Communication

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Supporting Information Placeholder

ABSTRACT: Vinigrol is a structurally and stereochemically complex natural product that displays various potent pharmacological activities, including the capability to modulate TNF-α. A new and efficient synthetic route towards this natural product has been developed to complete the asymmetric synthesis of (−)-vinigrol and provide over 600 mg material, manifesting the power of macrocyclic stereocontrol and transannular Diels-Alder reaction.

First isolated from a fungal strain in Japan by Hashimoto and co-workers, vinigrol (**1**, Fig. 1) occupies a special position in natural product small molecules.[1] Among the structurally diverse terpenoids, vinigrol is the only one that is characterized by the 6-6-8 tricyclic ring system with the axial four-carbon tether bridging the densely decorated *cis*-decalin core. This natural product displays potent antihypertensive and platelet aggregation-inhibiting properties,[2] and has been reported as an antagonist for tumor necrosis factor α (TNF-α),[3] which intrigues us the most.

Numerous research efforts have been oriented towards the chemical synthesis of vinigrol since its discovery in 1987, which have been reviewed.[4] However, to date there are only three routes to accomplish this molecule (Fig. S1).[5] The first and most efficient synthesis of racemic vinigrol was reported by Baran group in 2009, which promptly constructed the vinigrol skeleton by Diels–Alder reactions and the Grob fragmentation, while the endgame functionalization took another 12 steps.[5a] Afterwards, the approach reported by Barriault and co-workers used a Claisen rearrangement and a type II intramolecular Diels-Alder reaction to forge the vinigrol carbocyclic core, but again another 12 steps were needed to afford the target molecule.[5b] Based on this approach, Kaliappan group completed an enantioselective formal synthesis by intercepting the vinigrol carbocyclic core.[5d] Another remarkable achievement was reported by Njardarson and co-workers, which creatively carried out a sequence of oxidative dearomatization/IMDA reaction, cascade Heck cyclization, and fragmentation to construct the 6-6-8 tricyclic ring system, but another 14 steps were required to finish vinigrol.[5c] Therefore, the challenges of chemical synthesis of vinigrol reside in not only the prominent and complex molecular framework but also 8 continuous stereogenic centers with unique substitution patterns. Herein, we wish to report a new strategy that provides a simple solution to both problems, leading to a scalable synthesis of (−)-vinigrol to facilitate the mechanism-of-action studies of this natural product.

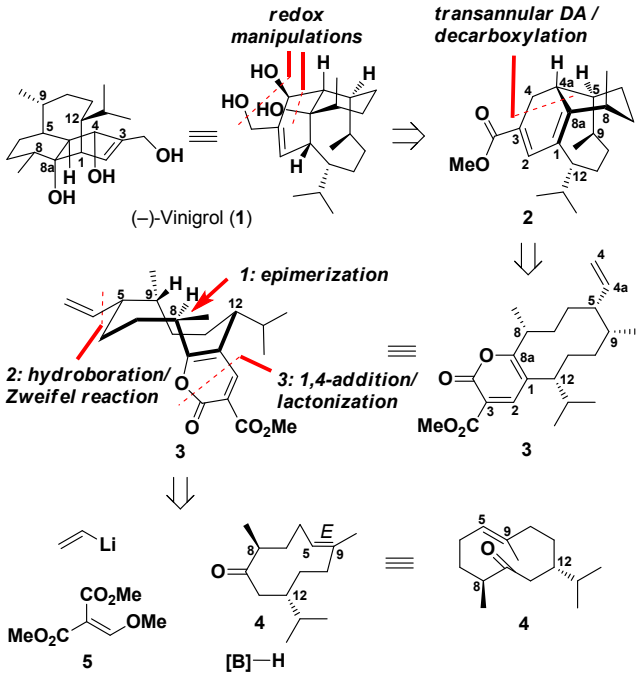


Figure 1. Retrosynthetic analysis of (−)-vinigrol (**1**).

In contrast to previous tactics, we envisioned that the three hydroxyl groups in vinigrol could be derived from redox manipulation of diene **2**, a highly strained intermediate with the bridgehead alkene.[6] The disconnection using inverse-electron-demand transannular Diels-Alder reaction followed by in situ extrusion of CO_2 traced back to electron-deficient α-pyrone **3**. In order to achieve a highly efficient approach, we were intrigued by the possibility of synthesizing **3** from substituted cyclodec-5-enone **4**, the enantiomer of which had been prepared by both Wu group and Mehta group starting from (*R*)-(−)-carvone and (*R*)-(+)-limonene, respectively (Fig. S2).[7] Therefore, the other key strategic disconnections involved: (1) epimerization of C8 stereogenic center (vinigrol numbering, throughout); (2) hydroboration of C5-C9 olefin followed by Zweifel reaction;[8] and (3) constructing the α-pyrone motif via the condensation of dimethyl methoxymethylenemalonate **5** with an appropriate ketone.[9] Given

the strong transannular (C8-C9) and A(1,3) interactions (C8-C12) in **3**, we envisioned the first task to be executed lastly. In the second task, even though the hydroboration of the C5-C9 *E*-olefin would secure the trans relationship of C5 vinyl and C9 hydrogen after the Zweifel reaction, the absolute stereochemistry would be subjected to the cyclodecene macrocyclic stereocontrol.[10] The third task seemed straightforward but significant amount of experimental exploration was anticipated, which would fine-tune the transformation sequence to address the subtlety of stereocontrol and minimize the use of protecting groups.

We commenced our work by preparing enantiopure **7** from (*S*)-(−)-limonene (**6**) (Scheme 1).[11] In comparison to the reported protocols (Fig. S2),[7] we carried out further optimizations to scale up the preparation of (+)-**4**. It was therefore discovered that the addition of the organocerium reagent to the ketone in **7** robustly afforded alcohol **8** in 84% isolation yield on a decagram scale, whereas the epimer was obtained in 11% yield and could be converted to a equilibrated mixture containing **8** (see SI for details).[12] Regarding to the subsequent oxy-Cope rearrangement, it was necessary to quench the enolate intermediate at −78 °C by MeOH to afford cyclodecenones **4** and **9** in excellent yield, with a ratio of 3.4:1 as determined by ^{1}H-NMR (Table S1). However, given **4** and **9** were hardly separable by routine flash chromatography on silica gels, they were subjected to $LiAlH_4$ reduction to furnish a pair of separable diastereomeric alcohols, **10** and **11**. Pure **4** and **9** were obtained by oxidation of **10** and **11**, respectively; the minor product, **11**, could therefore be recycled to **4** via oxidation and epimerization (see SI).

It was noteworthy that the X-ray diffraction of ketone **4** revealed a chair-chair-chair conformation, whereas alcohol **10** adopted a boat-chair-boat conformation that shielded the *Si* face of C5-C9 olefin (Fig. 2). To our delight, hydroboration of **10** followed by the formation of pinacol boronate afforded **12** as the major product (hydroboration from the *Si* face), while **13** (hydroboration from the *Re* face) turned out to be the minor one. Their structures were determined by the X-ray diffraction of corresponding diols **23** and **24** obtained by H_2O_2 oxidation (Fig. 2). Whether the observed selectivity was under control by the Curtin−Hammett principle[13] or the hydroxyl-directed hydroboration,[14] which could also depend on the reagents and reaction conditions employed, invites further investigations (see Fig. S3 and discussion in SI for details). After extensive optimizations (see Table S2 and discussion in SI for details), the best result was obtained by applying a one-pot procedure: reaction of **10** with (+)-$IpcBH_2$ was followed by treatment with acetaldehyde to remove (−)-α-pinene,[15] and the resulting diethylboronic ester underwent transesterification with excess pinacol, affording **12** in 71% isolated yield on 5-gram scale.

Subsequently, the Zweifel olefination reaction of **12** provided **14** in 92% yield, though excess vinyllithium was employed providing the alcohol was not protected. Oxidation of **14** afforded ketone **15** in excellent yield, setting the stage for the installation of the α-pyrone. Using the method developed by Boger's group,[9] cyclodecanone **15** was smoothly converted to α-pyrone **16**. By heating **16** in the presence of DBU in toluene at 100 °C for 24 h, 92% of **16** could be epimerized to **3**; this pair of epimers were readily separated. Subjecting **3** to the microwave irradiation at 200 °C in 1,2-dichlorobenzene led to the desired product, **2**, and the major side products were identified to be **17** and **18**; the mechanism for the formation of them was proposed (Fig. S4). The confirmation of the strained tricyclic skeleton of **2** was achieved by obtaining the X-ray crystallography of the DIBAL reduction product, alcohol **25** (Fig. 2). The mixture of **2**, **17** and **18** could be used directly in the next step on the gram-scale reaction, in which highly facial-selective cycloaddition of $^1O_2$ across the diene of **2** afforded **19** (87% yield) and **17**/**18** were completely recovered. Reductive cleavage of the resultant peroxide linkage and hydrogenation of the olefin in **19** were achieved concomitantly to give diol **20** in quantitative yield. In comparison, treatment of **19** with SmI_2 only reduced the peroxide to give diol **26**, as confirmed by X-ray crystallography (Fig. 2).

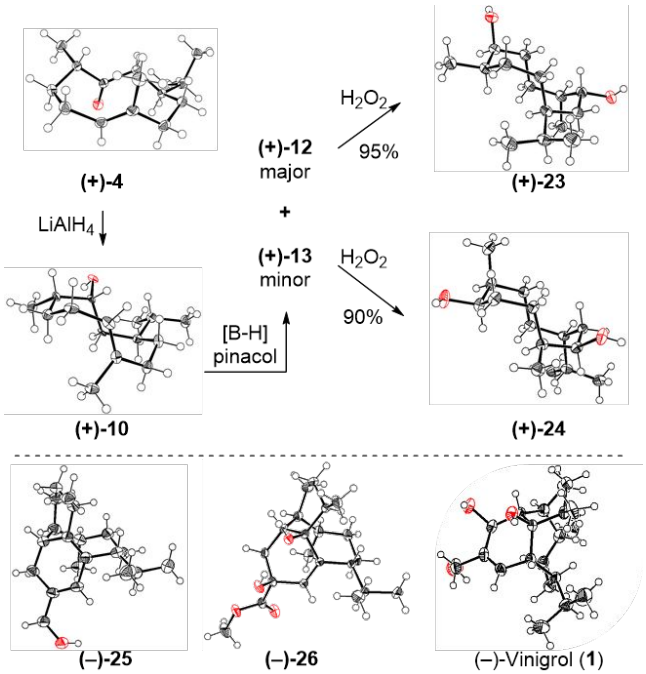
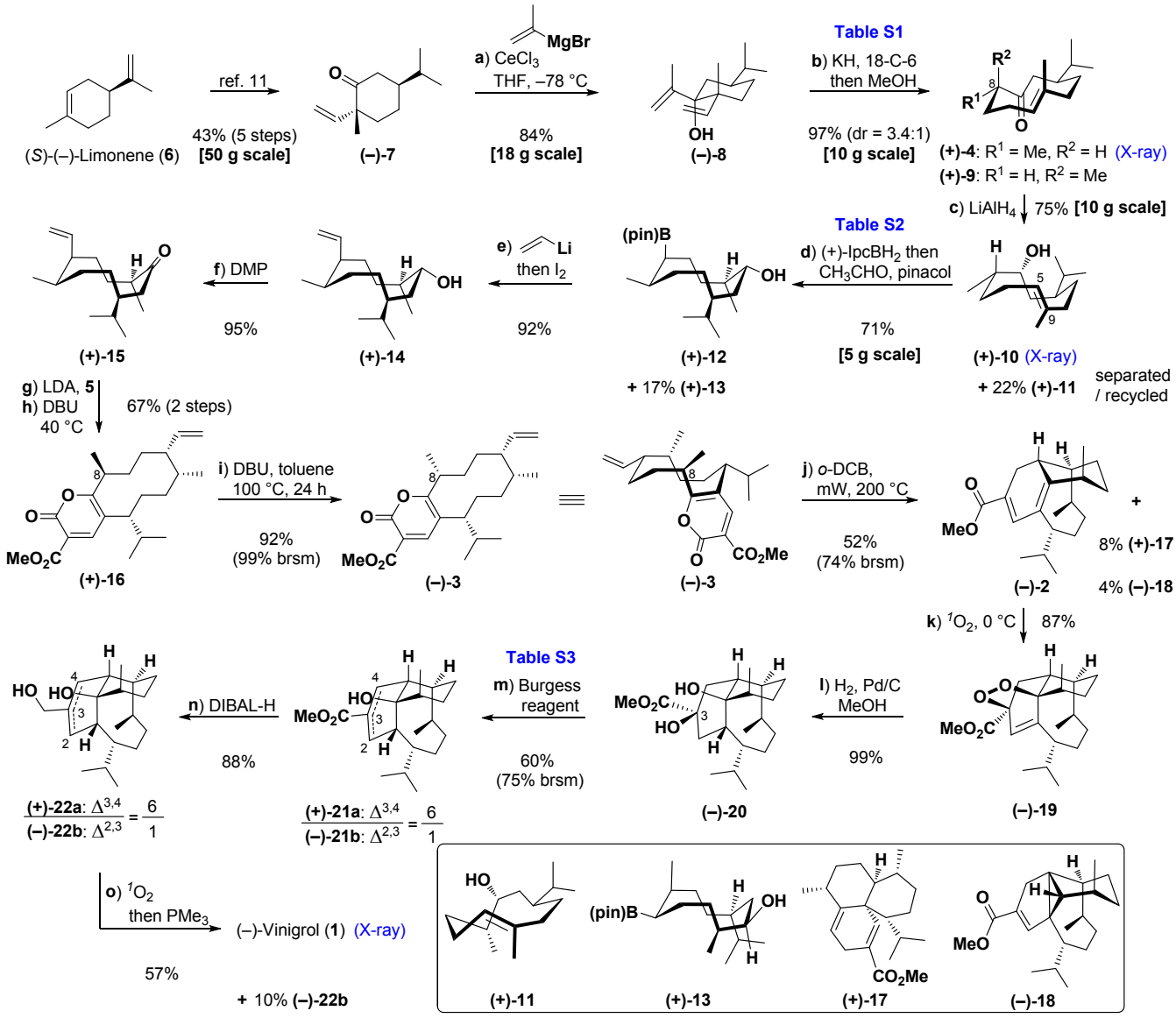


Figure 2. ORTEP of (−)-vinigrol (**1**), synthetic intermediates and related derivatives.

Scheme 1. Synthesis of (−)-Vinigrol (1)[a]



[a]***All reactions were carried out on a gram-scale if not specified.*** Reagents and conditions: a) $CeCl_3$ (2.0 equiv), Isopropenylmagnesium bromide (2.0 equiv), THF, −78 °C, 81%; b) KH (1.2 equiv), 18-C-6 (1.2 equiv), then MeOH, −78 °C, 97% (dr = 3.4:1); c) $LiAlH_4$ (2.2 equiv), rt; **10**, 75%; **11**, 22%; d) (+)-$IpcBH_2$ (2.4 equiv), THF, 0 °C, then CH_3CHO (20 equiv); pinacol (4.0 equiv), DCM, 40 °C; **12**, 71%; **13**, 17%; e) Tetravinyltin (2.5 equiv), *n*-BuLi (5.0 equiv), rt to −78 °C, 2 h, −40 °C, 0.5 h, THF/Et_2O, then I_2 (5.1 equiv), −78 °C, then NaOMe (7.0 equiv), −78 °C to rt, 92%; f) DMP (2.0 equiv), Pyridine (6.0 equiv), DCM, rt, 95%; g) LDA (1.1 equiv), **5** (1.2 equiv), THF, −78 °C; h) DBU (4.0 equiv), toluene, 40 °C, 67% (2 steps); i) DBU (1.0 equiv), toluene, 100 °C, 92%, 99% brsm; j) *o*-DCB, mW, 200 °C; **3**, 52%, 74% brsm; **17**, 8%; **18**, 4%; k) TPP (0.01 equiv), air (1 atm), $CHCl_3$, 0 °C, 87%; l) Pd/C (0.25 equiv), NaOAc (0.3 equiv), H_2 (1 atm), MeOH, rt, 99%; m) Burgess reagent (1.1 equiv), toluene/DCM, −40 to 40 °C, 60%, 75% brsm; n) DIBAL-H (3.0 equiv), DCM, −78 °C, 88%; o) TPP (0.01 equiv), O_2 (1 atm), $CDCl_3$, rt; **1**, 57%; **22b**, 10%. $IpcBH_2$, monoisopinocampheylborane; DMP, Dess-Martin periodinane; LDA, lithium diisopropylamide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; *o*-DCB, 1,2-dichlorobenzene; TPP, *meso*-tetraphenylporphin.

The rigid and strained skeleton of **20** allowed for the selective elimination of the C3 hydroxyl group, delivering **21** in 60% yield with 6:1 selectivity for $\Delta^{3,4}$ unsaturation (**21a**) over $\Delta^{2,3}$ (**21b**). By varying the elimination conditions, different ratios of **21a** and **21b** could be obtained, with one extreme affording only **21b** (Table S3). DIBAL reduction of **21** afforded diols **22a/b** in high yield, which were then subjected to the singlet oxygen ene reaction. We took advantage of the solvent deuterium isotope effect to improve the efficiency of the last step,[16] completing (−)-vinigrol (**1**) on a gram scale reaction (57% isolation yield), whereas **22b** was not oxidized and recovered after the reaction. All of the analytic data for the synthesized sample of **1** were consistent with those reported in the

literature (Table S4).[1,5] Besides **1**, **4**, **10**, **23**, **24**, **25** and **26**, the structures of **11**, **17** and **18** were also determined by the X-ray diffraction of corresponding derivatives (see SI).

In summary, we have developed a concise and scalable synthesis to accomplish (−)-vinigrol. Each step of this route has been optimized and validated on a gram-scale reaction whereas all the reagents shown in Scheme 1 were commercially available. But the synthetic approach is not without flaw. Even if the efficiency of our approach in terms of the overall steps is high (20 steps from *S*-limonene), the overall yield (1.4%) is lower than that of Baran's for racemic vinigrol (2.7%).[5a] If (+)-vinigrol is required, (*R*)-(+)-limonene would be needed. Nonetheless, our new strategy enabled the execution of carefully orchestrated transformations to construct such a strained framework and uniquely substituted stereogenic centers without the use of protecting groups. The investigation of the biological activities of (−)-vinigrol are ongoing, which will be reported in due course together with the evolution of our synthetic strategies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystallographic data for **(−)-1** (CIF)
X-ray crystallographic data for **(+)-4** (CIF)
X-ray crystallographic data for **(+)-10** (CIF)
X-ray crystallographic data for **(+)-23** (CIF)
X-ray crystallographic data for **(+)-24** (CIF)
X-ray crystallographic data for **(−)-25** (CIF)
X-ray crystallographic data for **(−)-26** (CIF)
X-ray crystallographic data for **(−)-S4** (CIF)
X-ray crystallographic data for **(+)-S5** (CIF)
X-ray crystallographic data for **(+)-S6** (CIF)
X-ray crystallographic data for **(−)-S7** (CIF)

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Notes

The authors declare the following competing financial interest(s): T. L., Y. X. and L. X. are inventors on patent application ZL201811276421.1 submitted by Peking University that covers the synthesis of (−)-vinigrol and related analogs.

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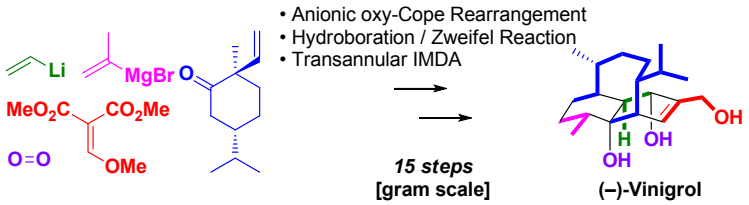
Li
MgBr
O
MeO2C
CO2Me
O=O
OMe
• Anionic oxy-Cope Rearrangement
• Hydroboration / Zweifel Reaction
• Transannular IMDA
15 steps
[gram scale]
OH
H
OH
OH
(–)-Vinigrol