and terminal alkenes. The desired material consisting of a mixture of diol **8** and the derived lactone **9** was obtained in 47% combined yield. The optical purity of diol **8** as determined by Mosher ester analysis was greater than 92%.[12] The undesired diol **10** could be recycled to **7** in a single step by treatment under conditions for alcohol iodination. Reduction of the mixture of **8** and **9** with DIBALH, followed by acetonation of the resulting triol, afforded **11**, the precursor to **5**. Similarly, using AD-mix-α instead of AD-mix-β afforded *ent*-**11** in similar yields, in greater than 95% ee. Thus, **11** and *ent*-**11** were easily available in three straightforward steps from **7**.

Alcohols **11** and *ent*-**11** were next converted to their aldehyde derivatives and subjected to Wittig olefination with $Ph_3P{=}CHCO_2Me$ and $Ph_3P{=}CH(CH_2)_3OLi$, respectively.[13] DIBALH reduction or pivalylation of the individual olefination products provided the isopropylidene alkene precursors **5** and **6**. Alkene **5** was obtained as a single (*E*)-isomer in 77% overall yield from **11**. Alkene **6** was obtained as a 3:1 *Z*:*E* mixture, in 61% from *ent*-**11**.

Scheme 3 [a]



[a] Reaction conditions: (a) PCC, CH_2Cl_2; (b) $Ph_3P{=}CHCO_2Me$, 79% (two steps); (c) DIBALH, CH_2Cl_2, −78 °C, 97%; (d) IDCP, CH_3CN, 89%; (e) K_2CO_3, MeOH, 91%; (f) TBDMSCl, imidazole, CH_2Cl_2, 90%; (g) $CH_3(CH_2)_8MgBr$, CuBr, THF, 82%; (h) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 98%; (i) Bu_4NF, THF, 92%; (j) Swern oxidation, 89%; (k) $Ph_3P{=}CH(CH_2)_3OLi$, toluene, −78 °C, 83%; (l) PivCl, pyridine, DMAP, 82%; (m) as in d, 79%; (n) Bu_3SnH, toluene, AIBN, reflux, 82%; (o) Ac_2O, EtOAc, DMAP, 86%.

Synthesis of THF-Alkene Subunits 3 and 4. Iodoetherification reactions of **5** and **6** were carried out using iodonium dicollidine perchlorate (IDCP) in wet acetonitrile. The

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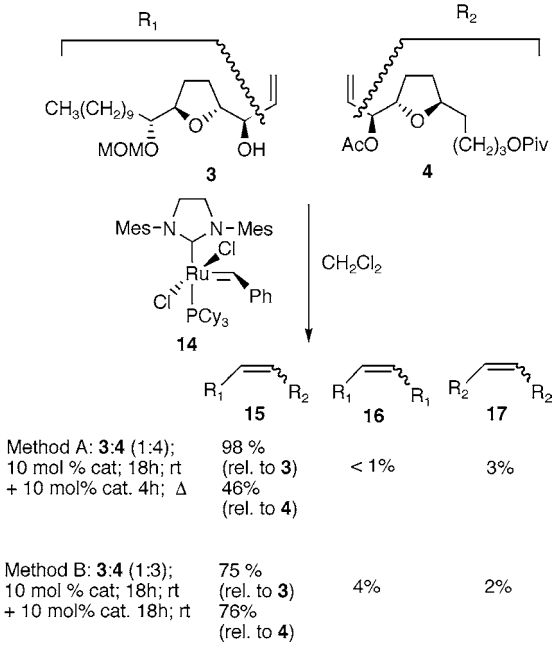
reaction of **5** gave a single trans THF **12** in 89% yield. The cyclization of the alkene mixture **6** led to a mixture of THF diastereomers **13** (79%). The ratio of trans and cis THFs was determined to be 11:1 from ^{1}H NMR analysis of the deiodinated derivative of **13** (vide infra). By comparison, the iodocyclizations of the vicinal diol derivatives of **5** and **6** showed low stereoselectivity (trans:cis = 4:1 and 7:3, respectively). THF stereochemistry was assigned on the basis of the stereoselectivity observed for very similar substrates,[6,14] and by comparison of the ^{13}C NMR of selected THF derivatives with the corresponding data for cis and trans THF reference compounds.[15]

The THF products **12** and **13** were next transformed to the precursors for the metathesis step. Iodohydrin **12** was converted to the silyoxy-epoxide derivative by treatment with sodium methoxide, followed by alcohol silylation. Reaction of this epoxide with nonylmagnesiumbromide in the presence of copper(I) bromide, followed by processing of alcohol protecting groups in the product, gave the THF subunit **3**, in 61% overall yield from **12**. The mixture of iodides **13** was transformed to a single THF isomer **4** in two straightforward operations: Bu_3SnH reduction of the iodide, followed by acetylation of the secondary alcohol, and chromatographic separation of the minor, cis isomeric product at each step.

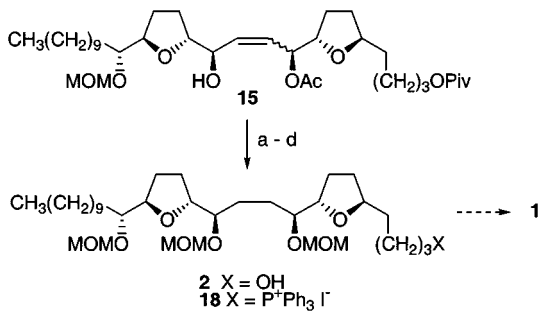
Cross metathesis of **3** and **4**. Our initial plan for the coupling of **3** and **4** was a segment-tethering−ring-closing metathesis (RCM) protocol.[7] However, this approach was severely hampered by low yields in the RCM step and in the synthesis of the tethered precursor. For these reasons, as well as the inherent experimental simplicity, a cross-metathesis strategy was pursued. However, homodimer formation presented a potential problem with this approach. In view of the deactivating effect of allylic alcohol esters in olefin metathesis reactions,[6b] we speculated that the reaction of an allylic alcohol (e.g., **3**) and an excess of the allylic ester partner **4** would provide the heterodimer **15** as the predominant metathesis product, and the unreacted ester **4**.[16] The homodimers **16** and **17** are disfavored on the basis of statistical and reactivity considerations. The combination of excess ester **4** with alcohol **3** (as opposed to the pairing of an excess of the acetate of **3** and the alcohol precursor to **4**) was preferred, because **4** is more easily prepared than the acetate of **3**. Accordingly, metatheses of alcohol **3** and varying molar equivalents of acetate **4** were performed for different catalyst concentrations, reaction temperatures, and reaction times. Two procedures were found to be practical. In method A, a 1:4 ratio of **3**:**4** and 10 mol % catalyst (relative to alcohol **3**) was stirred at room temperature for 18 h. A second batch of catalyst was then introduced and stirring continued at this temperature for an additional 18 h. Under these conditions, the heterodimer **15** was obtained as the major product together with unreacted alcohol **3** and acetate **4** (86 and 48% consumption, respectively). The yield of **15** (E:$Z \approx 3$:1) was 98 and 46% on the basis of consumed **3** and **4**. A small amount of homodimer **17** (3%) was also observed. The homodimer **16** was not detected. Method B was similar to A, except for the molar ratio of **3**:**4** (1:3 vs 1:4) and the conditions after addition of the second batch of catalyst (18 h at reflux vs 18 h at room temperature). These conditions led to heterodimer **15** in 75 and 76% yield on the basis of **3** and **4** (67 and 100% consumption, respectively). Homodimers **16** and **17** were also obtained in 2 and 4% yields, respectively. The kinetic and thermodynamic effects that underpin these results remain to be elucidated.

Bis-THF **15** was next converted to the primary alcohol **2**, a precursor for phosphonium salt **18** that would be required for a Wittig approach[17] to bullatanocin. Thus, hydrogenation of alkene **15**, followed by selective hydrolysis of the acetate, formation of the bismethoxymethyl ether of the derived diol, and finally removal of the pivalate ester afforded alcohol **2**. In summary, a convergent synthesis of nonadjacently linked THFs that uses an olefin cross-metathesis as the segment-coupling reaction has been illustrated. Attractive aspects are the simplicity of the coupling reaction, the easy accessibility of the reaction precursors, and the potential for application

Scheme 4



Scheme 5 [a]



[a] Reaction conditions: (a) H_2, Pd/C, EtOAc, 97%; (b) K_2CO_3, MeOH, 91%; (c) MOMCl, ^{i}Pr$_2$NEt, CH_2Cl_2, (d) NaOMe, MeOH, 95%, two steps.

of the method to libraries of bis-THF compounds. The transformation of **2** to bullatanocin and extension of the cross-metathesis concept to other structural motifs are currently underway.

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Supporting Information Available: Experimental procedures and NMR and MS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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