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Asymmetric Total Synthesis of (2*R*)-Hydroxynorneomajucin, a Norsesquiterpene from *Illicium jiadifengpi*

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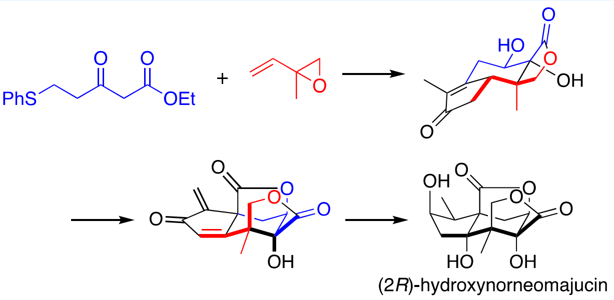
ABSTRACT: We report the first total synthesis of (2*R*)-hydroxynorneomajucin, a norsesquiterpene derived from the *Illicium* genus. This natural product displays neurotrophic properties. Small molecule neurotrophins have potential as therapeutics in neurodegenerative diseases. Key steps of our synthesis include a Tsuji−Trost reaction, a Pauson−Khand cyclization, and a Nagata hydrocyanation. A simple sequence of reductions and a Mukaiyama hydration introduce the A-ring substituents with the correct configurations. The overall synthesis was completed in 17 steps (longest linear sequence, LLS).



Seco-prezizaane sesquiterpenes from the *Illicium* genus of flowering plants, Figure 1, have captivated synthetic chemists for decades owing to their highly oxidized structures and potent biological activity.[1] The bioactivity of these natural products seems to be dictated by the oxidation pattern around the core of the molecule.[2] For example, anisatin, bearing a β-lactone, is known to cause convulsions while jiadifenin, jiadifenolide, majucin, and (2*R*)-hydroxynorneomajucin (**1**) display neurotrophic effects.[3] The neurotrophic properties of these latter natural products are particularly attractive, as small molecule neurotrophins have potential as therapeutics in neurodegenerative diseases such as Parkinson's or Alzheimer's disease.

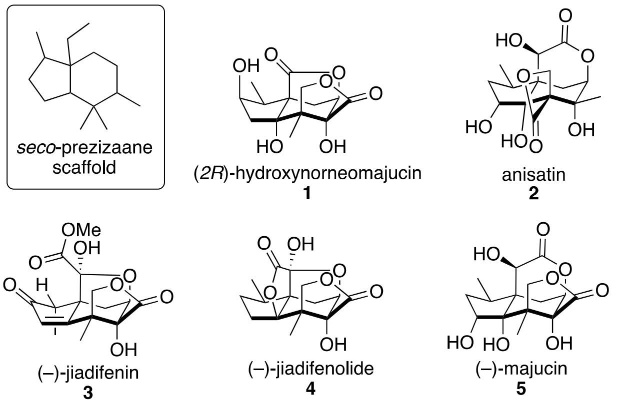


Figure 1. Structures of seco-prezizaane natural products. Many of these compounds show neurotrophic activity.

There has been significant synthetic work toward the *seco*-prezizaanes, particularly in the past decade.[1b] There have been several elegant approaches reported to anisatin,[4] jiadifenin,[5] majucin,[6] and jiadifenolide.[7] However, since its isolation in 2012, there has only been one report targeting (2*R*)-hydroxynorneomajucin. Interestingly, **1** was the first norsesquiterpene isolated from the *Illicium* genus of plant.[8] In 2016, Gademann reported an approach to **1**, which gave access to late-stage intermediates but fell short of the natural product.[9] Herein, we report the first asymmetric total synthesis of **1**, proceeding in 17 steps (LLS, longest linear sequence).

Our retrosynthesis is shown in Figure 2. Initially, we envisioned deriving the natural product through late-stage redox manipulations, leading back to tetracycle **6**. The A- and B-rings of the molecule could be disconnected through a Pauson−Khand reaction, leading back to enyne **7**.[10] We initially pursued this route, but under all conditions tested, we were unable to enact this Pauson−Khand reaction (for details, see Supporting Information). In light of this setback, we investigated the retrosynthesis presented in Figure 2B. We once again envisioned deriving the natural product from **6**, but the final lactone could be formed at a later stage, leading back to tricycle **8**. Tricycle **8** is derived from an intermediate in Zhai's synthesis of jiadifenin[5c] and could be brought back to enyne **9** through a Pauson−Khand reaction (PKR). Enyne **9** could be derived from β-keto lactone **10** through a sequence of functional group manipulations. Finally, we imagined forming the quaternary center in the first step by utilizing the Tsuji−

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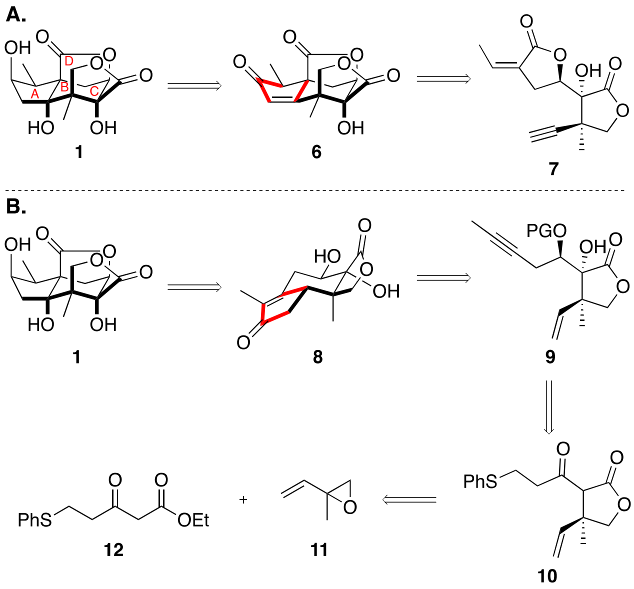


Figure 2. Initial retrosynthetic strategy A and the revised retrosynthetic strategy B developed for the synthesis of (2*R*)-hydroxynorneomajucin (**1**).

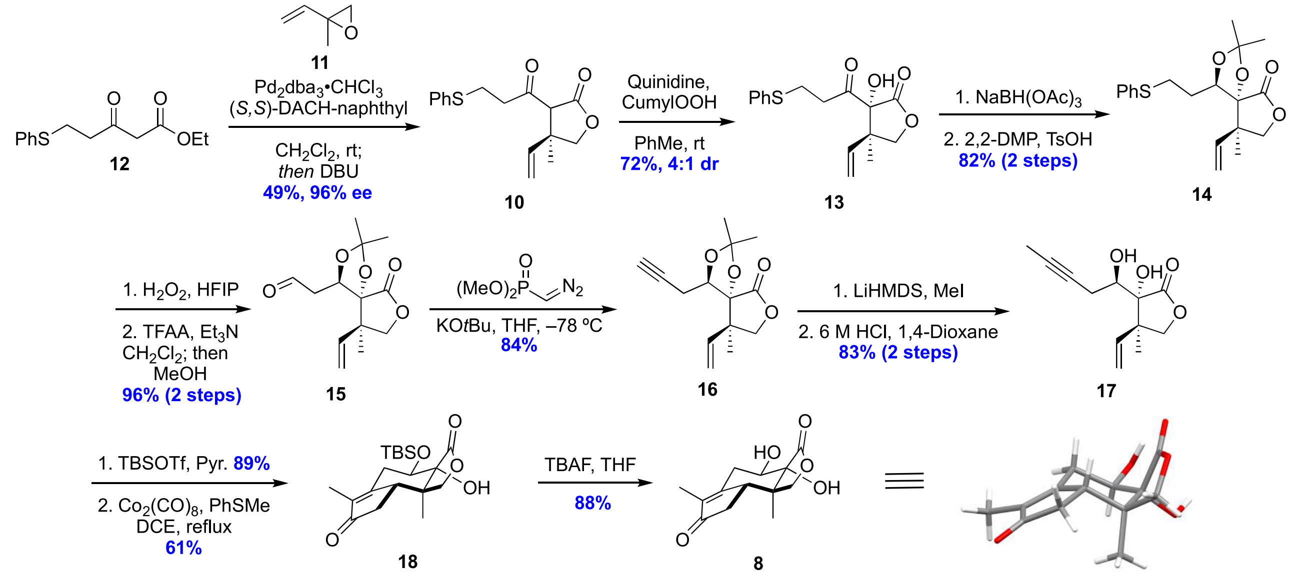
Trost/lactonization of isoprene monoxide (**11**) and ketoester **12**.[11]

We initially investigated the Tsuji–Trost asymmetric allylation with an alkyne preinstalled in the *β*-keto ester. However, the material was difficult to synthesize due to isomerization to a conjugated allene, and the Pd-catalyzed reaction was unsuccessful on the mixture of isomers. The phenylsulfide **12** was selected as an alternative substrate for the Tsuji–Trost allylic alkylation with isoprene monoxide (Scheme 1). The phenylsulfide left a functional group for later incorporation of the necessary alkyne. Trost has reported a similar reaction in their approach to the core of viridenomycin, and through modification of their reaction conditions, we were able to access **10** in 49% yield, and 96% ee with respect to the newly formed quaternary center.[12] Diastereoselective oxidation of the keto-lactone was achieved by applying conditions developed by Jørgensen.[13] Treatment of **10** with catalytic quinidine in the presence of cumyl hydroperoxide led to *α*-ketol **13** in 72% yield as a 4:1 mixture of separable diastereomers. Notably, it is necessary to cool the reaction to limit the amount of side products derived from sulfide oxidation. Reduction of the *α*-ketol, followed by protection of the diol intermediate, afforded acetonide **14** in good yield.

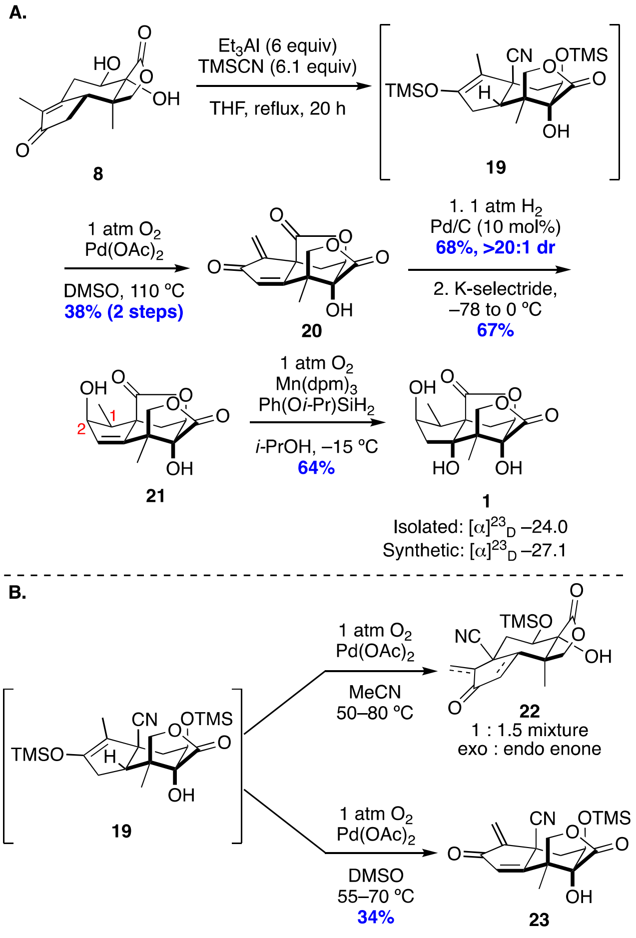
With the diol protected as an acetonide, we next needed to install an alkyne for the key Pauson–Khand cyclization. The thioether was first converted to an aldehyde through oxidation to the sulfoxide, followed by Pummerer rearrangement mediated by TFAA, yielding aldehyde **15** in excellent yield. Seyferth–Gilbert homologation[14] of the aldehyde led to alkyne **16**, which could subsequently be methylated and deprotected to access diol **17**. We attempted several Pauson–Khand reactions with the free diol, and with varying protecting strategies, but had very little success. As such, we elected to silylate the secondary alcohol in a similar manner to Zhai and utilize this substrate for the Pauson–Khand reaction.[15,5c] Treatment of this intermediate with $Co_2(CO)_8$ and thioanisole in refluxing DCE led smoothly to tricyclic enone **18** in 61% isolated yield. While this exact Pauson–Khand is known, we elected to modify the reaction conditions for simplicity. The published conditions utilize tributylphosphane sulfide as an additive for the reaction, but this compound is not commercially available.[16] Additionally, it has long been known that readily accessible sulfides serve as effective additives in the PKR, and we achieved a very similar result using commercially available thioanisole.[17] Desilylation occurred upon treatment with TBAF, affording compound **8** in 88% yield. The connectivity and absolute configuration of tricycle **8** were determined unambiguously through X-ray crystallography.[18]

Having established the core of the natural product, we needed to install the final quaternary center, as well as close the final lactone, Scheme 2A. We investigated several strategies,

Scheme 1. Synthesis of the Advanced Tricyclic Intermediate 8



Scheme 2. (A) Functionalization of the A-Ring from Intermediate 8 and Completion of the Synthesis; (B) Divergent Results of Saegusa−Ito Oxidation Based on Reaction Conditions



but hydrocyanation proved to be the most effective.[19] Using conditions similar to Utimoto, hydrocyanation of enone **8** was achieved by treatment with triethylaluminum and TMSCN in refluxing THF.[20] Unfortunately, hydrolysis of the silyl enol ether led to the incorrect methyl epimer with respect to the final natural product. After experimenting with epimerization strategies, we discovered that oxidation to the dienone through sequential Saegusa−Ito reactions allowed for diastereoselective and chemoselective reduction of the *exo*-olefin to give the desired stereochemistry at C1. Additionally, we found that it was possible to oxidize the crude intermediate **19** to the dienone directly with superstoichiometric Pd(OAc)$_2$ under an oxygen atmosphere. Interestingly, the outcome of the dehydrogenation was sensitive to the temperature and solvent, as reactions in acetonitrile at 50−80 °C gave incomplete conversion to the dienone, often forming a mixture of regioisomeric monoenones **22** (Scheme 2B). When the oxidation was conducted in DMSO at 55−70 °C, the *β*-cyano dienone **23** was often isolated. Conveniently, when the mixture was heated to 110 °C in DMSO, the double dehydrogenation occurred with concomitant hydrolysis of the nitrile, leading directly to dienone **20** in 38% yield over 2 steps. While relatively low yielding, this two-step sequence formed the final quaternary center and lactone readily, and afforded an intermediate with suitable functional handles to complete the synthesis.

To complete the synthesis of **1**, we needed to manipulate the oxidation state of the A-ring. Chemo- and diastereoselective hydrogenation of the *exo*-enone of **20** was achieved by simple hydrogenation with Pd/C, affording the desired methyl stereocenter at C1 in 68% yield as a single diastereomer. Initial attempts at hydrogenation led to lower stereoselectivity due to residual Pd in the material following Saegusa−Ito oxidation. Careful chromatographic removal of the residual Pd after the prior step allowed for much greater diastereoselectivity in the hydrogenation.[21] We next needed to achieve a diastereoselective 1,2-reduction of the remaining enone. Based upon precedent from other *seco*-prezizaane syntheses,[5d] we were certain that standard Luche conditions would favor the incorrect diastereomer. However, in a related system, Wicha has shown that this bias can be reversed by using the bulkier reducing agent K-selectride.[22] Reduction of our intermediate enone with K-selectride at −78 °C led to alcohol **21** in 67% yield, once again as a single diastereomer. The relative configuration of this newly installed stereocenter was confirmed through NOE correlations. Final Mukaiyama hydration was achieved using Mn(dpm)$_3$ and Ph(O*i*-Pr)SiH$_2$ at −15 °C, affording the first synthetic sample of **1** in 64% yield as a single diastereomer.[23] The spectral data for our synthetic sample are consistent with those reported by Fukuyama.[8] Optical rotation of the synthetic sample was similar to that reported for the natural product.[8] Combined with the X-ray structure of intermediate **8**, this confirms the absolute configuration of the natural product.

Our work also sheds light on the prior synthetic approach to natural product **1**.[9] The advanced intermediate reported by Gademann appears to be epimeric to the natural product at C2, a consequence of the stereochemical preference of the Luche reduction used (see Scheme S1 for details).[9b] Our current strategy provides a simple alternative to correctly set the configuration of this center.

In summary, we have achieved the first total synthesis of (2*R*)-hydroxynorneomajucin in 17 steps from *β*-ketoester **12**. Key steps in the sequence include a Tsuji−Trost asymmetric allylic alkylation, a Pauson−Khand reaction, and a Nagata hydrocyanation. The route introduces the A-ring functionality in a straightforward sequence that generates the correct configuration at the four stereogenic centers in this ring. This synthetic approach lays the groundwork for further investigation of the biological activity of this interesting neurotrophic natural product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01207.

> Experimental details, compound characterization, NMR data, and X-ray data (PDF)
>
> FAIR data, including the primary NMR FID files, for compounds **1**, **8**, **10**, **13**, **14**, **15**, **16**, **17**, **18**, **20**, **21**, **23**, and **S21** (ZIP)

Accession Codes

CCDC 2164643 contains 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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Notes

The authors declare no competing financial interest.

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