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Synthesis of the Tricyclic Core of Vinigrol via an Intramolecular Diels–Alder Reaction

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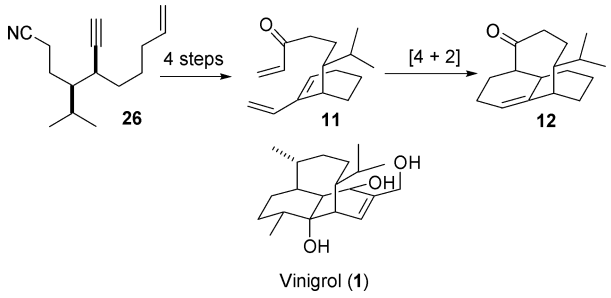
ABSTRACT



Herein, we present a successful synthesis of the tricyclic core of vinigrol (1). Our approach takes advantage of a highly regioselective intramolecular Diels–Alder reaction of the diene 11 to construct two rings of the tricyclic vinigrol skeleton 12.

Vinigrol (**1**) is a diterpenoid isolated in 1987 from the fungal strain *Virgaria nigra* F-5408 by Hashimoto and co-workers (Figure 1).[1] A cursory inspection of the structure reveals a tricyclic core containing a cis-fused [4.4.0] system bridged by a four-carbon unit and eight contiguous stereocenters. An evaluation of the biological activity of vinigrol (**1**) shows antihypertensive and platelet aggregation-inhibiting properties.[2] A patent filed by Norris and co-workers indicated that vinigrol was identified as a tumor necrosis factor (TNF) antagonist.[3] This discovery stimulated further investigations on vinigrol applications. Fujisawa Pharmaceutical Co. Ltd. found that **1** could be used as an alternative therapy for the treatment of HIV.[4] A recent study revealed that combination of vinigrol (**1**) with COX-2 inhibitors has potential in the treatment of inflammation.[5]

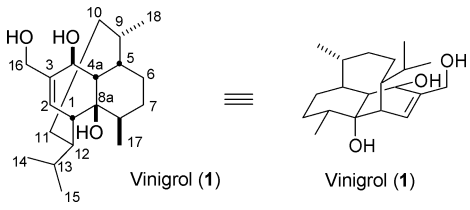


Figure 1. Structure of vinigrol (**1**).

Due to its unusual chemical architecture combined with its promising biological activity, vinigrol (**1**) has attracted a significant attention from the synthetic community.[6] Despite considerable synthetic efforts, no total synthesis of vinigrol (**1**) has been reported yet. In fact, Hanna and co-workers

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(2) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25. (b) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.

(3) Norris, D. B.; Depledge, P.; Jackson, A. P. PCT Int. Appl. WO 91 07 953; *Chem. Abstr.* **1991**, *115*, 64776.

(4) Nakajima, H.; Yamamoto, N.; Kaizu, T.; Kino, T. Jpn. Kokai Tokkyo Koho JP 07-206668; *Chem. Abstr.* **1995**, *123*, 246812.

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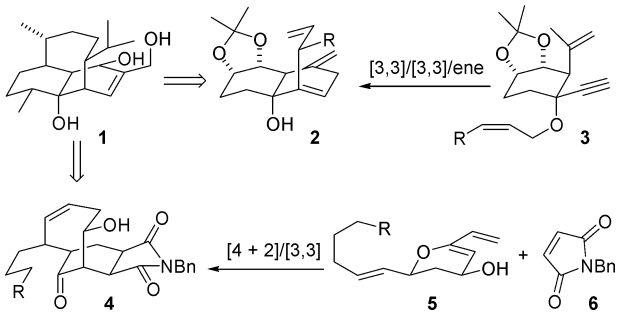
described the only synthesis of a tricyclic framework of vinigrol (**1**).[6f,g,o] Recently, we reported the formation of the *cis*-decalin and bicyclo[5.3.1]undecenone vinigrol subunits **2** and **4** using tandem pericyclic reactions (Scheme 1).[6a,b]

Scheme 1. Previous Approaches



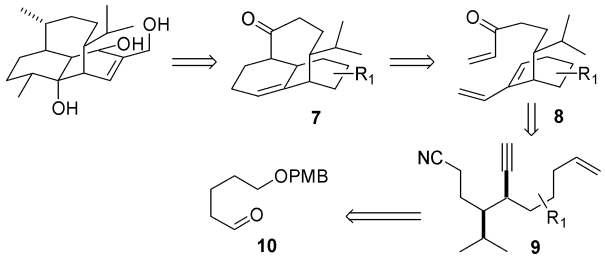
However, these initial approaches were plagued by an incapacity to form the final eight-membered or six-membered rings via various ring-closing reactions. From our approaches and those reported by the others groups, we learned that the formation of two of the three rings of vinigrol can be achieved without posing serious problems. However, the formation of the third ring, especially the eight-membered ring, via alkylation-type reactions or ring-closing metathesis, remains problematic.[6a,e,h] We suggest that the preferential conformation and the compact nature of the substrate are the responsible factors that inhibit the desired cyclization.

On the basis of these results, we contemplated the generation of two rings in one step. Thus, we envisaged the synthesis of tricycle **7** via an intramolecular Diels−Alder reaction of triene **8** (Scheme 2). The latter could be formed from an enyne metathesis reaction of alkyne **9** which could be derived from readily available aldehyde **10**.[7]

A close inspection of the intramolecular Diels−Alder of diene **11** reveals that two endo cycloadducts **12** and **13** could be formed (Scheme 3). At first glance, one might propose that electronic and steric factors should favor the formation of **12** over **13**. In order to validate this approach, we investigated the synthesis of a Diels−Alder precursor of triene **11**.

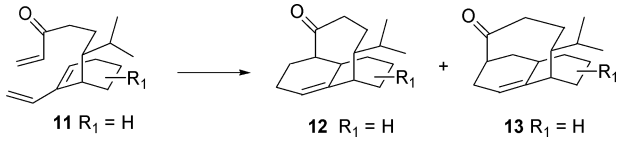
The synthesis began by a Takai olefination of aldehyde **14** to give iodide **15** in 72% yield (Scheme 4).[8] Buchwald's

Scheme 2. Proposed Retrosynthesis



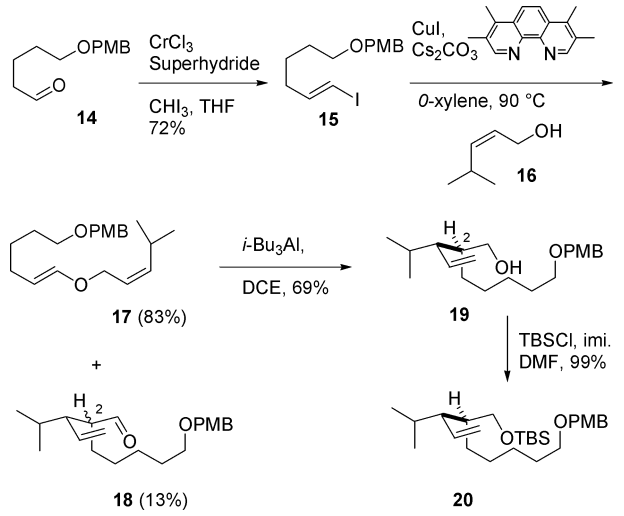
copper(I)-mediated coupling between iodide **15** and alcohol **16**[9] in the presence tetramethylphenantroline and cesium

Scheme 3



carbonate at 90 °C led to the desired enol ether **13** in 83% yield along with aldehyde **18** in 13% yield as a mixture of epimer at C2.[10] This reaction was particularly sensitive to

Scheme 4



the thermal conditions as a slight increase of the temperature above 90 °C led to a significant increase in the amount of the Claisen rearrangement product **18**. Owing to the facile epimerization of the resulting aldehyde **18**, we turned our attention toward the use of a Lewis acid that will catalyze the sigmatropic rearrangement and at the same time reduce

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(7) Pattenden, G.; Smithies, A. J.; Tapolczay, D.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 7.

(8) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

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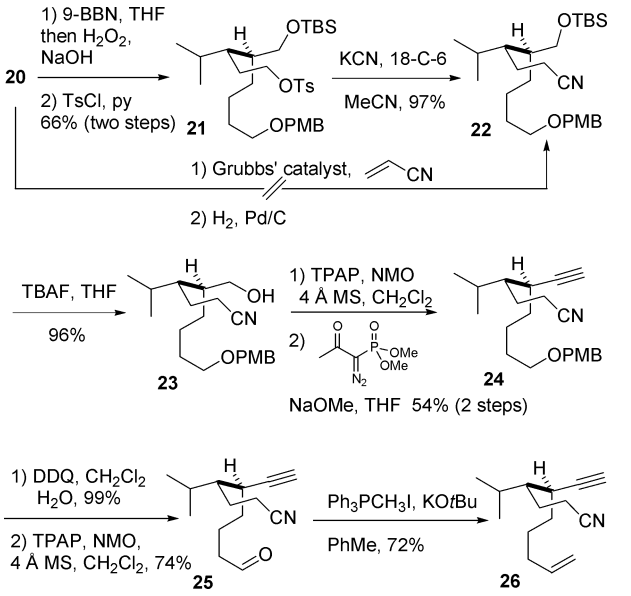
the aldehyde moiety. To this end, enol ether **17** was subjected to triisobutylaluminum (1 M in toluene) in dichloroethane to give alcohol **19** in 69% yield as the sole detectable diastereomer.[11] Protection of the primary alcohol as a siloxy ether using TBSCl and imidazole in THF provided **20** in 99% yield.

At this point, we envisaged the conversion of olefin **20** to an unsaturated nitrile through a cross-metathesis reaction which after hydrogenation should give nitrile **22** (Scheme 5). We scanned several ruthenium carbene catalysts in

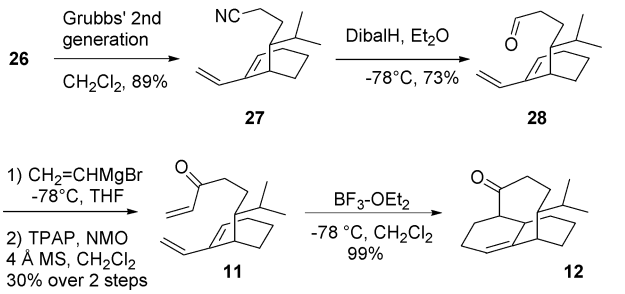
Scheme 5



various solvents. In all cases, the formation of the desired cross-metathesis product was not observed; only starting material was recovered. Other coupling partners such as methyl acrylate and *N*,*O*-dimethyl acrylamide were tried without success. To circumvent this problem, olefin **20** was treated with 9-BBN followed by an oxidative workup to give the corresponding primary alcohol. The latter was exposed to TsCl in pyridine to afford the desired tosylate **21** in 66% yield over two steps. Treatment of **21** with potassium cyanide and 18-crown-6 ether in acetonitrile led to nitrile **22** in 97% yield. Removal of the TBS group in the presence of fluoride anion gave alcohol **23** in 96% yield. TPAP oxidation of **23** generated the corresponding aldehyde, which was immediately subjected to a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate and K_2CO_3 in MeOH (Ohira's protocol).[12] The desired alkyne **24** was obtained, although, as a mixture of epimers at C2. This problem was solved using a modified version of the Ohira's protocol.[13] The sensitive aldehyde was treated with dimethyl (1-diazo-2-oxopropyl)-phosphonate in the presence of sodium methoxide in THF to provide the desired alkyne **24** as the sole diastereomer in 54% yield over two steps (64% brsm). Removal of the PMB group with DDQ followed by TPAP oxidation alcohol provided aldehyde **25** in 74% yield for two steps. Wittig olefination using Conia conditions proceeded smoothly to afford **26** in 72% yield.[14]

Transformation of **26** to diene **27** using 10 mol % of Grubbs' second-generation catalyst was achieved in 89% yield (Scheme 6).[15] Attempts to directly convert the nitrile

Scheme 6



group on **27** to the corresponding enone **11** employing vinylmagnesium bromide or vinyllithium in the presence of various additives were fruitless. However, the formation enone **11** was realized over a three steps sequence. Dibal-H reduction of the nitrile group gave the aldehyde **28** in 73% yield.

Subjection of the latter to vinylmagnesium bromide afforded the corresponding allylic alcohol which upon exposure to TPAP and NMO led to enone **11** in 30% yield over two steps. Treatment of enone **11** to BF_3·OEt_2 in dichloromethane at −78 °C gave the cycloadduct **12** in nearly quantitative yield. 2-D NMR experiments such as NOESY (blue arrow), COSY, HMQC, and HMBC (red arrow) confirmed the correct carbon−carbon connectivity of structure **12** (Figure 2).[16]

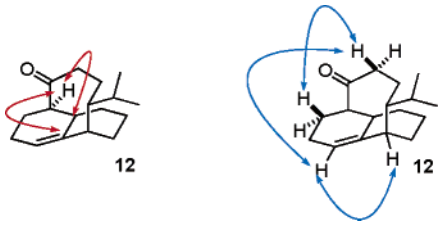


Figure 2. Sample correlations. Red = HMBC, blue = NOESY.

In addition to this, DFT calculations of the Diels−Alder reaction of triene **11** also predicted the exclusive formation

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(12) (a) Roth, G. J.; Muller, S.; Bestmann, H. J. *Synthesis* **2004**, 59. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
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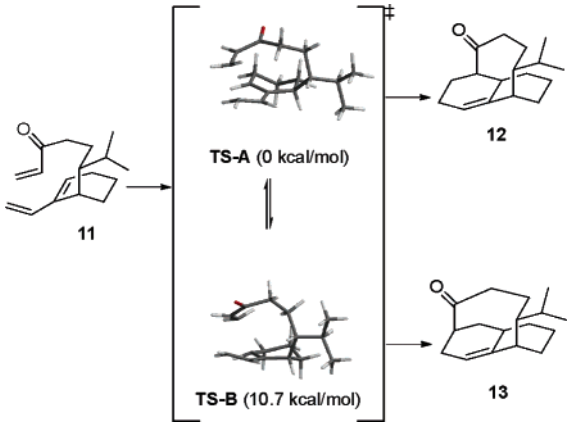
(15) Divers, S. T.; Giessert A. J. *Chem. Rev.* **2004**, *104*, 1317 and references cited therein.
(16) For a detailed analysis, see the Supporting Information.

Scheme 7



of the cycloadduct **12** over **13** (Scheme 7). DFT calculations of gas-phase relative free energies at 298 K were obtained on the Jaguar 6.0 program[17] using Khon-Sham DFT[18] at the B3LYP[19] level of theory with a 6-31G** basis set.[20] It was found that **TS-B** is 10.7 kcal/mol higher in energy than **TS-A**. This is in accord with the experimental findings.

Herein, we present a successful synthesis of the tricyclic core of vinigrol (**1**). Our approach takes advantage of a highly regioselective intramolecular Diels−Alder of the diene **11** to construct simultaneously two rings of the tricyclic vinigrol skeleton. Continued efforts toward the completion of the total synthesis of vinigrol (**1**) are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR for new compounds. NOESY, HMBC, COSY, and HMQC spectra for compound **12** are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Frequency calculations were performed to confirm that the saddle points had only one imaginary frequency.