Communication

Asymmetric Total Synthesis of (-)-Vinigrol

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Asymmetric Total Synthesis of (−)-Vinigrol

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Supporting Information Placeholder

ABSTRACT: A new strategy was developed for the asymmetric total synthesis of (−)-vinigrol. The strategy involved a linear sequence of 15 steps from 3-methyl-butanal (14 steps from chloro-dihydrocarvone) and did not need protecting groups. The synthetically challenging 1,5-butanodecahydronaphthalene core was constructed efficiently via a type II intramolecular [5+2] cycloaddition, followed by a unique ring-contraction cascade.

(−)-Vinigrol (**1**, Fig. 1), a unique, compact and biologically significant diterpene, was isolated by Hashimoto and co-workers in 1987 from the fungal strain *Virgaria nigra* F-5408.[1a] Structurally, (−)-vinigrol has an unprecedented and highly rigid 1,5-butanodecahydronaphthalene core with eight contiguous stereocenters. Notably, the strained bicyclo[5.3.1]undecane ring system in **1** is an unusual bridged framework that is also present in the well-known terpene taxol.[2] Vinigrol synthesis is therefore a formidable challenge. Vinigrol displays a number of promising biological activities,[1] e.g., it inhibits human platelet aggregation (IC_{50} = 52 nM)[1b] and is an antagonist of tumor necrosis factor (TNF-α).[1d]

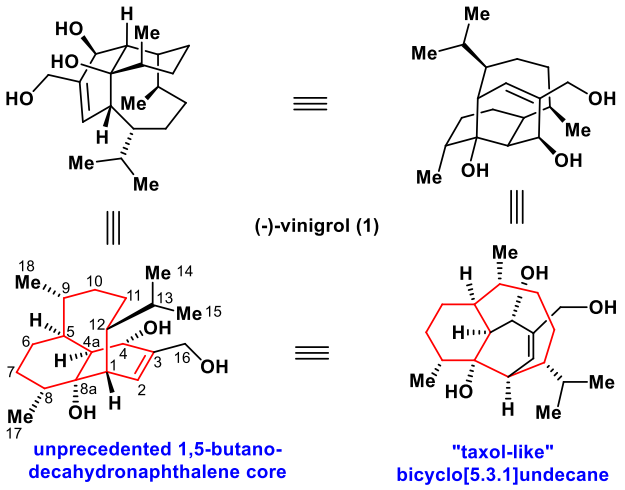
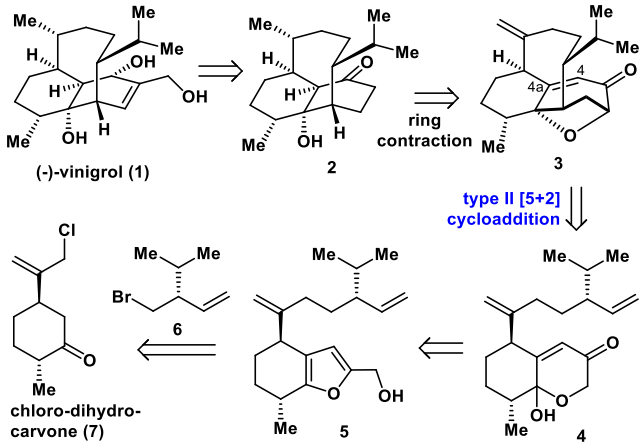


Figure 1. Structural features of (−)-vinigrol (**1**).

A combination of the complex structure and impressive pharmacological properties of vinigrol has prompted significant interest from the synthetic community for more than three decades.[3,4,5] In 2009, Baran and co-workers completed the first and most efficient total synthesis of (±)-vinigrol, with Diels–Alder reactions and Grob fragmentation as the key steps.[6] This work was a landmark achievement in vinigrol synthesis. In 2012, Barriault and co-workers reported an elegant formal synthesis of (±)-vinigrol that involved a notable type II intramolecular Diels–Alder reaction.[7a] In 2013, Njardarson and co-workers reported another elegant total synthesis of (±)-vinigrol, with remarkable oxidative dearomatization and intramolecular Diels–Alder reactions as the key steps.[8] Very recently, Luo and co-workers reported the first asymmetric total synthesis of (−)-vinigrol via a well-designed transannular Diels–Alder reaction as the key step.[9] In all of these noteworthy achievements the Diels–Alder reaction was a crucial element in the synthetic strategy of vinigrol. However, the development of a new strategy for the synthesis of **1** and its analogues is still desirable. Herein, we wish to describe the asymmetric total synthesis of (−)-vinigrol using a type II intramolecular [5+2] cycloaddition as a new strategy.

Scheme 1 shows the bond disconnections in (−)-vinigrol that led to the concise strategy used in our synthetic program. It was envisioned that (−)-**1** could be generated from the tricyclic core **2** through a series of functional group transformations. Compound **2**, which has a 1,5-butanodecahydronaphthalene core, would be synthesized from **3** or its derivative by ring-contraction reactions.[10] In turn, the bridged framework **3** with a strained bridgehead double bond[11] at C4–C4a (vinigrol numbering throughout) could be synthesized diastereoselectively from **4** by a type II intramolecular [5+2] cycloaddition.[12,13] Compound **4** can be derived from **5** through an Achmatowicz reaction. Lastly, compound **5** can be prepared from readily available bromide **6** and commercially available chloro-dihydrocarvone (**7**) as the chiral pool[14] via several simple functional group transformations.

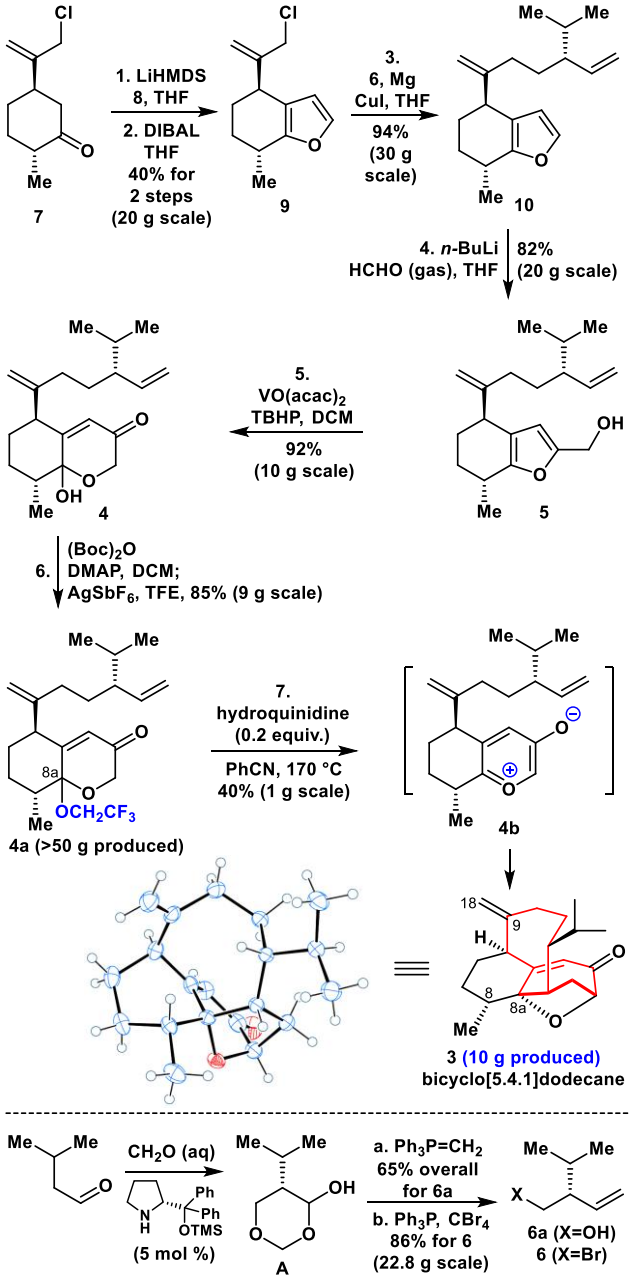
Scheme 1. Retrosynthetic analysis of (−)-vinigrol (1)



The synthesis began with an asymmetric preparation of

compound **5** (Scheme 2). The starting material **7** was treated with LiHMDS and 2-chloroacetyl chloride (**8**) in THF, followed by reduction of the resulting furanone with DIBAL to give furan **9** in an overall yield of 40% (20 g scale). The bromide **6**[15] was produced on a large scale by organocatalytic enantioselective α-hydroxymethylation of 3-methyl-butanal,[15c] followed by Wittig olefination and brominating. Treatment of chloride **9** with a Grignard reagent formed from bromide **6** in the presence of CuI in THF gave compound **10** in 94% yield (30 g scale). Hydroxymethylation at the α position of the furan ring in **10** with *n*-BuLi and formaldehyde provided **5** in 82% yield (20 g scale). Oxidative rearrangement of **15** with $VO(acac)_2$ and TBHP in DCM gave **4** in 92% yield (10 g scale), which was the precursor for the type II intramolecular [5+2] cycloaddition.

Scheme 2. Asymmetric Synthesis of 3



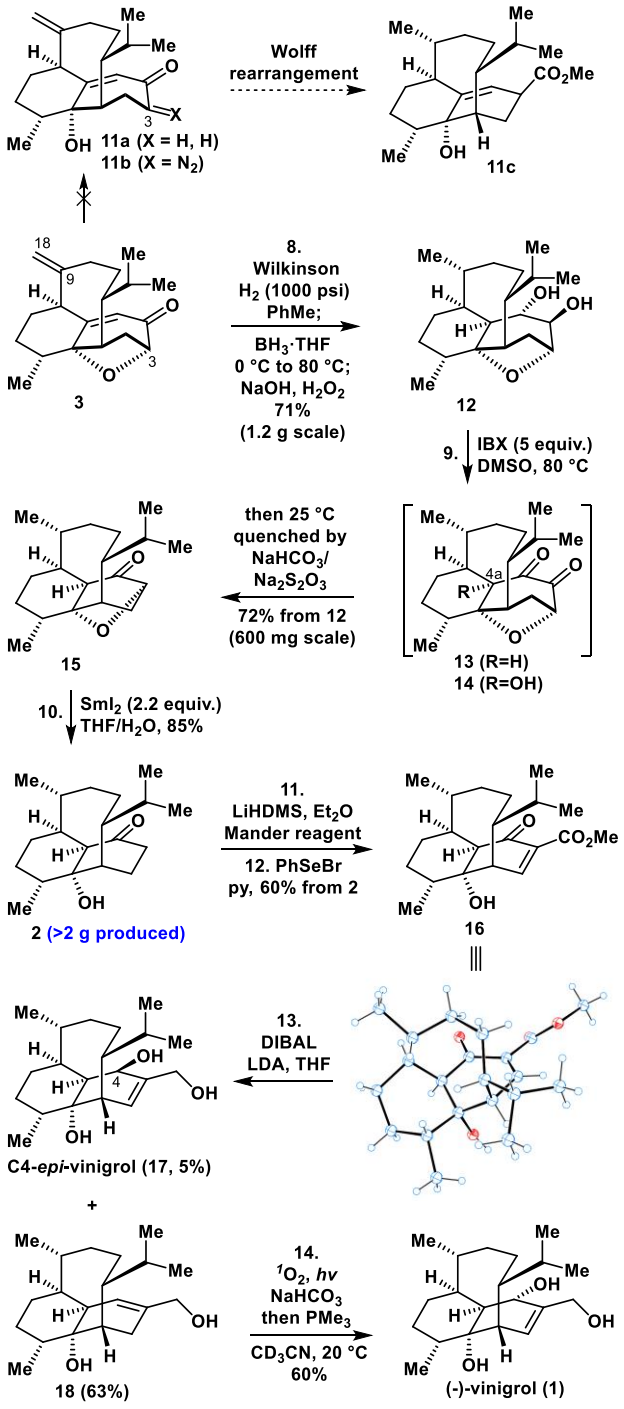
The key step of the type II intramolecular [5+2] cycloaddition reaction was developed by our group in 2014.[12a] The reaction involves the oxidopyrylium ylide and a simple alkene such as **4b**. It enables the efficient, diastereoselective, and direct construction of various highly functionalized and synthetically challenging bridged skeletons such as **3**. However, the presence of the additional C9–C18 double bond in the bicyclo[5.4.1]dodecane or bicyclo[5.3.1]undecane ring system of **3** (highlighted in red in Scheme 2), which has not previously been reported, increases the strain in the molecule.[12] To the best of our knowledge, there are no reports in the literature to date pertaining to intramolecular [5+2] cycloaddition reactions (a) of aliphatic ring-fused oxidopyrylium ylides such as **4b** or (b) to construct eight-membered ring systems in natural product synthesis.[12,13] Furthermore, the formation of a C8a quaternary stereogenic bridgehead carbon center in a bridged ring system in **3** makes this reaction particularly challenging.

After extensive experimentation (Scheme 2), we found that compound **4a** with a trifluoroethoxyl group at C8a was a good and stable precursor of the oxidopyrylium ylide **4b** for the type II intramolecular [5+2] cycloaddition. Compound **4a** was prepared from **4** with Boc anhydride in the presence of DMAP,[12b] followed by trifluoroethoxylation with 2,2,2-trifluoroethanol (TFE) in the presence of $AgSbF_6$[16] in one pot (85% yield, 9 g scale). Under optimized conditions (see the Supporting Information (SI) for details), the type II intramolecular [5+2] cycloaddition of **4a** was realized using a catalytic amount of hydroquinidine (0.2 equiv.) as a base with heating, giving the [6–8–7] tricyclic core-containing **3** in 40% yield (1 g scale). This was confirmed by X-ray crystallography. To the best of our knowledge, this work represents the first reported example of the use of a trifluoroethoxyl leaving group to generate the oxidopyrylium ylide in a [5+2] cycloaddition.[13] This route provided facile access to a total of 10 g of **3** (see SI for details), which highlights the robust nature of the chemistry. It is worth noting that our type II intramolecular [5+2] cycloaddition enabled efficient construction of the taxol-like bicyclo[5.3.1]undecane framework in **3**. Furthermore, this reaction enabled the concise, diastereoselective, and direct installation of the C8a oxyl and C8 methyl groups, which has previously proved to be a difficult task because of their *cis* orientation.[3x,4f,6,7a,8a]

With compound **3** in hand, we investigated our proposed synthesis of the 1,5-butanodecahydronaphthalene skeleton of vinigrol by a ring-contraction reaction (Scheme 3). We initially tried a Wolff rearrangement[17] to obtain **11c**. It was expected that selective cleavage of the C3–O bond and installation of a diazo group at C3 would give the precursor **11b** for the Wolff rearrangement. Although a wide variety of conditions were screened (i.e., SmI_2, Li/NH_3, Na/NH_3, and $Li/EtNH_2$[12c]), none of these reactions afforded any of the desired product **11a** by selective cleavage of the C3–O bond. Extensive experimentation suggested that diketone **13** would be a good precursor for the preparation of the α-keto diazo compound.[17e] Therefore, chemoselective hydrogenation of the C9–C18 olefin in **3** with Wilkinson's catalyst employing 1000 psi of H_2 in PhMe, followed by diastereoselective hydroboration–oxidation of the enone with BH_3•THF in a one-pot sequence, gave diol **12** in an overall yield of 71% (1.2 g scale). Subsequent treatment of **12** with 2-iodoxybenzoic acid (IBX, 2.0 equiv) in DMSO at 80 °C gave the unexpected product **14** (30%), a certain amount of mono-ketone product **S4** (see SI, 30%), the surprising ring-contraction product **15** (10%), and some unidentified byproducts. However, none of the expected **13** was isolated. We reasoned that formation of the 1,5-butanodecahydronaphthalene core **15** probably occurred via the following pathway (Scheme 4). In the presence of IBX in DMSO at 80 °C, diketone **13**, produced from **12**, was spontaneously oxidized to C4a-hydroxyl diketone **14**. Intramolecular attack of the C4a-hydroxyl group in **14** on the less hindered carbonyl group would yield oxetanone[18] **14a**, which could undergo rearrangement of the C3 to the C4-carbonyl group to give unstable β-lactone **14b**, which can be isolated and whose structure was determined by 2D-NMR, MS and IR (see SI for details). Subsequent spontaneous decarboxylation of the β-lactone[19] gave enol **14c**, which underwent keto–enol

tautomerization to generate the desired product **15** diastereoselectively. We further optimized the reaction conditions and finally identified the following optimum protocol. When **12** was treated with IBX (5.0 equiv.) in DMSO at 80 °C for 2 h, followed by quenching with $NaHCO_3/Na_2S_2O_3$ in one pot, **15** was obtained in 72% isolated yield (600 mg scale). Under the similar conditions, the isolated **14** or **14b** reacted further to give **15** in good yield, respectively.

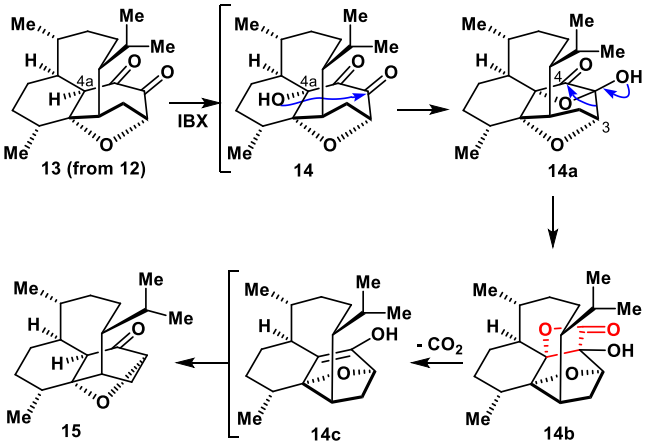
Scheme 3. Asymmetric Total Synthesis of (−)-Vinigrol



It is worth noting that there are few reports in the literature pertaining to this direct ring-contraction reaction of cyclic 1-hydroxyl-2,3-diones,[20] which could also be precursors for synthesis of α-keto diazo compounds for the Wolff rearrangement.[17e] This mild reaction could be an alternative method for ring contraction in some cases. Further studies of the use of this reaction in total synthesis, and a mechanistic study, are currently underway in our laboratory.

Next, treatment of **15** with SmI_2 (2.2 equiv.) in THF/H_2O afforded compound **2** in 85% yield. The ketone **2** was treated with LiHDMS and Mander's reagent (methyl cyanoformate) in Et_2O, followed by phenylselenylation with PhSeBr and spontaneous elimination[21] to give enone-ester **16** in 60% yield (77% yield based on recovered starting material). This was confirmed by X-ray crystallography.[22] Then, we tried to reduce the ketone and ester groups of **16** diastereoselectively and chemoselectively in one step, to obtain (−)-**1**. However, it was found that this was a very challenging task after extensive experimentation. Interestingly, treatment of **16** with DIBAL in the presence of LDA in THF gave C4-*epi*-vinigrol **17** (5%) and compound **18** (63%) (see SI for more details). Finally, a slightly modified version of a previous procedure[9,23] for the singlet oxygen–ene reaction of **18** was used, completing the asymmetric total synthesis of (–)-**1** in 60% yield.

Scheme 4. Proposed pathway from 13 to 15



In summary, we have achieved the concise asymmetric total synthesis of (−)-vinigrol (**1**) via a linear sequence of 15 steps[24] from 3-methyl-butanal (14 steps from chloro-dihydrocarvone), without the need for protecting groups.[25] Notably, the synthetically challenging 1,5-butanodecahydronaphthalene core of (−)-**1** was synthesized efficiently via a type II intramolecular [5+2] cycloaddition of a new precursor, **4a**, using a catalytic amount of base, followed by a unique IBX-induced decarboxylative ring-contraction cascade. To the best of our knowledge, this work represents the first example of an intramolecular [5+2] cycloaddition to construct eight-membered ring systems in natural product synthesis. Furthermore, the eight contiguous stereocenters, including the challenging C8a oxyl and C8 methyl groups in a *cis* orientation, were constructed simply and diastereoselectively. This new strategy will enable the diverse synthesis of vinigrol analogues from various analogues of **6** or **7** to facilitate further biological research, which is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedure, and ^1H NMR and ^{13}C NMR spectra, as well as X-ray data information are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(22)Owing to the small size of the crystal, the intensity of reflections at high 2theta is too weak to be collected. Thus, its absolute configuration was not determined.

(23)CD_3CN was used instead of $CDCl_3$ because it was found that vinigrol was slightly decomposed in $CDCl_3$ in our case. We also found that the temperature had a great influence on the yield of this reaction. When the reaction occurred at room temperature (about 30 °C) in Shenzhen, the yield is less than 10%.

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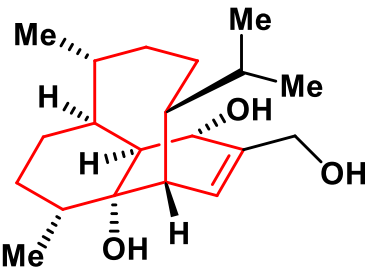

unprecedented 1,5-butano-decahydronaphthalene core

(-)-vinigrol

- **14 or 15 steps**
- **Type II [5+2]**
- **IBX-induced decarboxylative ring contraction**