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Remote C−H Activation Strategy Enables Total Syntheses of Nortriterpenoids (±)-Walsucochin B and (±)-Walsucochinoids M and N

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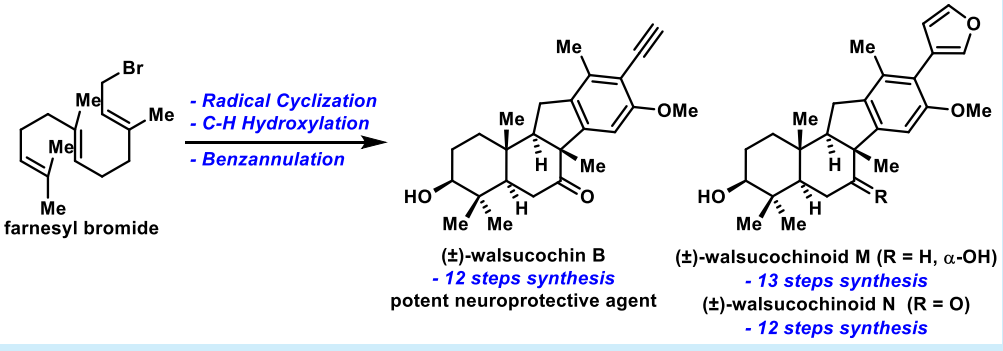

ABSTRACT: Total syntheses of (±)-walsucochin B and (±)-walsucochinoids M and N have been achieved from farnesyl bromide. The key steps of the synthetic sequence are the titanocene-mediated radical cyclization and base-induced cycloaromatization for the rapid construction of the 6/6/5/6-fused tetracyclic skeleton. Importantly, a Cu-mediated remote C−H hydroxylation reaction has been developed to site-selectively install the oxygen function at the C-7 position of the target molecules, thus solving the biggest challenge for the synthesis of the compounds.

The plant genus *Walsura* (Meliaceae) produces a rich array of structurally diverse and biologically active natural products.[1] In a search for naturally occurring neuroprotective agents, Yue and co-workers isolated the structurally unique C_{24} nortriterpenoids walsucochins A (**1**) and B (**2**) from *Walsura cochinchinensis* (Baill.) (Figure 1).[2] The two compounds showed significant cell-protecting activities against H_2O_2-induced PC12 cell damage,[2] associated with various neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD).[3] More recently, walsucochinoids M and N (**3** and **4**) and other new rearranged limonoids were also identified from the same species.[4] However, the poor accessibility of these nortriterpenoids poses a barrier to further and extensive biological evaluation. Considering this, we became interested in their efficient synthesis.

Structurally, walsucochin B (**2**) and walsucochinoids M and N (**3** and **4**) possess a complex 6/6/5/6-fused tetracyclic ring skeleton featuring a phenylacetylene or phenylfuran motif fused into the five-membered C-ring. There are several continuous stereocenters and a chiral hydroxyl group in the A/B ring, which is typical in the apotirucallane-type triterpenoids. Biogenetically, piscidinol D was postulated to be the precursor of walsucochin B (**2**) through an oxidative degradation involved pathway.[2] The unique 6/6/5/6-fused ring is also present in other biologically significant secondary

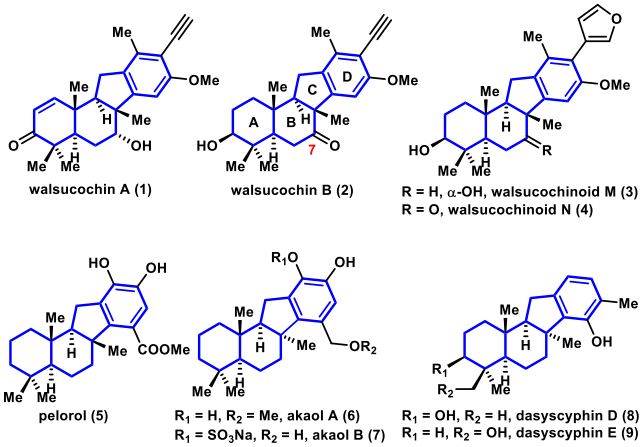

Figure 1. Complex terpenoids with 6/6/5/6-fused tetracyclic skeleton.

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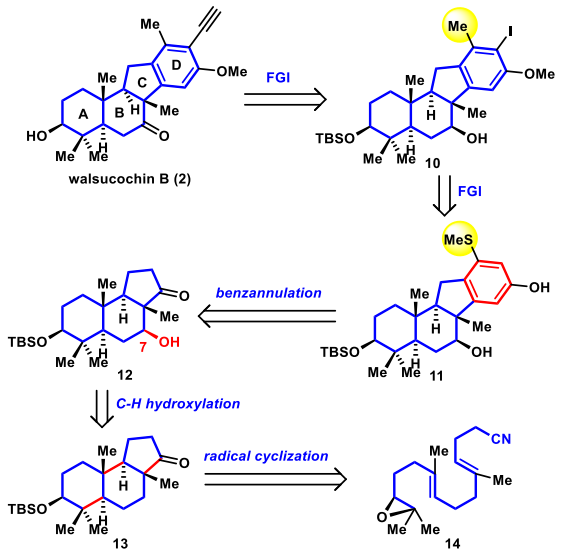
metabolites, such as SHIP1-activating pelorol (**5**),[5] akaol A and B (**6** and **7**),[6] and the antifungal dasyscyphins D and E (**8** and **9**).[7]

Due to the novel structure and significant biological properties of these natural products, extensive efforts have been devoted to their synthesis.[5c,8] The complex structure of walsucochin B (**2**), containing oxygen at the C-7 position, has proven to be a formidable synthetic challenge. In 2014, She and co-workers reported the first synthesis of (−)-walsucochin B (**2**) in 18 chemical steps via a cationic polyolefin cyclization.[8g] While this synthesis certainly gave invaluable synthetic insight for the other related natural products, many steps were required to introduce the oxygen function at the C-7 position. Herein we describe a remote C−H activation-based strategy to resolve this synthetic problem. Utilizing this strategy, we are able to gain highly concise routes to walsucochin B (**2**) and walsucochinoids M and N (**3** and **4**) from commercially available materials.

We chose walsucochin B (**2**) as our initial synthetic target. As shown in Scheme 1, the highly functionalized D-ring of

Scheme 1. Retrosynthetic Analysis of Walsucochin B (2) to the Precursor 14



walsucochin B (**2**) was retrosynthetically reduced to the intermediate iodide **10**. The ethynyl and methyl groups could be installed by metal-catalyzed cross coupling reactions. In developing a synthetic route to the 6/6/5/6-fused tetracyclic (decahydrobenzofluorene) skeleton, we viewed a phenol annulation as potentially capable of constructing such ring system.[9] To our knowledge, this annulation has not been widely applied in natural products synthesis. Therefore, it was envisaged that the key molecule **11** could be obtained from the ketone precursor **12**. The hydroxyl group at the C-7 position in **12** was expected to be introduced by the Schönecker's Cu-mediated oxidation method, which has been applied for the synthesis of steroidal natural products containing oxidation at C-12 position.[10] Considering the potential of radical cyclization in the assembly of polycyclic ring systems, we proposed that the ketone **13** with ABC rings could thus be produced in only one step from the epoxide **14**.

Our synthetic studies commenced with the construction of epoxide **14** (Scheme 2). Alkylation of the commercially available farnesyl bromide (**15**) with (cyanomethyl)cuprate afforded the nitrile **16** in 68% yield.[11] Epoxidation of the terminal alkene with *N*-bromosuccinimide (NBS) via the intermediacy of a bromohydrin delivered the epoxide **14** with high regioselectivity in 60% yield. With the precursor **14** in hand, we then focused on the reductive, titanocene-mediated epoxide opening radical cascade reaction, which has been envisioned to be the foundation for syntheses of numerous natural products.[12] Under the conditions reported by Fernández-Mateos and co-workers (Cp_2TiCl_2 (3.3 equiv), Zn^0 (6.6 equiv), THF, 23 °C),[13] we obtained the desired ketone **13** in 52% after protection of the secondary alcohol as TBS ether. Observed in Maimone's synthesis of berkeleyone A,[14] elevated temperature is essential for the success of certain titanium(III)-mediated tandem radical cyclization; however, performing the cyclization from epoxide **14** at increased temperature results in a lower yield. The cyclization proceeds via a favored chair conformation and gives a single diastereomer. Notably, the 6/6/5-fused ring system with six continuous stereocenters in walsucochin B (**2**) was forged in only one step as an efficient and concise path.

With substrate **13** accessible efficiently, we were well positioned to investigate the Cu-mediated oxidation reaction (Table 1). We initially focused our attention on Baran's oxidation protocol,[10f] which has proven useful and potentially practical in the synthesis of polyoxypregnane natural products. The imine **17** was first formed by treatment of the ketone **13** with 2-picolylamine and catalytic *p*-toluenesulfonic acid monohydrate (PTSA·H_2O). The imine is partially hydrolyzed upon column chromatography, and a two-step protocol was therefore examined. Pleasingly, treatment of **17** with Cu-$(MeCN)_4PF_6$ (1.3 equiv) and sodium ascorbate in acetone/methanol (1:1), followed by the introduction of O_2, resulted in the formation of **12** in 22% yield as a single diastereomer (entry 1). In the presence of 2.0 equiv of $Cu(MeCN)_4PF_6$ (entry 2), a slight increase in the product yields was observed (6% increase). Next, $Cu(OTf)_2$ (2.0 equiv) was employed to give the desired molecule in moderate yield (39%) (entry 3). Seeking alternative Cu-based oxidation methods for C−H hydroxylation, we were drawn to the recent work by Garcia-Bosch and co-workers who reported an exceedingly mild and practical reaction by using H_2O_2 as oxidant.[15] Gratifyingly, when $Cu(NO_3)_2{\cdot}3H_2O$ (1.1 equiv) and H_2O_2 (5.0 equiv) were used, a substantial increase in yield was observed (entry 4). Increasing the $Cu(NO_3)_2{\cdot}3H_2O$ to 2.0 equiv allowed the formation of **12** in 69% yield upon isolation from **13** (entry 5). Notably, this oxidation reaction could be performed on a gram scale without decreasing the efficiency. Further optimization by increasing the amount of $Cu(NO_3)_2{\cdot}3H_2O$, or running the reaction under evaluated temperature to further improve the yield was unsuccessful (entries 6 and 7). Reaction with other sources of $Cu^{I/II}$ were also examined but led to decreased yields (entries 8 and 9).

With tricyclic ketone **12** secured, all that remained to construct the decahydrobenzofluorene ring system was the construction of the aromatic D-ring. When attempting the reported phenol annulation conditions (NaH, DMF),[9] we noticed that the substrate **12** has poor solubility in DMF and no product was obtained. Ultimately, it was discovered that the conjugated addition conditions (*t*-BuOK, THF, 23 °C), utilized for similar dithioacetal substrate,[16] were active in this context, affording trace amounts of desired product **11**. The diketone **19** was formed in this reaction as major product via a

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Scheme 2. Total Synthesis of (±)-Walsucochin B (2)

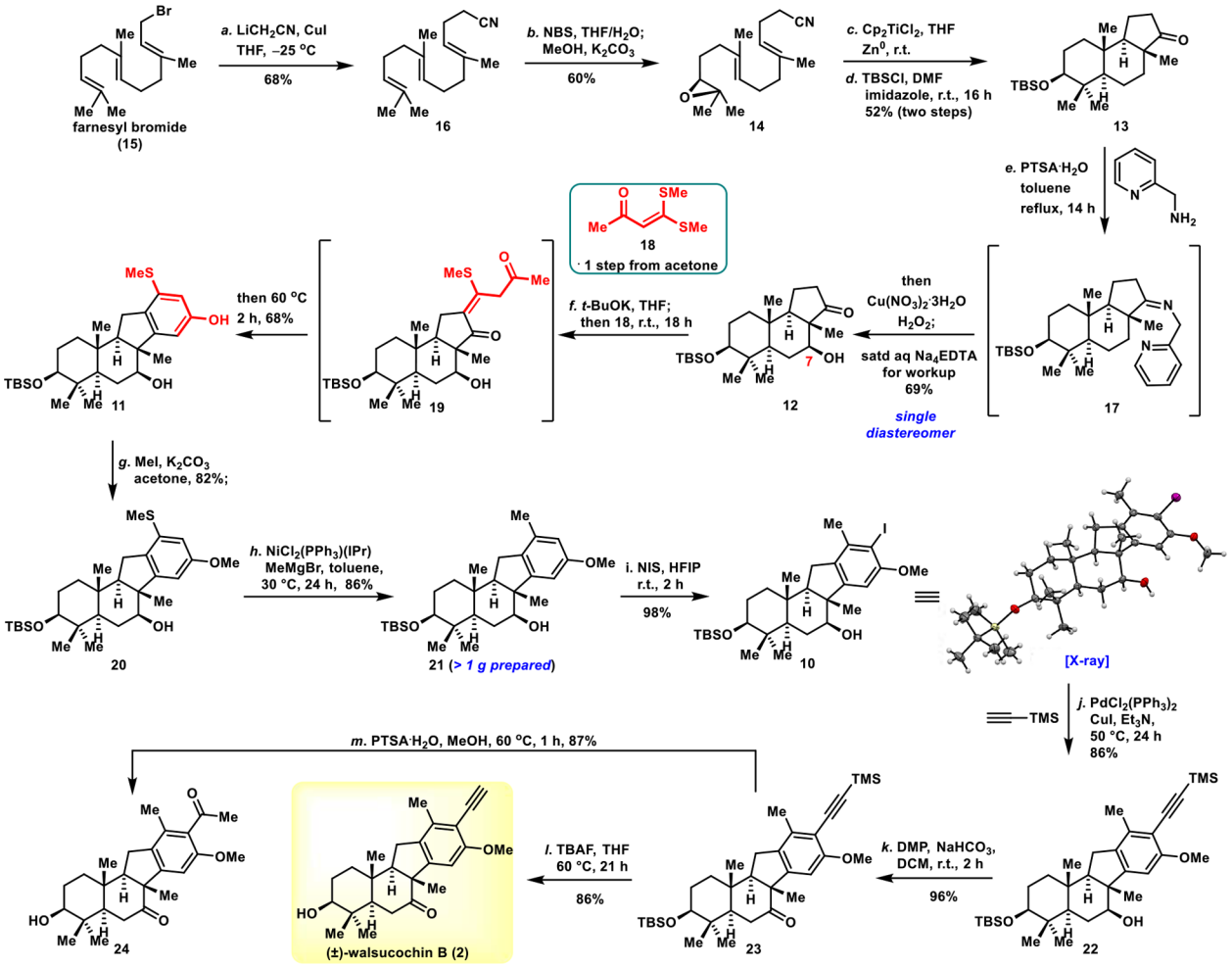
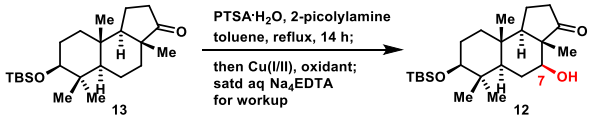


Table 1. Cu-Mediated Oxidation C−H Hydroxylation of 13[a]



entry	conditions	T/time (°C/h)	yield[b] (%)
1[c]	$Cu(MeCN)_4PF_6$ (1.3 equiv), O_2	50/1.5	22
2[c]	$Cu(MeCN)_4PF_6$ (2.0 equiv), O_2	50/1.5	28
3[c]	$Cu(OTf)_2$ (2.0 equiv), O_2	50/1.5	39
4[d]	$Cu(NO_3)_2{\cdot}3H_2O$ (1.1 equiv), H_2O_2	23/2.0	63
5[d]	$Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv), H_2O_2	23/2.0	69
6[d]	$Cu(NO_3)_2{\cdot}3H_2O$ (3.0 equiv), H_2O_2	23/2.0	69
7[d]	$Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv), H_2O_2	50/2.0	67
8[d]	$Cu(OTf)_2$ (2.0 equiv), H_2O_2	23/2.0	46
9[d]	$Cu(MeCN)_4PF_6$ (2.0 equiv), H_2O_2	23/2.0	22

[a]Reactions were performed on a 250 mg scale, and satd aq Na_4EDTA was used for workup. [b]Yield of the isolated product. [c]Sodium ascorbate (2.0 equiv) was used as reducing agent, and acetone/methanol (1:1, 0.15 M) was used as solvent. [d]30% H_2O_2 (5.0 equiv) was used as oxidant, and THF (0.2 M) was used as solvent.

Michael addition−elimination−isomerization sequence. The complete conversion was observed under elevated temperatures (60 °C) to forge the 6/6/5/6-fused ring system in 68% isolated yield.

Having a six-step synthesis of the full 6/6/5/6-fused tetracyclic skeleton complete, only functional group interconversions were required to complete the target. The phenol **11** was first methylated with MeI, and methyl ether **20** was obtained in 82% yield. Then, the C(sp^2)−SMe methylation of the thioether with MeMgBr by using $NiCl_2(PPh_3)(IPr)$ as the catalyst led to **21** in 86% yield.[17] This coupling reaction is also suitable for the modification of aryl thioether with other functional groups and, therefore, may serve as a suitable platform to access a library of walsucochin structures for biological investigation. To install the acetylene moiety through the Sonogashira reaction, regioselective iodination was then investigated. Much to our delight, the reaction proceeded smoothly using *N*-iodosuccinimide (NIS) in hexafluoroisopropanol (HFIP) and generated **10** in quantitative yield;[18] its relative configuration was confirmed by X-ray crystallography. Subsequent direct Sonogashira coupling (TMSCCH, CuI, $PdCl_2(PPh_3)_4$, Et_3N) was capable of installing the final requisite trimethylsilylethynyl group in excellent yield. Ultimately, Dess−Martin periodinane (DMP) oxidation of secondary alcohol **22** to the corresponding ketone **23**, and desilylation with tetrabutylammonium fluoride (TBAF) finished the synthesis of (±)-walsucochin B (**2**). Acidic cleavage of the *tert*-butyldimethylsilyl ether (PTSA·H_2O/MeOH, 60 °C) afforded Markovnikov hydration product **24** in 87% yield. Overall, only 12 steps were needed to access this complex C_{24} nortriterpenoid from commercially available

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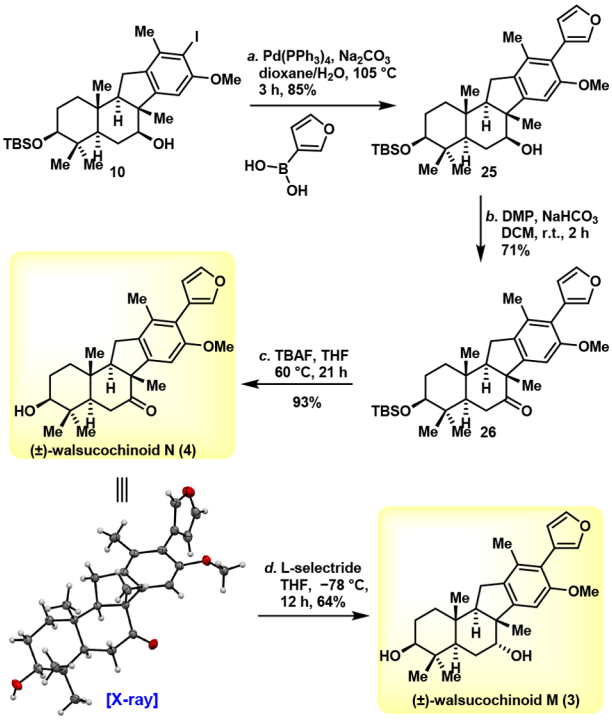
Org. Lett. 2020, 22, 6993−6997

farnesyl bromide. The absolute structure of (±)-walsucochin B (**2**) was determined as previously reported.[2,8g] Moreover, it is envisioned that intermediate iodide **10** could serve as a versatile intermediate for the synthesis of walsucochin analogues.

With the key intermediate iodide **10** in hand, we subsequently focused on the synthesis of novel limonoids walsucochinoids M and N by following the strategy depicted in Scheme 3. The synthesis commenced with the installation of a

Scheme 3. Total Synthesis of (±)-Walsucochinoids M (3) and N (4)



furan ring into the D-ring. A Suzuki−Miyaura cross-coupling reaction by using 3-furanylboronic acid as the partner led to compound **25** in 85% yield. Finally, a DMP oxidation of the secondary alcohol, followed by deprotection of the TBS group, successfully afforded the (±)-walsucochinoid N (**4**), for the first time, in 66% yield over two steps. Subsequent stereoselective reduction of ketone at the C7-position gave (±)-walsucochinoid M (**3**) with a 7α-hydroxyl group in 64% yield. The spectroscopic data of the synthetic material were in full agreement with those reported for the natural products. The stereochemistry of the (±)-walsucochinoid M (**3**) was confirmed by a 1D NOE experiment.

In summary, we have accomplished a highly concise synthetic approach to the (±)-walsucochin B (**2**) and (±)-walsucochinoids M and N (**3** and **4**) in 12, 13, and 12 steps, respectively, from farnesyl bromide. The key features of our synthesis involve titanocene-mediated radical cyclization and a remote Cu-mediated C−H hydroxylation reaction for the rapid construction of tricyclic common scaffold **12**, a base-induced cascade reaction to construct aromatic motif with proper substitution in a single operation. The 6/6/5/6-fused carbocyclic skeleton is forged via a simple, six-step sequence, and the common intermediate **10** appears to be suitable for straightforward construction of walsucochin analogues. Moreover, the general strategy described herein is expected to be applied to the synthesis of other complex natural products with related chemical structures, and they will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02548.

Experimental procedure, structural characterizations, and spectral data of synthetic compounds (PDF)

Accession Codes

CCDC 2006740 and 2007658 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

‖X.C. and D.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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