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Enantioselective Total Synthesis of (−)-Walsucochin B

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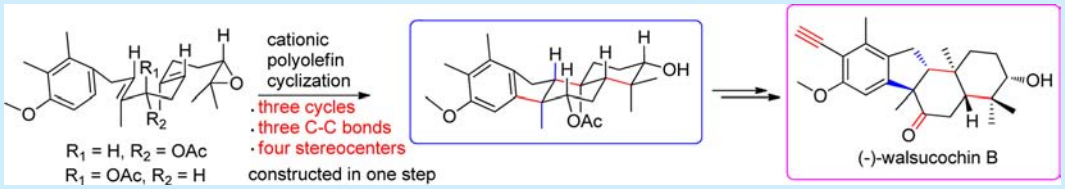
Supporting Information



ABSTRACT: The first enantioselective total synthesis of the structurally unique nortriterpenoid (−)-walsucochin B has been accomplished through the cationic polyolefin cyclization initiated by chiral epoxide. The core framework and the stereocenters in the natural product were all constructed in this step. A site-selective, late-stage free-radical halogenation and Seyferth−Gilbert homologation was adopted to install the acetylene moiety to synthesize the phenylacetylene. The absolute configuration of walsucochin B was confirmed through enantioselective total synthesis.

Walsucochins A and B (Figure 1, **1** and **2**) are the first examples of C_{24} nortriterpenoids featuring a phenyl-

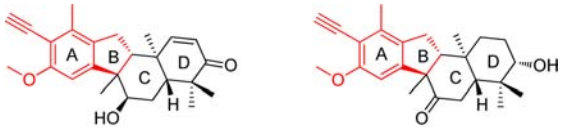


Figure 1. Structures of (+)-walsucochin A (**1**) and (−)-walsucochin B (**2**).

acetylene moiety fused onto a contracted five-membered ring. They were isolated from the leaves and twigs of *Walsura cochinchinensis* by Yue and co-workers in 2007.[1] The fused tetracyclic ABCD frameworks of the walsucochins not only include a common A/B ring but also a C/D ring system typical of the apotirucallane-type triterpenoids. The B/C ring is also trans-fused, which makes the whole molecules more torsionally inflexible and difficult to synthesize. Walsucochin B also has a 6/5/6/6 fused ring system with four continuous stereocenters (including two quaternary carbon centers) and a chiral hydroxyl group. The CD exciton chirality method was applied to determine the absolute configuration of walsucochin A, but the CD spectrum of walsucochin B did not provide convincing evidence that allowed assignment of its absolute configuration.

Biogenetically, walsucochin A and B coexist in the same plant and are probably produced via the same plausible biosynthetic pathway. The absolute configuration of walsucochin B is proposed to be the same as walsucochin A for biogenetic reasons. The two novel C_{24} nortriterpenoids exhibit significant cell protecting activity against H_2O_2-induced PC12 cell damage. Due to the unique structure and interesting biological properties of these molecules, we investigated these synthesis by a strategy that uses a cationic polyolefin cyclization initiated by chiral epoxide. This has led to the first enantioselective total synthesis of (−)-walsucochin B (**2**).

Our retrosynthetic analysis of (−)-walsucochin B (**2**) is outlined in Scheme 1. It was envisaged that the target molecule **2** could be obtained from the tetracyclic precursor **3** via oxidation and deprotection. Aldehyde **4** would be converted to **3** through a Seyferth−Gilbert homologation reaction. Aldehyde **4** could be obtained by site-selective bromination and oxidation of the methyl group in the tetracyclic precursor **5**. Considering the potential of cationic polyolefin cyclization in the assembly of polycyclic ring systems,[2] we envisaged that the unique 6/5/6/6 tetracyclic skeleton with a carbonyl group in the six-membered C ring could be constructed by a cation-initiated polyolefin cyclization. To our knowledge, the application of cationic polyolefin cyclization to synthesize such a 6/5/6/6 tetracyclic skeleton has been seldom reported previously.[3] The BCD rings would thus be produced in only one step in an efficient and concise way. The key polyolefin precursor epoxide **6** could be formed from compound **7**, which could be prepared from **8** and **9** by an allylation reaction in a convergent pathway.

Our synthesis began with the stepwise preparation of dithiane **8** and allylic bromide **9** (Scheme 2). Bromination[4] of the commercially available 2,3-dimethylanisole (**10**) afforded the aryl bromide **11** in 98% yield, which was subsequently treated with *n*-BuLi and reacted with ethylene oxide in THF at −78 °C to give the desired phenylethanol **12** in 82% yield.[5]

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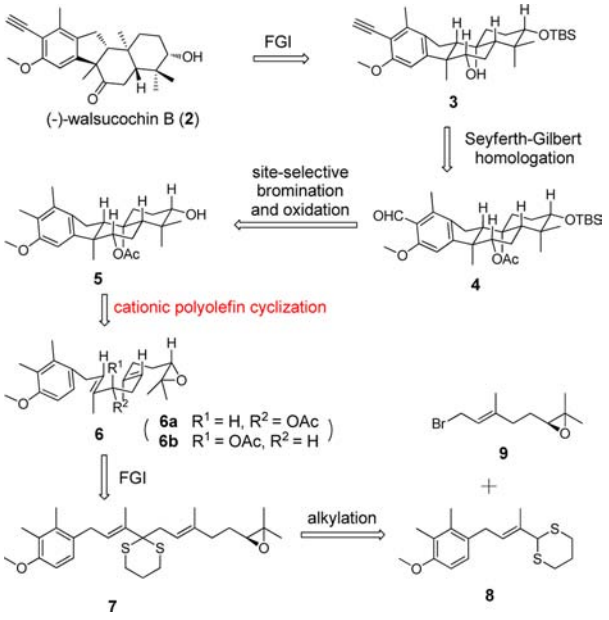
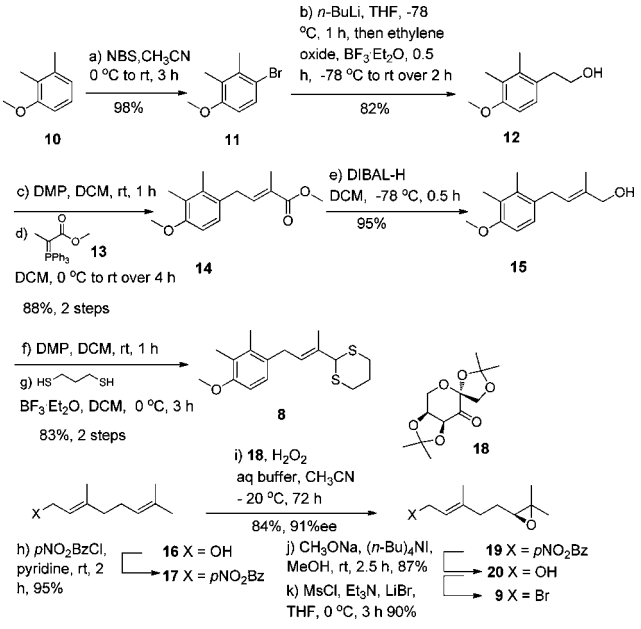
Scheme 1. Retrosynthetic Analysis of (−)-Walsucochin B (2)



Scheme 2. Synthesis of the Fragments 8 and 9

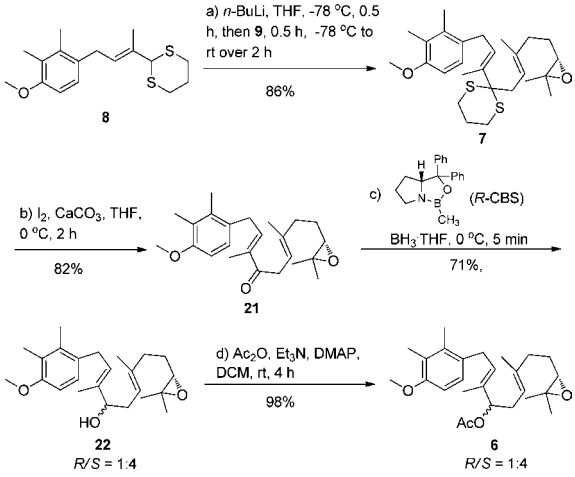


Oxidation of the primary hydroxy in **12** with Dess−Marin periodinane (DMP) followed by a Wittig olefination with methyl propionate ylide **13** delivered the α,β-unsaturated methyl ester **14** with high stereoselectivity (E/Z >99:1)[6] in 88% yield over two steps. The α,β-unsaturated ester **14** was reduced with DIBAL-H, and the allylic alcohol **15** was obtained in high yield. Oxidation of the allylic alcohol **14** with DMP produced an unstable α,β-unsaturated aldehyde, which was used in the next step without further purification. The aldehyde was immediately treated with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ at 0 °C, which led to dithiane **8**[7] in 83% yield over two steps.

Protection of geraniol (**16**) with *p*-nitrobenzoyl chloride (*p*-NO_2BzCl) gave the ester **17**, and a subsequent Shi asymmetric epoxidation[8] using the sugar-derived catalyst **18**[9] afforded the epoxide **19** in 84% yield with 91% ee. Saponification of ester **19** gave (*R*)-6,7-epoxynerol (**20**), which was then converted to the desired allylic bromide **9** via the corresponding mesylate. This allylic bromide **9** was also used in the next step without further purification.

Having efficiently synthesized the necessary fragments, we turned our efforts toward the coupling of allylic bromide **9** with the organolithium reagent derived from treatment of dithiane **8** with *n*-BuLi and afforded the desired polyolefin epoxide **7** in 86% yield (Scheme 3).[10] Subsequent dedithianation of **7** with I_2

Scheme 3. Synthesis of the Key Step Precursor 6 of the Cationic Polyolefin Cyclization



and $CaCO_3$ at 0 °C gave the α,β-unsaturated ketone **21** in 82% yield, and the epoxy group survived. Asymmetric reduction of the ketone **21** with the *R*-CBS reagent afforded the alcohol **22** in 71% yield.[11] ^{1}H NMR analysis indicated that **22** was an inseparable diastereomeric mixture (R/S = 1:4). Alcohol **22** was protected with an acetyl group to give the desired key cyclization precursor **6** as an inseparable mixture (R/S = 1:4) in 98% yield.[12]

With the stage set for our key cascade reaction, a variety of Lewis acids were used to probe the cationic polyolefin cyclization.[13] Pleasingly, the inseparable diastereomeric mixture of **6a** and **6b** could be converted to the corresponding core tetracyclic framework **5** as a single diastereomer via cationic polyolefin cyclization in the presence of Et_2AlCl in dichloromethane for 10 h at −78 °C in 62% yield (Scheme 4).[14] The proposed cyclization proceeds via a favored chair conformation. Notably, the cascade cyclization of **6a** gave the tetracycle skeleton as a single diastereomer, while the minor diastereomer **6b** could not undergo the cascade cyclization to give the corresponding product. This cascade reaction formed three C−C bonds, the 5/6/6 tricycle, and four contiguous stereocenters (two of which are all-carbon quaternary centers) established in one step. The tetracyclic alcohol **5** was subsequently reacted with 4-bromobenzoyl chloride (p-BrC_6H_4COCl) to give tetracyclic ester **23** in 93% yield. The structure and the relative configuration were confirmed by single-crystal X-ray diffraction analysis.[15]

Since we had constructed the core skeleton, only functional group interconversions remained to complete the synthesis of (−)-**1** (Scheme 5). Alcohol **5** was protected with TBSOTf, and ether **24** was obtained in 96% yield.[16] An initial attempt to directly transform **24** to aldehyde **4** by site-selective oxidation[17] of the requisite methyl group on the aromatic ring ($CuSO_4$,

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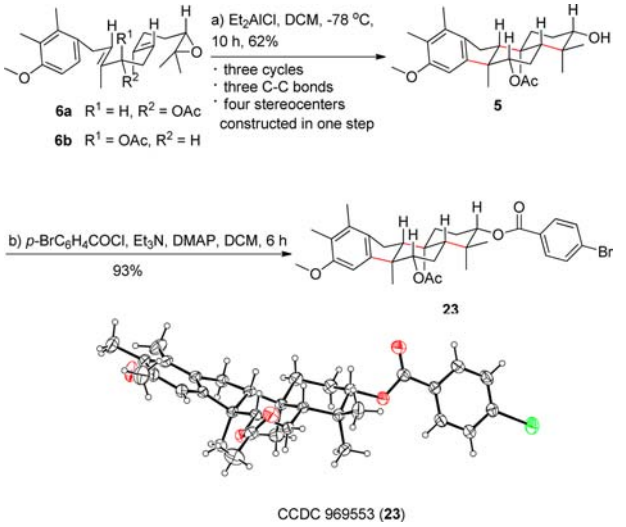
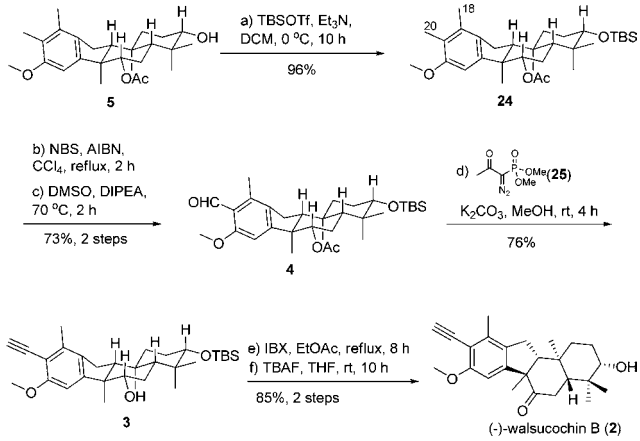
Scheme 4. Synthesis of the Core Tetracyclic Framework 5 via Cationic Polyolefin Cyclization



Scheme 5. Completion of the Synthesis of (−)-Walsucochin B (2)



$K_2S_2O_4$, CH_3CN/H_2O, reflux) proved unsuccessful, causing decomposition of the substrate. Therefore, a two-step protocol was examined that involved the site-selective radical bromination[18] of the C(20) methyl in **24**, with NBS and AIBN in CCl_4 at reflux, followed by oxidation with DMSO to give **4**[19] in 73% yield over two steps. Corey−Fuchs homologation[20] could not be applied to our substrate because it led to deprotection of the TBS group. Alternatively, K_2CO_3 and $(MeO)_2P(O)CN_2C(O)CH_3$ **25** in MeOH converted aldehyde **4** to the phenylacetylene, and the acetyl group was also removed to give secondary alcohol **3** in 76% yield through a one-pot Seyferth−Gilbert homologation[21]/hydrolysis sequence. Finally, IBX oxidation of secondary alcohol **3** to the corresponding ketone and desilylation with tetrabutylammonium fluoride (TBAF) completed the first enantioselective total synthesis of (−)-walsucochin B (**2**). The spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) of the synthetic material were in full agreement with those reported for the natural product. The sign of rotation for our synthetic **2** $[[\alpha]^{21.7}_D = -42.0$ (*c* 0.1, MeOH)] was consistent with that reported for natural walsucochin B $[[\alpha]^{24.5}_D = -45.0$ (*c* 0.1, MeOH)]. Therefore, we could confirm the absolute configuration of walsucochin B.

In summary, we have accomplished the first enantioselective total synthesis of the (−)-walsucochin B (**2**) and confirmed its absolute configuration. A convergent pathway was used to arrive at the cyclization precursor. The cationic polyolefin cyclization constructed the core architecture **3** as a single diastereomer. Site-selective, late-stage free-radical halogenation and oxidation were utilized to accomplish oxidation of one of the two methyl groups on the aromatic ring. A Seyferth−Gilbert homologation installed the acetylene moiety to construct the phenylacetylene. Additional efforts to apply the strategy to (+)-walsucochin A (**1**) along with other related natural products are currently being pursued in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Descriptions of experimental procedures for compounds and analytical characterization.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) CCDC 969553 (**23**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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