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The Synthesis of Asimilobin and the Correction of Its Tetrahydrofuran Segment's Configuration

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Abstract

A highly efficient synthetic method for the *trans/threo/trans*- bis-tetrahydrofuran (THF) ring building block was established. The title compound was synthesized in thirteen steps from *trans*-1,4-dichloro-2-butene *via* a convergent route with a Wittig reaction as the key step. The absolute configuration of the THF segment of naturally occurring asimilobin should be corrected.

Keywords: Asimilobin; Sharpless AD; $Co(modp)_2$; Wittig Reaction

In recent years, the rapidly growing class of naturally occurring Annonaceous acetogenins has received considerable attention, due to their broad spectrum of biological activity such as cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal and immunosuppressive effects.[1] Asimilobin, a relatively rare bulladecin type acetogenin,[1] was isolated by McLaughlin's group both from the seeds of *Asimina triloba* [2] and the bark of *Goniothalamus giganteus* (Annonaceae),[3] and showed cytotoxicity values comparable with adriamycin against six human solid tumor cell lines. Its absolute configuration has been determined to be **1** by spectroscopic analysis (Figure 1). The striking characteristics are the adjacent *threo/trans/threo/trans* bis-THF ring and one flanking hydroxyl group at the α-position of THF core.

Although several total syntheses of adjacent bis-THF acetogenins bearing two flanking hydroxyl groups at the α,α′-positions have been reported,[4-8] no successful synthesis of those bis-THF acetogenins with only one flanking hydroxyl group has been achieved to date. Herein we wish to report our facile route to the first total synthesis of asimilobin.

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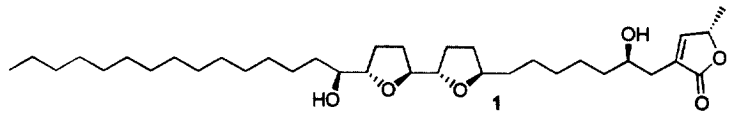
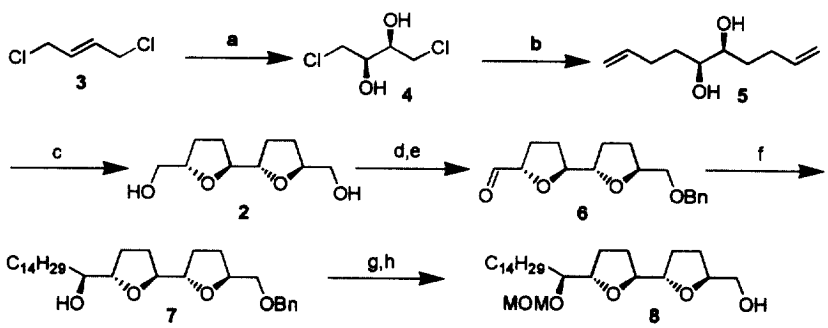
Figure 1



We had developed a highly efficient and stereocontrolled synthetic method to construct the *trans/threo/trans* bis-THF ring building block **2** in three steps (Scheme 1). Sharpless AD [9] reaction on the starting material **3** installed the two stereogenic centers, with greater than 94% ee, [10] in the bis-THF ring backbone. The resulting diol **4** was subsequently treated with NaH and allylmagnesium chloride in the presence of CuI to produce compound **5** in 79% yield. This was smoothly oxidized and cyclized to form a C_2-symmetrical bis-THF compound **2** in 78% yield using $Co(modp)_2$ [bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentane-dionato) cobalt(II)] [11] as a catalyst under an oxygen atmosphere. Compound **2** was confirmed to have 96% de by GC/MS analysis of its dimethyl ether derivative. To the best of our knowledge, this synthetic route is much shorter and more convenient than that reported in the literature [12] so far.

Scheme 1



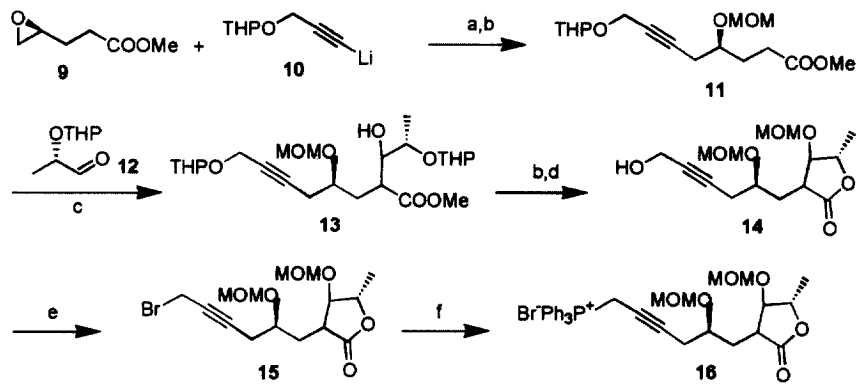
Conditions: a) $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, ^tBuOH:H_2O (1:1), 0 °C; 84%. b) 1) NaH, THF 2) allylmagnesium chloride, CuI, THF, -50°C; 79%. c) $Co(modp)_2$, TBHP, O_2, *i*-PrOH; 78%. d) NaH, BnBr, THF; 71%. e) Swern oxidation. f) $CH_3(CH_2)_{13}MgCl$, $CuBr{\cdot}SMe_2$, Et_2O, -78 -0 °C; 49% (two steps). g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2;87%. h) H_2, Pd/C, EtOH; 93%.

Mono protection of the diol **2** as a benzyl ether followed by Swern oxidation, gave the aldehyde **6**, which reacted with $CH_3(CH_2)_{13}MgCl$ in the presence of $CuBr{\cdot}SMe_2$ [13] affording the adduct **7** with diastereoselectivity (7.1:1) in 49% yield. Protection of the secondary alcohol **7** as a MOM ether, and subsequent removal of the benzyl group by catalyic hydrogenation over Pd/C gave the bis-THF segment **8** in 93% yield.

The preparation of the other segment **15** is shown in Scheme 2. The epoxide **9** [14] was opened by lithium alkynylide **10** in the presence of $BF_3{\cdot}OEt_2$ and the resulting alcohol was treated with MOMCl/*i*-Pr_2NEt to give **11**. Aldol condensation of the enolate of **11** and aldehyde **12** [15]

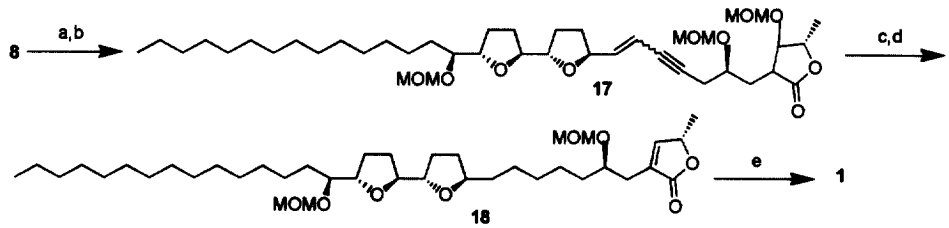
produced the compound **13** (mixture of diastereoisomers). Protection of the newly generated hydroxyl group in **13** as a MOM ether and treatment with 9% H_2SO_4:THF (1:3) afforded the lactone **14**.[15] Bromination of the propargyl alcohol **14** gave the segment **15**, which was then reacted with PPh_3 to afford the Wittig salt **16**.

Scheme 2



Conditions: a) $BF_3{\cdot}OEt_2$, THF, -78 °C; 83%. b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; 86%. c) LDA, THF, -78°C; then **12**; 80%. d) 9% H_2SO_4, THF; 65% (two steps). e) PPh_3, CBr_4, CH_2Cl_2; 89%. f) PPh_3, PhH, 87%.

Scheme 3



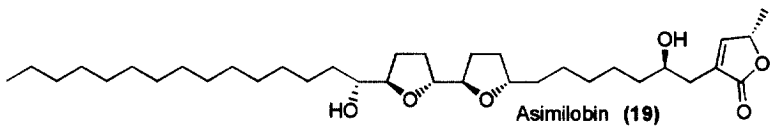
Conditions: a) Swern oxidation. b) **16**, ^tBuOK, THF, -78 -0 °C; 32% (two steps). c) Pd/C, H_2, EtOH. d) DBU,THF; 56% (two steps). e) $BF_3{\cdot}OEt_2$, DMS; 79%.

The coupling reaction between the aldehyde prepared from **8** *in situ* and the ylid prepared from **16** gave the enyne **17** (Z-isomer predominated) in 32% yield. Compound **17** was hydrogenated over Pd/C, and then treated with DBU to afford **18** in 56% yield. Deprotection of **18** with $BF_3{\cdot}OEt_2$ gave **1** in 79% yield.

The spectral data (^1H and ^{13}C nmr, HRMS) of the synthetic compound **1** are completely consistent with those reported for the title compound in literature.[2, 3] However, the specific rotation is opposite to that reported. {Our synthetic compound **1**: $[\alpha]_D^{20}$ -11.4 (c 0.70, $CHCl_3$), $[\alpha]_D^{26}$ -11.9 (c 0.43, CH_2Cl_2); Lit.[2] $[\alpha]_D$ +6.0 (c 0.05, $CHCl_3$); Lit.[3] $[\alpha]_D$ +11.3 (c 1.00, CH_2Cl_2)}. In order to clarify this problem, we immediately synthesized diastereoisomer **19** (Figure 2) using the enantiomer of segment **8** made via the same procedures as those mentioned

above. We found that **19** has the same spectral data and close specific rotation as that reported in literature. { $[\alpha]_D^{24}$ +6.4 (c 0.36, $CHCl_3$); $[\alpha]_D^{25}$ +7.0 (c 0.10, CH_2Cl_2) }. Thus, this work strongly suggests the natural product has the opposite absolute configuration on the bis-THF unit to that reported in the literature.

Figure 2



Asimilobin (**19**)

In conclusion, we have developed an efficient procedure for the stereocontrolled synthesis of adjacent *trans/threo/trans* bis-THF ring units and a convenient route to couple this key intermediate with other building blocks. The first total synthesis of the title compound has been achieved in thirteen steps from the starting material **3**. In order to disclose the relationship between structure and biological activity, syntheses of asimilobin analogs are in progress.

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Reference and Notes

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10. The ee of the resulting diol **4** {$[\alpha]_D^{20}$ +11.6 (c 1.70, CH_2Cl_2)} is determined by comparing the specific optical rotation with its opposite enantiomer {$[\alpha]_D^{19}$ -11.1 (c 2.75, CH_2Cl_2); Lit. $[\alpha]_D$ -11.7 (c 1.5, CH_2Cl_2)} reported in literature [Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469].
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