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Stereoselective synthesis of bis-hydroxy-tetrahydrofurans using cross metathesis☆

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Abstract—A short asymmetric approach for the synthesis of bis-tetrahydrofuran units of various annonaceous acetogenins is described. The key steps of the synthesis are self-cross metathesis and Sharpless asymmetric dihydroxylation.
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The annonaceous acetogenins are a family of almost 400 natural products, which have been found in 37 different species of annonaceous plants.[1] A remarkably broad spectrum of biological activity has been reported for these agents, including cytotoxic, antitumor, antimalarial, pesticidal, antifeedent and most importantly, in vivo antitumor behavior. They have also been shown to be active against multidrug-resistant tumors.[1] Biogenetically, the acetogenins are characterized by a long lipophilic tail, a central polyoxygenated core, and a terminal α,β-unsaturated γ-lactone. Diversity within this family arises principally from variations in stereochemistry, the location of the THF and THP units and various hydroxylation patterns.[1,2]

An important structural feature that appears in most of the annonaceous acetogenins having high biological activity is a C_{10} fragment containing two adjacent bis-THF groups, flanked by two hydroxy groups. Usually the two THF rings are linked in a *threo* arrangement with trans substituents at the 2,5-positions. Owing to their biological activity and limited availability from natural sources, these compounds have attracted worldwide attention and have been the targets of total synthesis for a number of groups.[3] The crucial component in the synthesis of any of these natural products is the stereoselective preparation of the polyoxygenated central fragment, that is, the adjacent dihydroxy bis-THF unit (Fig. 1). Taking the above into consideration along with our continued interest in metathesis reactions,[4] we envisaged the bis-tetrahydrofuran unit **1**, as a precursor of the acetogenins, which could be synthesized via cross metathesis.[5,6] The self-metathesis reaction is one of the more successful tools for constructing C_2 symmetric compounds by dimerization of single molecules.

The synthesis of **1** started from known optically pure epoxide **3**, prepared from readily available L-ascorbic acid.[7] Regioselective opening of epoxide **3** using allylmagnesium bromide gave homoallylic alcohol **4** in good yield. The key cross metathesis reaction of olefin **4** using Grubbs' first-generation olefin metathesis catalyst (10 mol %) afforded the C_2 symmetric compound **8** as an inseparable *E*, *Z* mixture of isomers in a ratio of 85:15.[8] In order to improve the *E*-selectivity,[5] the cross metathesis reaction was carried out with substrates **5** and **6**, which possesses electron withdrawing groups to give compounds **7** and **9** in good yields with *E*:*Z* isomer ratios of 93:7 and 70:30, respectively.[8] From the above comparative study it was interesting to note that acetate protection gave the best *E*/*Z* isomer ratios (in favor of the *E*-isomer). Accordingly, compound **7** upon treatment with K_2CO_3 in MeOH gave C_2-symmetric diol **8**, which was converted to di-tosylate **9** using *p*-toluenesulfonyl chloride and triethylamine in DCM. Compound **9** upon Sharpless asymmetric dihydroxylation (SAD) using AD-mix-β afforded exclusively diol **10**.[9] Finally, cyclisation of **10** using NaH in THF furnished

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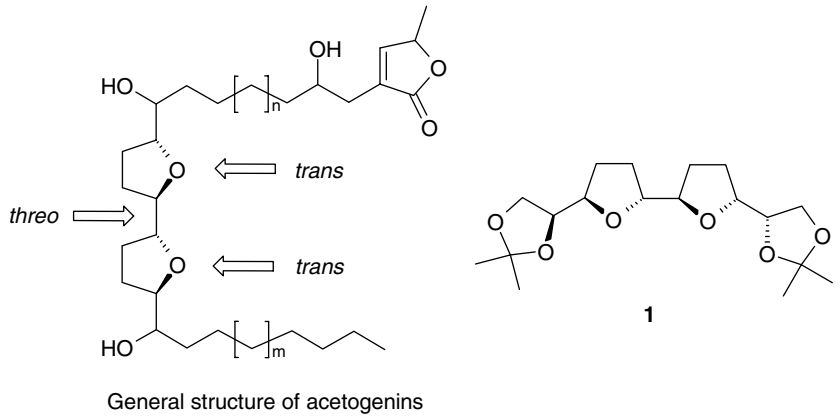
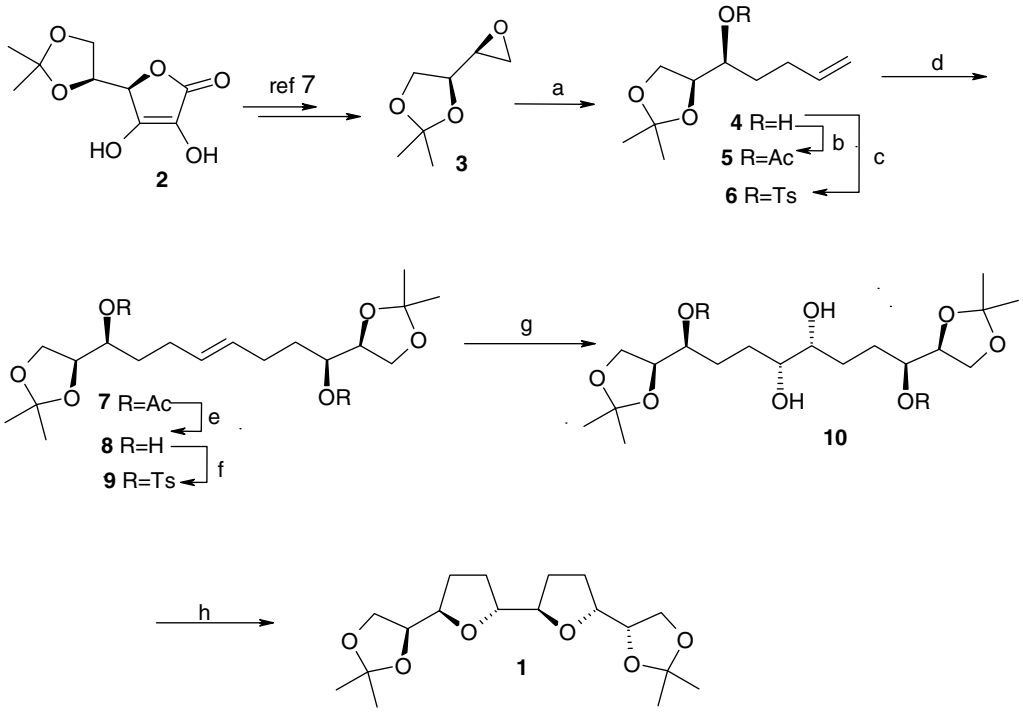


Figure 1.



Reagents and conditions: (a) CH_2=CH-CH_2MgBr, CuI, ether, -20 °C, 12 h, 85%; (b) $(CH_3CO)_2O$, TEA, DMAP, DCM, 0 °C to rt, 3 h, 90%; (c) *p*-TsCl, TEA, DMAP, DCM, 0 °C to rt, 24 h, 87%; (d) 10 mol% Grubbs' 1st generation catalyst, DCM, 40 °C, 12 h, for **7** 90%,for **8** 85%, for **9** 82%; (e) K_2CO_3, methanol, 0 °C to rt, 2 h, 85%; (f) *p*-TsCl, TEA, DMAP, DCM, 0 °C to rt, 36 h, 87%; (g) AD mix-β, H_2O: *t*-BuOH (1:1) 0 °C, 12 h, 85%; (h) NaH, THF, 0 °C to rt, 6 h, 80%;

the desired compound **1** after column chromatography as a light yellow syrup in 80% yield.[10]

In conclusion, we have demonstrated a short asymmetric approach for the synthesis of a dihydroxy bis-tetrahydrofuran unit via cross metathesis. It was also observed in the above case that the presence of an acetate protecting group gave a better *E*/*Z* isomer ratio in comparison to a tosyl group and the unprotected hydroxyl group in cross metathesis. An extension of this study for the synthesis of annonaceous acetogenins is in progress.

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References and notes

1. Recent review, see: Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.
2. Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066.
3. (a) Nattrass, G. L.; Diez, E.; Mclachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580, and references cited therein; (b) Jennifer, M. T.; William, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818; (c) Yan-Tao, H.; Song, X.; Tai-Shan, H.; Zhu-Jun, Y. *Tetrahedron Lett.* **2005**, *46*, 5393.
4. (a) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915; (b) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5103; (c) Madhan, A.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 564; (d) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049.
5. Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
6. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
7. Elie, A.; Purushotham, V.; Robert, W. L.; Haribansh, K. S.; Amarendra, B. M.; David, C. J.; Racha, S.; Raymond, P. P. *J. Org. Chem.* **1988**, *53*, 2598.
8. The *E*:*Z* isomer ratios of compounds **7** and **8** were determined by GC–MS and by ^{1}H NMR spectroscopy for compound **9**.
9. SAD generally gives excellent ee's in the case of C_2 symmetric *E*-olefins. (a) Kolb, H. C.; Van Nieuwenhze, S. M.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Li, P.; Yang, J.; Zhao, K. *J. Org. Chem.* **1999**, *64*, 2259; (c) Wagner, H.; Koert, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1873.
10. Analytical data for compound **1**: $[\alpha]_D^{28}$ −11.0 (*c* 1.25, $CHCl_3$); IR ν_{max} (neat): 2984, 2878, 1370, 1254, 1214, 1063, 849 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$: δ 4.04 (dd, 2H, $J = 5.6$, 8.0 Hz), 3.93–3.76 (m, 8H), 2.16–2.04 (m, 2H), 2.01–1.87 (m, 2H), 1.83–1.66 (m, 4H), 1.37 (s, 6H), 1.31 (s, 6H); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 109.2, 82.0, 80.5, 77.9, 67.6, 28.6, 28.2, 26.6, 25.3; EIMS: 327 $[M-15]^+$; ESI-HRMS: calcd for $C_{18}H_{31}O_6$ $[M+H]^+$ 343.2120, found 343. 2114.