Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Domino Enyne/IMDA Approach to the Core Structure of (−) Vinigrol

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Supporting Information

ABSTRACT: We report here an enantioselective formal synthesis of vinigrol involving a 1−2−3 strategy: one pot and two reactions with the formation of three rings leading to the core structure of vinigrol from its stereochemically well-defined acyclic precursor.

Vinigrol (**1**),[1] a unique diterpene encompassing the decahydro-1,5-butanonaphthalene carbon skeleton, was isolated by Hashimoto and co-workers in 1987 and has been shown to exhibit a broad spectrum of biological activity (Figure 1).[2−4] Besides the multiple sites of oxygenation, vinigrol

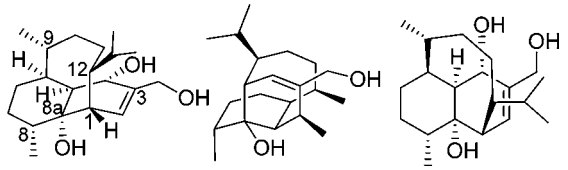


Figure 1. Structure of vinigrol **1**.

contains a tricyclic core having a *cis*-fused [4.4.0] system bridged by an eight-membered ring with eight contiguous stereocenters. Vinigrol, together with well-known diterpene systems such as the ingenanes, taxanes, and phomactins, posed a formidable challenge to the synthetic community across the globe (Figure 2).[5,6] The complexity rendered by this venerable molecule made its total synthesis a daunting task for more than two decades[6−8] until Baran[9] reported its first racemic total synthesis involving Grob fragmentation and Diels−Alder reaction as the key steps. A few years later, Barriault[10] reported its formal synthesis also using intramolecular Diels−Alder (IMDA) reaction. Early last year, Njardarson[11] reported the second total synthesis of this fascinating molecule using oxidative dearomatization and Diels−Alder reaction as key steps. Herein, we report the first enantioselective formal synthesis of vinigrol based on domino enyne metathesis followed by an IMDA reaction.

The unique molecular architecture having significant biological properties, coupled with the fact that no enantioselective synthesis is reported until date, prompted us to develop a program toward an enantioselective total synthesis of vinigrol.

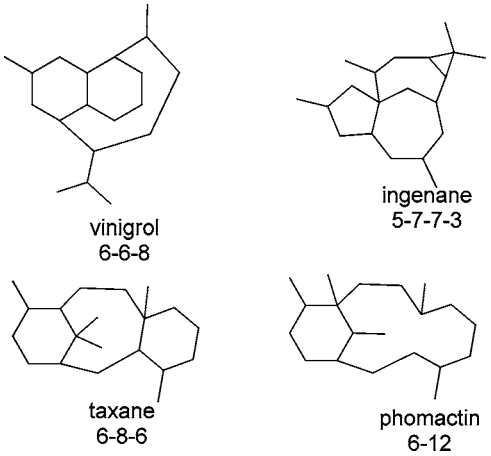
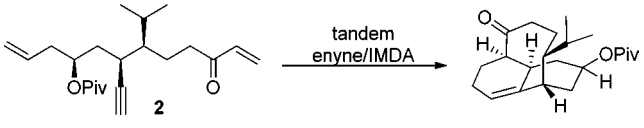


Figure 2. Historically challenging diterpene skeletons.

Further, it was evident from the earlier approaches that the construction of an eight-membered ring on the pre-existing *cis*-decalin framework is difficult. To circumvent this problem, we envisaged a conceptually simple, one-pot, domino enyne metathesis−IMDA reaction for the construction of all three rings (6−6−8) of vinigrol from its stereochemically well-defined open chain precursor **2** (Scheme 1).

Scheme 1. Strategy for Vinigrol Core Structure

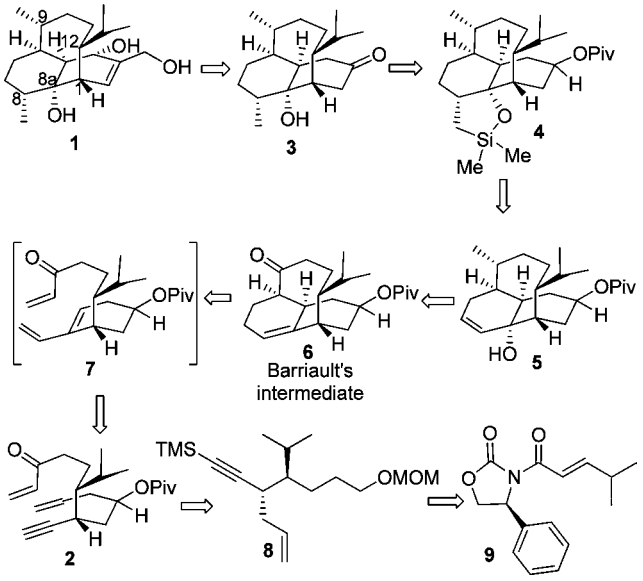


Received: August 24, 2014
Published: October 13, 2014

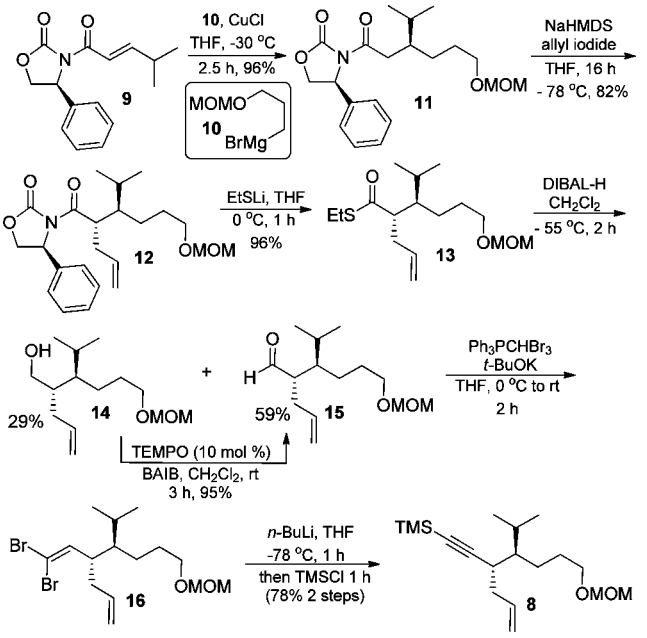
   dx.doi.org/10.1021/ol502497n | *Org. Lett.* 2014, 16, 5540−5543

As delineated in Scheme 2, retrosynthetic analysis suggested that vinigrol **1** could be readily obtained from the ketone **3**.[9]

Scheme 2. Retrosynthesis of Vinigrol



Scheme 3. Synthesis of Alkyne 8



The required C-8 methyl and C-8a hydroxy of the advanced intermediate **3** could be introduced by a radical cyclization of (bromomethyl)dimethylsilyl allylic ether followed by proto-desilylation of allylic alcohol **5**. It was anticipated that the five-membered siloxane ring of **4** could exhibit latent functionality for both the methyl as well as the hydroxy group with the required *syn* stereochemistry. The methyl group at the C-9 position was planned to be delivered by a regio- and stereoselective reduction of the exocyclic double bond after the Wittig reaction on the ketone **6**.[10] In the context of our main objective, we envisaged that the key domino enyne metathesis−IMDA reaction will furnish the tricyclic core of vinigrol **6** from its open chain dienyne **2**, having required groups appropriately placed. The Brown allylation of aldehyde resulting from the ozonolysis of alkene **8** not only could offer the introduction of oxygen functionality at the C-3 position required to carry out further necessary transformation but also would introduce the alkene required for enyne metathesis to generate the diene. Here, the stereochemistry of the newly generated hydroxy group was found to be important for stereoselective introduction of methyl at the C-9 position.[12] Alkyne **8**, having two chiral centers, could be synthesized from **9** by stereoselective conjugate addition followed by allylation and functional group manipulation.

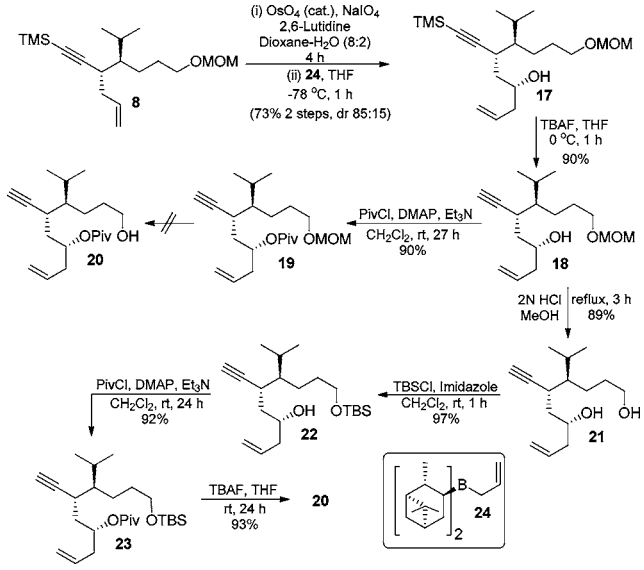
Our plan for an asymmetric synthesis of vinigrol sought to first introduce the chirality at C-12 and C-1 of **1** in its acyclic precursor. Thus, our synthesis began with the conjugate addition of Grignard reagent **10** on known Michael acceptor **9**[13] to furnish the expected product **11** as a single diastereomer (Scheme 3). The choice of protecting group was found to be crucial for the conjugate addition reaction, and MOM was found to be the best protecting group among the tried ones.[14] Subsequent α-allylation of the imide-enolate, formed *in situ*, by the treatment of **11** with NaHMDS followed by the addition of allyl iodide provided **12** with high diastereoselectivity[15] (>98%). Removal of the chiral auxiliary was found to be tricky, as conventional methods ($LiBH_4$, $LiAlH_4$, $NaBH_4$, H_2O_2/NaOH, etc.) led to either recovery of starting material or poor release of the product. To circumvent this problem, imide **12** was converted into the corresponding aldehyde **15** by sequential cleavage of the auxiliary with ethyl mercaptan and *n*-BuLi, to form the corresponding thioester[16] followed by reduction with DIBAL-H.[17] Although DIBAL-H reduction proceeded smoothly, it did not stop at aldehyde **15** and it always provided a separable mixture of alcohol **14** and aldehyde **15**. Nevertheless, the alcohol was easily oxidized to **15** which upon treatment with *in situ* generated ylide using Ramirez salt[18] (PPh_3CHBr_3, *t*-BuOK) furnished the dibromide **16** which was then converted into trimethylsilyl alkyne **8** using *n*-BuLi and TMSCl at low temperature.

With the requisite enyne **8** in hand, we then turned our attention to carry out the Brown allylation to introduce one more chiral center. The enyne upon oxidative cleavage followed by asymmetric allylation with **24**, derived from (+)-DIPCl,[19] afforded the homoallylic alcohol **17** in good yield with moderate *dr* (85:15) in favor of the required isomer. Removal of the TMS group with TBAF and protection of the hydroxy group as a pivolyl ester provided **19**. However, cleavage of MOM ether proved to be unsuccessful and, in all our attempts, the pivolyl group was found to undergo hydrolysis faster than the cleavage of MOM ether. This necessitated a two-step protocol that involved replacement of the MOM group with TBS ether (Scheme 4). Toward this end, MOM was initially removed to provide diol **21** and the primary alcohol was selectively protected as its TBS ether **22**. The secondary hydroxy group was then converted into its pivaloate ester, and subsequent removal of TBS group with Bu_4NF in THF delivered the alcohol **20**.

Having generated the requisite enyne moiety for metathesis reaction, our next objective has been to construct the enone moiety required of the intramolecular Diels−Alder reaction. This was accomplished as follows: primary alcohol **20** was oxidized to aldehyde, which upon vinyl Grignard addition followed by Swern oxidation afforded the enone **2**. The stage was now set for carrying out the key domino enyne/IMDA reaction. Thus, when the alkene **2** was treated with 15 mol % of

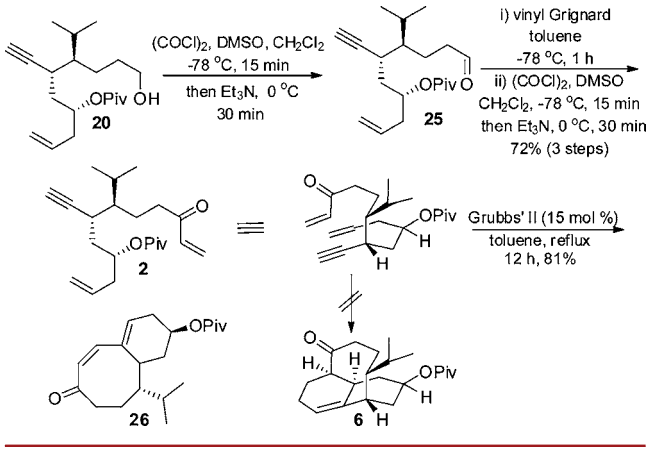
dx.doi.org/10.1021/ol502497n | *Org. Lett.* 2014, 16, 5540−5543

Scheme 4. Synthesis of Enyne 20



Grubbs' II catalyst, under a nitrogen atmosphere, enyne metathesis proceeded smoothly to give diene **7**, which, instead of undergoing intramolecular Diels–Alder reaction, underwent a ring closing metathesis with a monosubstituted alkene to give the bicylic compound **26** and the much anticipated IMDA product **6** was obtained only in traces (Scheme 5).

Scheme 5. Attempted Domino Reaction



Owing to this problem and also based on our earlier observation of the domino enyne/ring closing metathesis approach to angularly fused dioxatriquinanes,[20] where the use of an ethylene atmosphere did not facilitate the subsequent diene RCM after the intramolecular enyne metathesis (Scheme 6), it was decided to carry out this reaction under an ethylene atmosphere. Thus, when we carried out this key reaction under an ethylene atmosphere, we could immediately observe the formation of the required IMDA product **6**, though the diene RCM product (1:2.4) still continues to be the major product (Table 1). Carrying out the reaction at a lower temperature increased the ratio of the required IMDA product over RCM. After careful optimization, we found that stirring compound **2** with Grubbs' II at rt under an ethylene atmosphere gave the diene **7**, which on treatment with $SnCl_4$ at −78 °C underwent IMDA reaction in the same pot to deliver the required tricyclic product **6** and the unwanted bicyclic diene **26** in a 4:1 ratio.

Scheme 6. Cascade Enyne/Ring Closing Metathesis

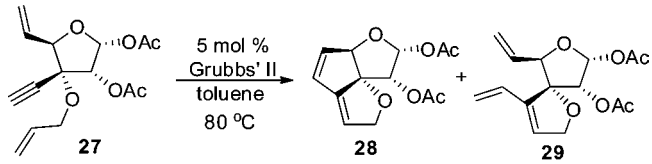
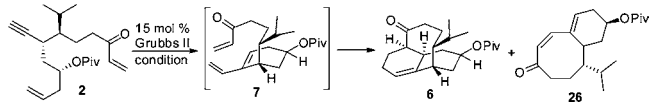


Table 1. Domino Enyne/IMDA Reaction

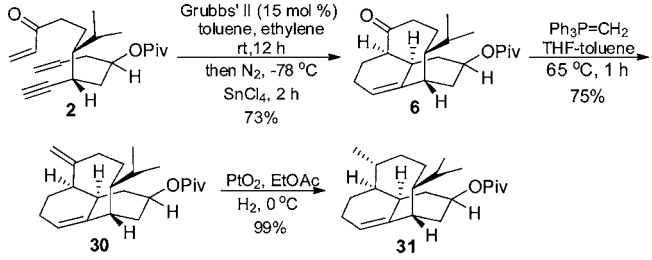


entry	conditions	(6:26)[a]
1	110 °C, N_2 atm	1:>98
2	100 °C, ethylene	1:2.4
3	80 °C, ethylene	1:1.3
4	60 °C, ethylene	1.8:1
5[b]	30 °C, ethylene, $SnCl_4$	4:1.0

[a]Based on NMR data of the reaction mixture. [b]Ethylene was replaced by nitrogen after complete conversion of starting material to diene **7**; temperature was reduced to −78 °C.

The remaining necessary operation involved stereoselective introduction of a methyl group at the C-9 position. In this regard, Barriault et al. reported in their synthesis the use of PtO_2 to stereo- and regioselectively carry out the reduction of the exocylic double bond. Therefore, ketone **6** was converted to olefin **30** followed by its treatment with PtO_2 under a hydrogen atmosphere to deliver the product **31** as a single diastereomer in quantitative yield (Scheme 7) which was the key intermediate in Barriault's syntheis of vinigrol.

Scheme 7. Domino Reaction



In summary, we have achieved the first enantioselective formal synthesis of vinigrol. The key features of our strategy include (i) introduction of two chiral centers by Evans chiral auxiliary and (ii) a one-pot domino enyne metathesis followed by intramolecular Diels–Alder reaction to construct the complex tricyclic core structure from an acyclic precursor. Total synthesis of (−) vinigrol using a 5-*exo*-trig radical cyclization is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experiment procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol502497n | *Org. Lett.* 2014, 16, 5540–5543

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The financial support by DST, New Delhi is acknowledged. V.V.B. and A.A.S. thank the Council of Scientific and Industrial Research for a fellowship. We also thank Prof. L. Barriault (University of Ottawa) for providing the spectral data for his key intermediate **31**.

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