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Stereocontrolled Synthesis of the Tetrahydrofuran Unit of Annonaceous Acetogenins

Keqiang Li,[1,2] Shikha Vig,[2] Fatih. M. Uckun[1*]

Drug Discovery Program[1] and Department of Chemistry[2]

Wayne Hughes Institute, Roseville, MN 55113

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Abstract: The THF-epoxide **8** has been prepared from benzyl (*R*)-(-)-glycidyl ether using a 10-step synthetic scheme in a stereocontrolled fashion. Compound **8** is a highly useful synthon for the synthesis of mono- and di-THF acetogenins. This new synthetic approach can also be applied to the generation of large chemical libraries of acetogenins.

Since the first discovery of uvaricin in 1982,[1] more than 220 annonaceous acetogenins have been reported. Considerable attention has been paid to this class of naturally occurring polyketide-derived fatty acids due to their pleiotropic biological activities, including their immunosuppressive and anti-neoplastic properties.[2] Acetogenins are chiral compounds frequently containing 1-3 tetrahydrofuran (THF) rings in the center of a long hydrocarbon chain. The stereochemistry of the substituted THF rings may affect the activity of acetogenins since it has been noticed that different stereoisomers of acetogenins display strikingly different biological activity profiles.[2a] However, very little is known about the structure-activity relationships contributing to these differences.[2a] Therefore, we set out to generate large chemical libraries of different stereoisomers of these compounds and elucidate the structure-activity relationships.

Earlier reports described schemes for total synthesis of mono- and di-THF acetogenins.[3] However, very few synthetic strategies yielding the central core THF-unit of mono-THF containing acetogenins are stereoselective and therefore require separation of the key diastereomeric intermediates.[4] We have now developed an efficient and stereocontrolled approach to synthesize the central core THF-unit of mono-THF containing acetogenins which allows each stereogenic center around the THF ring to be controlled.

The synthesis starts from benzyl glycidyl ether, which is commercially available in both enantiomers (Scheme 1). The epoxide in benzyl (*R*)-(-)-glycidyl ether is first opened with allyl magnesium bromide to provide a single regioisomer of homoallylic alcohol **1**. The hydroxyl group is then protected as the corresponding ethoxy ethyl ether and the terminal double bond is transformed into the aldehyde **2** under oxidative cleavage conditions. The aldehyde is converted to the pure (*E*)-α,β-unsaturated ester **3** via the Wittig-Horner reaction[5] and the ester group is then reduced to the corresponding allylic alcohol **4** using

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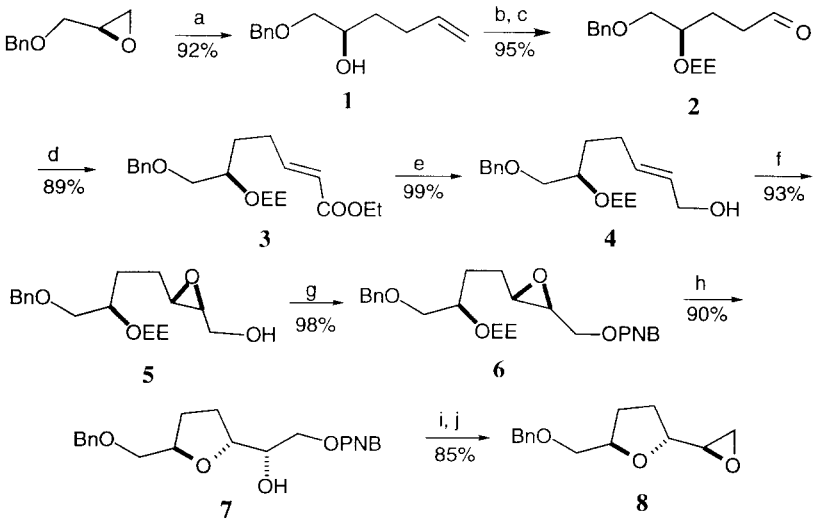
diisobutylaluminum hydride. Sharpless asymmetric epoxidation[6] using (L)-(+)-diisopropyl tartrate provides the corresponding epoxy alcohol **5** as the only diastereomer which can be detected by NMR spectroscopy.[7]

The hydroxyl group is then converted to benzoate **6** and the removal of the ethoxy ethyl ether group as well as the key ring-closure step are achieved in one step by treating compound **6** with Dowex resin in methanol to provide compound **7** as a single diastereomer, as determined by NMR analysis.[8] Epoxide formation is then accomplished by first transforming the secondary hydroxyl group into a mesylate followed by the treatment of the intermediary benzoate-mesylate compound with sodium methoxide in methanol to yield the corresponding THF-epoxide compound **8**.[9]

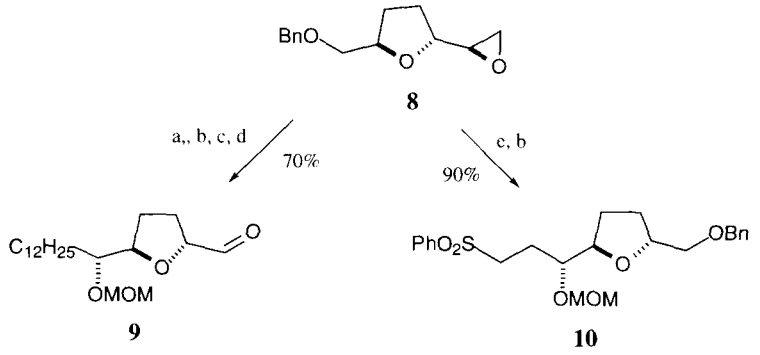
Scheme 1



(a) AllylMgBr, CuBr (cat.), THF, 0°C; (b) EVE, H^+, CH_2Cl_2 ; (c) OsO_4 (cat.), NMO, then $NaIO_4$, THF-H_2O; (d) $EtOCOCH_2P(O)(OEt)_2$, NaH, DME-benzene, 0°C; (e) DIBAL-H, CH_2Cl_2, -78°C; (f) L-(+)-DIPT, $Ti(OPr\text{-}i)_4$, TBHP, CH_2Cl_2, -25°C; (g) PNBCl, TEA, CH_2Cl_2; (h) Dowex-50, MeOH; (i) MsCl, TEA, CH_2Cl_2, 0°C; (j) NaOMe, MeOH, 0°C.

Compound **8** is a highly useful synthon since the epoxide can easily be opened by different nucleophiles leading to structures with a fixed stereochemical relationship around the THF-ring unit. For example, we have used undecylmagnesium bromide and methyl phenyl sulfone as nucleophiles and prepared compounds **9** and **10**[10] using the reaction sequence shown in Scheme 2. Both compounds **9** and **10** are useful intermediates for the synthesis of naturally occurring mono- and di-THF acetogenins. Compound **9** is the key intermediate used in the total synthesis of corossolone.[3d] Other members of mono-THF acetogenins possessing a threo-*trans*-threo stereochemistry around the THF ring could also be synthesized by chelation controlled addition of functionalized Grignard reagents to compound **9**.[11] Efforts toward the synthesis of non-adjacent di-THF acetogenins through the coupling of compounds **9** and **10** are underway in our laboratory.

Scheme 2



(a) $C_{11}H_{23}MgBr$, CuBr (cat.), THF, 0°C; (b) MOMCl, DIPEA, CH_2Cl_2;
(c) H_2, Pd/C, EtOAc; (d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78°C;
(e) $PhSO_2CH_3$, BuLi, BF_3-OEt_2, THF, -78°C.

In conclusion, we have developed an efficient procedure for the stereocontrolled synthesis of the THF ring units in annonaceous acetogenins. This new synthetic approach offers several advantages over previously described strategies. First, both enantiomers of benzyl glycidyl ether are commercially available and the stereochemical outcome in the Sharpless asymmetric epoxidation step can be selected by the use of either enantiomer of diisopropyl tartrate. Furthermore, the stereochemical outcome for the final epoxidation can also be varied by derivatizing either the primary or the secondary hydroxyl group into a leaving group. This approach can yield 8 stereoisomeric THF-epoxides which can be coupled with a variety of nucleophiles and thereby provide the opportunity to generate large chemical libraries of mono-THF containing acetogenins.

References and Notes

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7. Satisfactory analytical and spectroscopic data were obtained for all compounds reported in the paper.
8. Data for **7**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.69-2.09 (4H, m), 2.73 (1H, bs), 3.46-3.49 (2H, m), 4.09-4.12 (2H, m), 4.24-4.28 (1H, m), 4.34-4.40 (2H, m), 4.56-4.58 (2H, m), 7.33-7.35 (5H, m), 8.22-8.28 (4H, m); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 26.4, 28.5, 70.7, 72.0, 72.7, 73.3, 78.6, 79.3, 123.3, 127.3, 128.2, 130.6, 135.0, 137.9, 150.3, 164.6; IR (neat) ν_{max} cm^{-1}: 3241, 2873, 2356, 2335, 1726, 1347, 1291, 871.
9. Data for **8**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.67-1.93 (2H, m), 2.01-2.15 (2H, m), 2.68-2.78 (2H, m), 2.97-3.01 (1H, m), 3.46-3.48 (2H, m), 3.94-4.00 (1H, m), 4.18-4.26 (1H, m), 4.57 (1H, s), 7.27-7.35 (5H, m); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 28.3, 28.6, 44.0, 54.0, 72.5, 73.2, 78.4, 78.7, 127.3, 127.4, 128.1, 138.1; IR (neat) ν_{max} cm^{-1}: 2975, 2863, 1457, 1256, 1088, 886, 752; $[\alpha]_D^{22}$ -10.0 (c 0.2, $CHCl_3$); HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256 Found: 234.1259.
10. Data for **10**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.58-2.07 (8H, m), 3.23-3.35 (2H, m), 3.30 (3H, s), 3.44 (2H, d, J = 4.8 Hz), 3.55-3.61 (1H, m), 3.95-4.02 (1H, m), 4.10-4.16 (1H, m), 4.55 (2H, s), 4.59 (1H, d, J = 7.2 Hz), 4.72 (1H, d, J = 6.9 Hz), 7.26-7.93 (10H, m); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 24.5, 27.8, 28.4, 52.6, 55.7, 72.5, 73.1, 77.8, 78.2, 80.9, 96.8, 127.2, 127.3, 127.8, 128.1, 129.0, 133.4, 138.1, 138.8; IR (neat) ν_{max} cm^{-1}: 2928, 2892, 2356, 2338, 1447, 1308, 1146, 1031, 917, 748, 694.
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