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An iterative acetylene–epoxide coupling strategy for the total synthesis of longimicin C

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Abstract—Longimicin C, a naturally occurring annonaceous acetogenin possessing a C_2-symmetrical bis-THF moiety and a short hydrocarbon chain between its THF-containing region and a terminal γ-lactone, was synthesized for the first time. The total synthesis was successfully achieved by an iterative acetylene–epoxide coupling strategy. D-Mannitol was used to establish the bis-THF-containing segment, in which the additional stereochemistries were introduced by Sharpless dihydroxylations and intramolecular Williamson etherifications. Regioselective epoxide-openings by the appropriate terminal acetylenes allowed coupling and elaboration of all four fragments including the introduction of three essential hydroxyls into the proper sites of the target skeleton.

Annonaceous acetogenins are a family of natural polyketides of over 350 members, which have been found in 37 different species of *annonaceous* plants.[1] A broad spectrum of biological properties have been reported for these agents including cytotoxic, antitumor, antimalarial, pesticidal and antifeedant activities. Biogenetically, annonaceous acetogenins are derivatives of long-chain fatty acids, in which THF (tetrahydrofuran) and/or THP (tetrahydropyran) ring(s) as well as butenolide moieties act as key structural features. Diversity within this family arises principally from variations of stereochemistry and location of the THF(s) and/or THP as well as with various patterns of hydroxylation.[1,2] Longimicin C (Fig. 1) was isolated together with other acetogenins from the leaves and twigs of *Asimina longifolia* K. These natural products present asimicin-like structures, where the THF rings are shifted along their hydrocarbon chains by four methylene units relative to each other.[3] Among these, the spacer for longimicin C, that is, the distance from the hydroxyl-flanked THF region to the γ-lactone ring is quite short. In comparing its bioactivity with one of its structural isomers parviflorin, longimicin C showed only moderate cytotoxicity against several human tumor cell lines. The only structural difference between these two acetogenins lies in the above mentioned hydrocarbon spacer length.[3] Therefore, synthetic studies on longimicin C and parviflorin which could facilitate structural modifications using the methods established during synthesis, would be of great value for structure–activity relationship studies of these acetogenins. For example, it may be of interest to examine the effects of hydrocarbon spacers. Longimicin C possesses a buteneolide terminus containing a hydroxyl group at the C-4 position and a dihydroxylated bis-THF unit within its chain. During the past decade, significant effort by us[4] and others[5,6] has been devoted to the total syntheses of annonaceous acetogenins, which has led to the establishment of many useful and efficient synthetic methodologies. Herein, we report the first synthesis of longimicin C through a two-directional strategy in the synthesis of bis-THF core as well as iterative acetylene–epoxide openings for coupling of all four fragments.

Our retrosynthetic analysis is outlined in Figure 1. In consideration of synthetic efficiency, the structural skeleton was divided into four parts with the aid of FGA (functional group addition) operations. As a result, three triple bonds replaced the corresponding C–C single bonds. Further disconnections were made on the above positions based on acetylene–epoxide opening reactions, resulting in segments **2**,[7] **3**,[8] **4** and **5**. One

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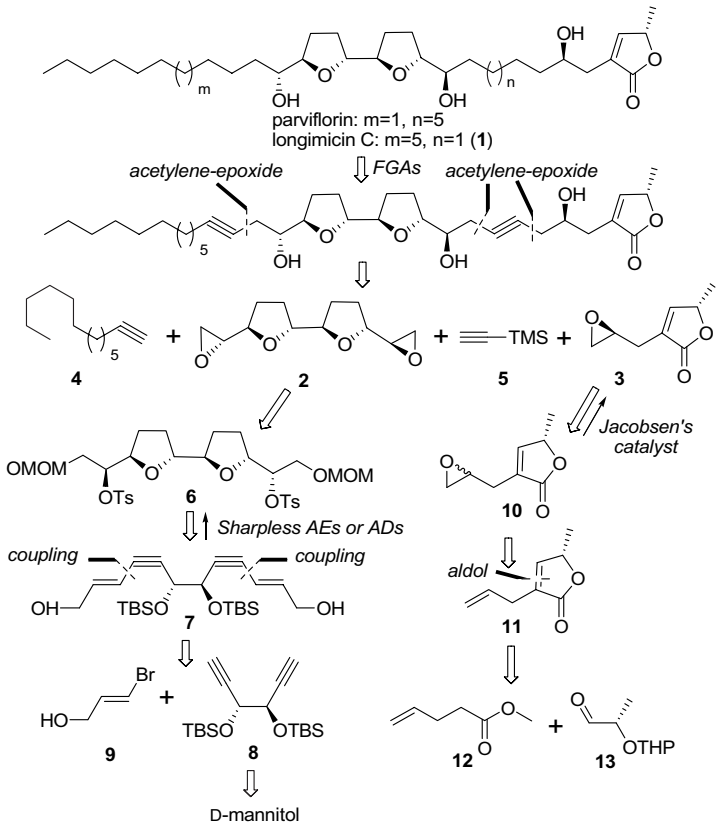
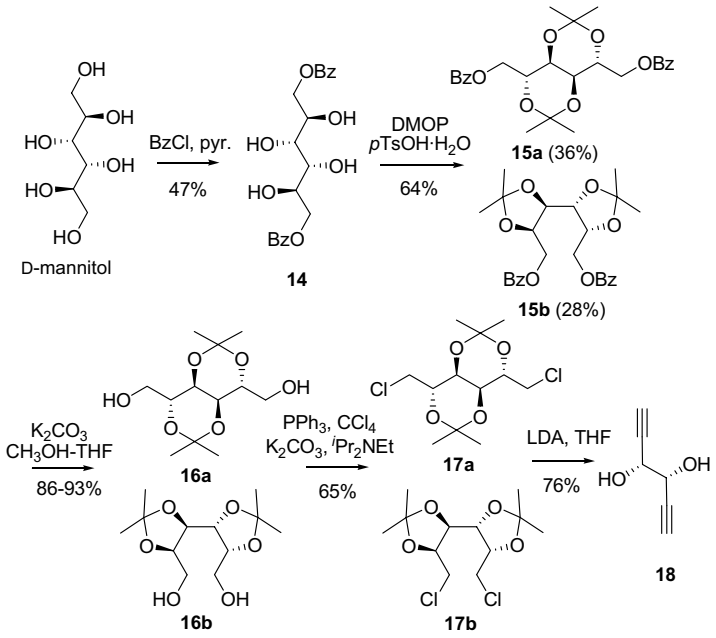


Figure 1. Structures of longimicin C and its isomer parviflorin, and retrosynthetic analysis of longimicin C.

key intermediate, the THF core **2**, has C_2 symmetry. It could be stereoselectively and bi-directionally constructed by Sharpless ADs[9] and intramolecular Williamson etherifications[10] starting from structure **7** or its equivalent. Symmetric allylic alcohol **7** was further disconnected into chiral alkyn-diol **8** and two units of 3-bromo-prop-2-en-1-ol **9**, both of which could be coupled by Sonogashiria reactions. The other key segment, γ-lactone **3**, could be prepared easily from compounds **12** and **13** according to our previously established procedure, where an aldol condensation and Jacobsen dynamic hydrolysis resolution served as key operations.[8]

The bis-THF-containing region of longimicin C is a major synthetic objective, in which multiple oxygenated stereogenic centers must be elaborated. Similar THF moieties are found not only in the annonaceous acetogenins but also in many other natural products.[11] Therefore, a wide array of methods have been established for the synthesis of various THFs. However, they are continuously supplemented by additional novel and efficient methods to prepare substituted and functionalized THFs, in particular those THFs that are not readily available through classical approaches. These methods include acid-induced ring closure of an epoxy alcohol, intramolecular hetero-Michael addition, metal-catalyzed oxidative cyclization of a hydroxyalkene, reduction of bicyclic ketals, oxabicyclic systems or spiro compounds, the intramolecular Williamson reaction, and [3+2] annulation of allysilanes and aldehydes, etc.[12] Considering the C_2 symmetry involved, our synthesis of bis-THF-containing segment **2** used D-mannitol, a commercially available and inexpensive chemical as starting material. A two-directional synthesis was adapted to substantially reduce the number of chemical operations. Development of such two-directional approaches would also be advantageous to apply to certain acetogenins in this family possessing similar C_2 symmetry in their bis-THFs central cores. Therefore symmetrical ene–yne **7** was envisaged as a pivotal intermediate. As the key substrate in this synthesis, compound **7** has two advantages: (1) its precursor compound **8** can be readily prepared from natural products in enantiomerically pure form (see Scheme 1) and (2) its construction from **8** can be easily achieved by Sonogashira reactions[13] with **9** in a single step.

Because the absolute configurations of both hydroxyls of hexa-1,5-diyne-3,4-diol **18** are consistent with those of D-mannitol (C3 and C4), the synthesis started from D-mannitol (Scheme 1). Treatment of D-mannitol 1,6-dibenzoate **14**[14] with a catalytic quantity of *p*-toluenesulfonic acid in 2,2-dimethoxypropane resulted in the formation of two cyclic acetals, **15a** and **15b**, which could be easily separable by column chromatography. Their structures were affirmed by their ^1H and ^{13}C NMR spectra, which fully agreed with the literature.[15] Of note, were the ^{13}C chemical shifts of the quaternary carbon at δ 109.8 ppm for **15a** and at δ 101.1 ppm for **15b**, respectively. The configuration of isomer **15a** was further confirmed by X-ray crystallographic analysis of derivative **17a**. Benzoates of compound **15** (both of **15a** and **15b**) were removed with K_2CO_3 in MeOH to afford diols **16a** and **16b**. Chlorination of **16a** and **16b**



Scheme 1. Synthesis of hexa-1,5-diyne-3,4-diol **18**.

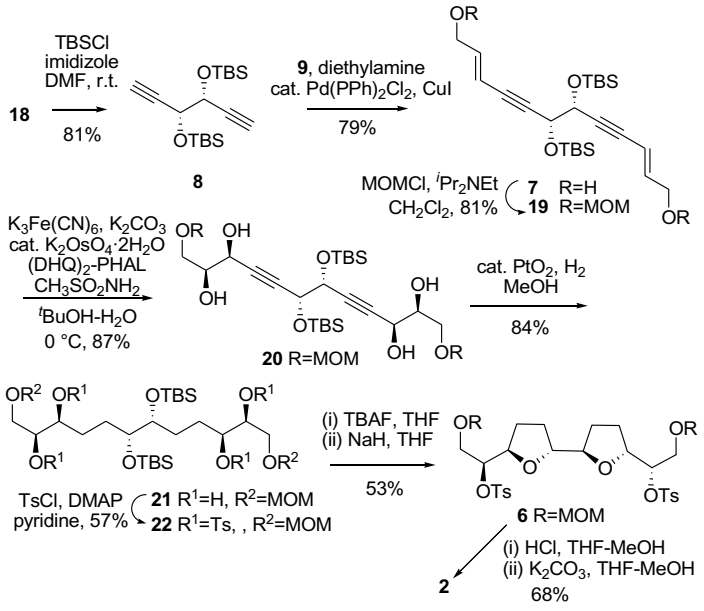
was then studied for an optimum chemical yield under a variety of conditions. Initial attempts using PPh_3 and CCl_4 with and without $NaHCO_3$ or K_2CO_3 as additive all led to lower yields of **17a** and **17b**. In contrast to these results, use of PPh_3 and CCl_4 in the presence of both K_2CO_3 and *N*,*N*-diisopropylethylamine greatly improved the transformation and provided **17a** and **17b** in a satisfactory yield. Diol **18** was obtained by elimination reactions of chlorides **17** using Yadav's conditions.[16] The enantiomeric purity of compound **18** was determined[17] prior to subsequent steps, though it has been stated that no epimerization takes place under Yadav's conditions.

The hydroxyls of diol **18** were protected as TBS ethers **8** before the coupling reaction. With both intermediates in hand, Sonogashira coupling of **8** and **9** (prepared from propargyl alcohol in two steps by Polt's protocol[18]) was carried out in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ and CuI in Et_2NH to afford the symmetric *E*-allylic alcohol **7** in good yield (Scheme 2). As a pivotal intermediate, bis-allylic alcohol **7** is very flexible. A variety of methods could be chosen for its further transformation, including dihydroxylation or epoxidation protocols. Finally, we decided to use Williamson's etherifications to elaborate the bis-THF rings and accordingly Sharpless asymmetric dihydroxylation was adopted to introduce the additional oxygenated centers into olefin **7**. MOM protected derivative **19** was subjected to Sharpless conditions using $(DHQ)_2PHAL$ as ligand to give tetraol **20** with a stereoselectivity of 20:1 per double bond (as determined by HPLC using a chiral column).

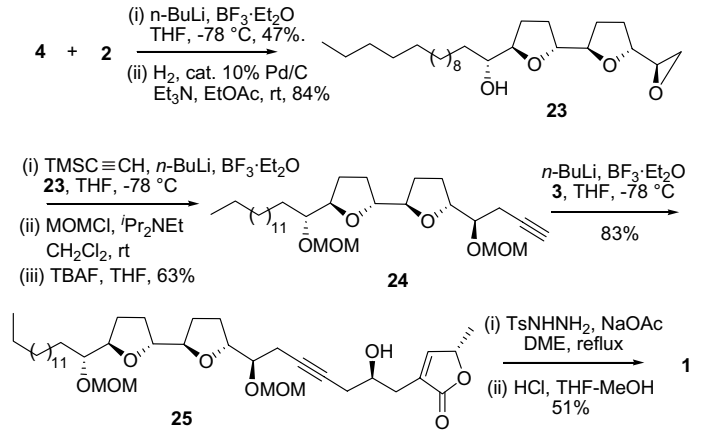
In order to obtain **22**, direct tosylation of **20** followed by reduction of the triple bond was attempted. However, this approach failed. Finally, reversing the order of the reactions was found to be successful (Scheme 2). Hydrogenation of the triple bonds of **20** followed by tosylation provided **22** in good yield.[19] It is noteworthy here, that hydrogenation of **20** catalyzed with 5% or 10% palladium on activated carbon did not give any desired product **21**, but resulted in severe side reactions. PtO_2 ultimately proved to be a good and effective catalyst for this reaction. Removal of TBS groups with TBAF and subsequent intramolecular Williamson reactions using NaH in THF resulted in THF ring formation to afford **6**, whose ^1H and ^{13}C spectra unambiguously showed its C_2 symmetrical characteristics. The key di-epoxide **2** was obtained after hydrolysis of the MOM ethers with aqueous HCl in MeOH–THF and cyclization with K_2CO_3 in MeOH. Both ^1H NMR spectrum and optical rotation of **2** are identical with those reported.[7]

The remaining key epoxide **3** was synthesized according to our previously reported procedures.[8] Excellent optical purity of epoxide **3** (dr >99:1, as determined by HPLC using a chiral column) was achieved by kinetic resolution of racemic epoxide **10** with Jacobsen's catalyst, (*S*,*S*)-salen-Co(OAc).[20] This method proved to be a useful approach for synthesizing the lactone unit of acetogenins having a C-4 hydroxyl group.

With all epoxides in hand, the original iterative coupling strategy was applied for segment assembly. The acetylene–epoxide coupling methodology is a powerful tool that is advantageous in terms of economics (identical reagents used) and ease of operation and duplication. Based on our previous analysis of longimicin C, regioselective epoxide openings[21] were devised not only to couple the four segments, but also to generate three new hydroxyls in the target molecule. The first operation was executed upon di-epoxide **2** using one-half equivalent of the alkyne **4** in the presence of *n*-BuLi and boron trifluoride etherate (Scheme 3). The triple bond of the



Scheme 2. Synthesis of bis-THF-containing segment **2**.



Scheme 3. Completion of total synthesis of longimicin C (**1**).

resulting product was immediately hydrogenated to provide mono-epoxide **23** (39% yield in two steps). Epoxide-opening of **23** with excess of trimethylsilyl acetylene **5** served as the second coupling operation to afford a diol intermediate. Protection of both free hydroxyls in this diol with MOMCl followed by removal of TMS furnished the desired terminal acetylene **24** in excellent yield (63% in three steps). The fully elaborated skeleton **25** was obtained by the same coupling protocol, in which alkyne **24** and epoxide **3** were joined under the same conditions. Finally, selective reduction of the triple bond with diimide and hydrolysis of the MOM ethers completed the total synthesis of longimicin C. All spectroscopic data of synthetic longimicin C were in full agreement with those reported for the natural sample.[3,22]

In summary, the first total synthesis of longimicin C has been achieved convergently. The bis-THF-containing segment was elaborated using D-mannitol as starting material with Sharpless dihydroxylations and intramolecular Williamson etherifications serving as key steps to establish additional stereochemistries. An iterative acetylene–epoxide coupling protocol was successfully applied in the couplings of all key segments, leading to the final construction of longimicin C. Expansion of the developed synthetic strategies will be explored in this laboratory for the synthesis of other structurally related annonaceous acetogenins, as well as for the design of new acetogenin mimetics of biological interest.

Acknowledgements

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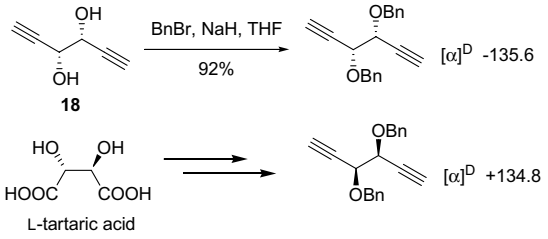
17. (a) Compound **18** was converted into the enantiomer of (3*S*,4*S*)-3,4-bis(benzyloxy)hexa-1,5-diyne, which was prepared by the known transformations from L-tartaric acid.[17b] The optical rotations of both enantiomers are matched each other.(b) Mukai, C.; Kasamatsu, E.; Ohyama, T.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 737.



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22. Data for synthetic **1**: $[\alpha]_D$ 11.3 (*c* 0.13, EtOH); lit. [3] $[\alpha]_D$ 14 (*c* 0.10, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (q, J = 1.8 Hz, 1H), 5.06 (qq, J = 6.9, 1.5 Hz, 1H), 3.86–3.88 (m, 1H), 3.81–3.86 (m, 4H), 3.37–3.41 (m, 2H), 2.52–2.54 (m, 1H), 2.40 (dd, J = 15.1, 8.1 Hz, 1H), 1.97–2.00 (m, 4H), 1.53–1.70 (m, 4H), 1.20–1.50 (m, 34H), 1.43 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.56, 151.77, 131.16, 83.16, 83.00, 81.78, 81.73, 77.93, 74.09, 73.82, 69.76, 37.20, 33.42, 33.37, 31.89, 29.70, 29.65, 29.62, 29.60, 29.58, 29.32, 28.92, 28.36, 28.33, 25.62, 22.65, 19.07, 14.01 ppm. HRMS (ESI, *m*/*z*) calcd for $(C_{35}H_{62}O_7+Na)^+$: 617.4388. Found: 617.4375.