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Stereoselective Synthesis of a Versatile Intermediate for the Total Synthesis of Mono- and Bis-THF Containing Annonaceous Acetogenins

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Abstract: Stereoselective synthesis of epoxy tetrahydrofuran (THF) **1**, a versatile synthetic precursor for mono-THF and bis-THF containing annonaceous acetogenins, is reported. Compound **1** was synthesized from tridecanal in 11 steps with an overall yield of 24%. The requisite configurations of the stereogenic centers in **1** were established by Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation. Formation of the THF-ring unit was accomplished by acid catalyzed epoxide ring opening and 5-*exo* cyclization reaction.

The diverse and potent biological activities displayed by the naturally occurring annonaceous acetogenins have prompted comprehensive efforts for their isolation, structural characterization, synthesis and biological evaluation. Since the first annonaceous acetogenin - uvaricin was reported in 1982,[1] more than 230 acetogenins have been isolated and identified from various annonaceous species.[2] Acetogenins display pleiotropic activities and show potential as anti-cancer, antiparasitic, antifungal, antimicrobial, immunosuppressive, and pesticidal agents.[2] Structurally, acetogenins possess a long chain C_{35} or C_{37} hydrocarbon skeleton featuring a terminal γ-lactone, a center unit containing 1 to 3 THF rings and several hydroxylated stereogenic centers along its carbon skeleton. The presence of multiple stereogenic centers in annonaceous acetogenins presents great challenge for their synthesis and structural characterization.[2,3] Despite their promising biological activity profile, very limited information is available regarding the structure-activity relationships that exist for this class of natural products.[4] Our interest in the mechanism of action and structure-activity relationships of mono- and bis-THF containing annonaceous acetogenins prompted us to develop a new synthetic approach for preparing versatile intermediates for their convergent synthesis. We report here the stereoselective synthesis of the epoxy THF **1**. Compound **1**, corresponding to the C_{16}-C_{34} unit of a C_{37} acetogenin or the C_{14}-C_{32} unit of a C_{35} acetogenin, can be converted to mono-THF and bis-THF containing acetogenins.

The commercially available long chain aliphatic aldehyde, tridecanal **2**, was extended to a γ,δ-unsaturated ethyl ester **4** by a two-step reaction sequence:[5] reaction with vinylmagnesium bromide to form allylic alcohol **3** followed by reaction with triethyl orthoacetate and a catalytic amount of propionic acid to form **4** via the Johnson-Claisen rearrangement.[6] The carbon chain of the γ,δ-unsaturated ethyl ester **4** was further extended by a four-step reaction sequence, commonly used in the application of Sharpless asymmetric epoxidation (AE), to form **8**.[7] The

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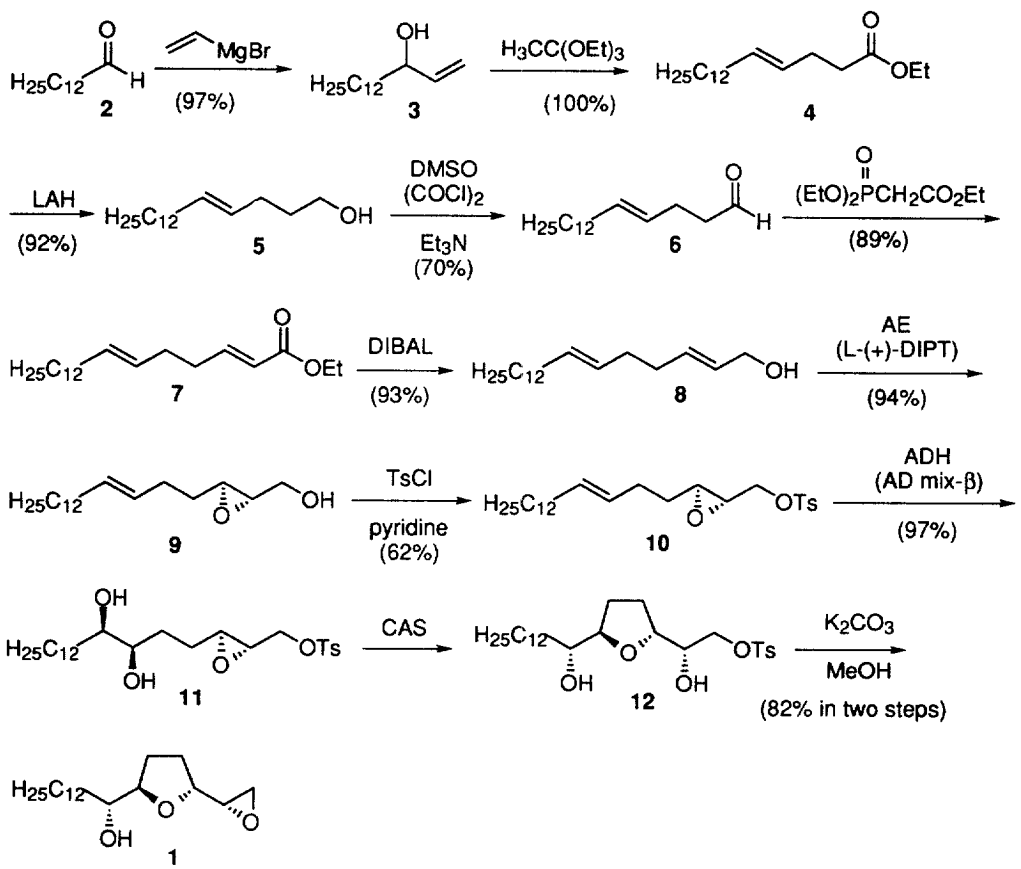
allylic alcohol **8** was converted to the epoxy alcohol **9** by Sharpless asymmetric epoxidation (AE) using diisopropyl L-tartrate (L-(+)-DIPT) as the chiral auxiliary.[7] The primary alcohol in **9** was converted to tosylate **10** which was subjected to Sharpless asymmetric dihydroxylation (ADH) by AD mix-β to form **11**.[8] The camphor sulfonic acid (CSA) catalyzed epoxide ring opening and simultaneously 5-*exo* cyclization of **11** afforded the desired THF unit in **12**. Treatment of **12** with K_2CO_3 in methanol afforded the epoxy THF **1**.[9]

Scheme 1.



In conclusion, compound **1** was synthesized in a straightforward fashion from the commercially available tridecanal **2** in 11 steps with an overall yield of 24%. The requisite configurations of the stereogenic centers in **1** were established by Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation.[3h] Formation of the 2,5-disubstituted THF-ring was accomplished by acid catalyzed epoxide ring opening and 5-*exo* cyclization

reaction. The epoxy THF **1** which is corresponding to the C_{16}-C_{34} unit of a C_{37} acetogenin or the C_{14}-C_{32} unit of a C_{35} acetogenin is a versatile synthetic precursor for mono-THF and bis-THF containing acetogenins. The epoxide group in **1** can be reacted with various nucleophiles. Furthermore, the stereogenic centers in **1** can easily be altered because: (i) the antipodes of the chiral auxiliaries used in our asymmetric induction steps are commercially available and (ii) the absolute configuration of the epoxide stereogenic center can be reversed by converting the secondary hydroxy group of the vicinal diol, instead of the primary hydroxy group, to a leaving group for the epoxide ring closure.

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9. Data for **1**: $[\alpha]_D^{23}$ +71.0° (c 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.83 (m, 1H), 3.37 (m, 1H), 2.99 (m, 1H), 2.78 (m, 1H), 2.60 (m, 1H), 2.25 (d, J = 3.5 Hz, 1H), 2.11-1.94 (m, 2H), 1.84-1.63 (m, 2H), 1.50-1.16 (m, 22H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 83.13, 78.50, 73.99, 53.26, 45.20, 33.52, 31.90, 29.64, 29.35, 28.40, 28.06, 25.62, 22.69, 14.13; GC/MS m/z 312 (M^+), 269, 199, 143, 125, 113; IR (neat) 3473, 2923, 2854, 1466, 1070 cm^{-1}.