Communications

Natural Products Synthesis

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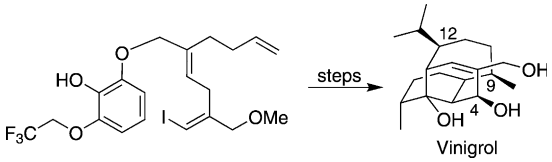
Total Synthesis of Vinigrol



Carbocyclic cage fight: The substrate controlled total synthesis of vinigrol features a strategic oxidative dearomatization/Diels–Alder cycloaddition reaction and a subsequent palladium-catalyzed cyclization cascade to construct the carbocyclic core. The C4, C9, and C12 stereocenters were installed using either reduction or oxidation reactions, and the diterpenoid core was unraveled by a ring fragmentation reaction.

Natural Products Synthesis

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Total Synthesis of Vinigrol**

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Diterpenoids are an important and structurally diverse class of natural products. In 1987, Hashimoto and co-workers reported a new diterpenoid with a unique bridged bicyclic core densely decorated with eight stereocenters.[1] The authors named this new natural product vinigrol. As evident from the three structural perspectives shown in Figure 1,

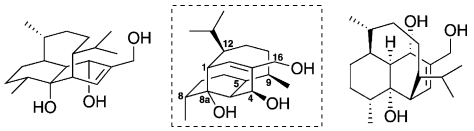


Figure 1. Vinigrol structural perspectives.

vinigrol's architecture is quite striking. Most notable is the axial four-carbon tether which bridges the two six-membered rings of the decalin in such a way that a very rigid and compact framework results. Vinigrol has been evaluated in numerous biological assays and shown to impact platelet aggregation,[2] and act as a tumor necrosis factor (TNF) antagonist,[3] as well as displaying other interesting properties.[4] Vinigrol's unprecedented structure and intriguing biological profile have prompted numerous attempts at its synthesis.[5] In 2009, Baran[6] and co-workers reported the first total synthesis of vinigrol and a few years later Barriault[7] published a formal synthesis of vinigrol.

Although details of our strategy have evolved over time,[8] we have remained faithful to several design features. The following reactions have been and still are critical to our vinigrol synthesis plan: 1) one-pot oxidative dearomatization/Diels–Alder reaction, 2) tandem 6-*exo*-trig cyclizations to form the carbocyclic core, 3) fragmentation to unravel the bridged bicyclic architecture, and 4) use of the rigid carbocyclic core to install stereocenters in a substrate-controlled manner. Our retrosynthetic analysis for vinigrol is outlined in Figure 2. Initial plans called for a late-stage carbanion-mediated fragmentation of the rigid cagelike structure **2**, wherein the functional groups for this key reaction would originate from the ketal **3**. The cage architecture (**4**) would

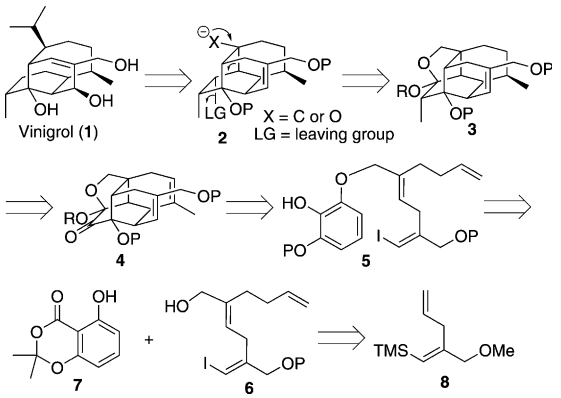
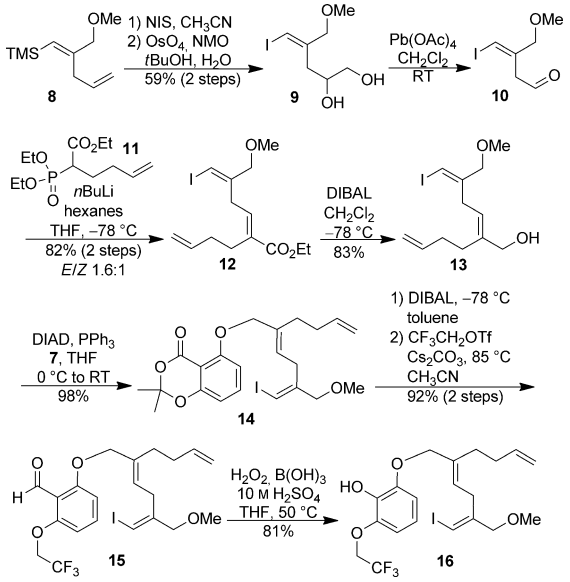


Figure 2. Vinigrol retrosynthesis.

direct installation of the C8 and C9 methyl stereocenters, and would be assembled in two steps by dearomatization of the pyrogallol ether **5**. The components for the oxidative dearomatization precursor (**5**) would be synthesized from the known compounds **7**[9] and **8**.[10]

Synthesis of the oxidative dearomatization precursor is presented in Scheme 1. After iodination of **8**, the terminal olefin was selectively dihydroxylated (**9**) and oxidatively cleaved to afford the aldehyde **10**. Horner–Wadsworth–Emmons olefination with the phosphonate **11**[11] yielded the



Scheme 1. Synthesis of oxidative dearomatization precursor. DIAD = diisopropylazodicarboxylate, DIBAL = diisobutylaluminum hydride, NMO = *N*-methylmorpholine-*N*-oxide, NIS = *N*-iodosuccinimide, THF = tetrahydrofuran.

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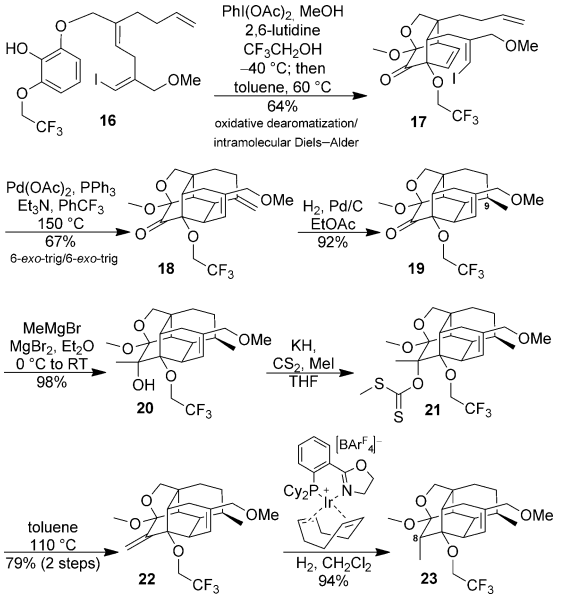
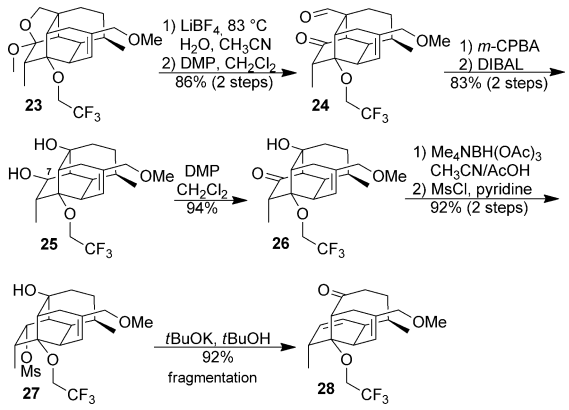
enoate **12**, which was then reduced to the corresponding allylic alcohol. Attachement of the aromatic moiety (**7**) was accomplished using a Mitsunobu reaction. To set the stage for the key oxidative dearomatization reaction, the carboxylate needed to be converted into a free phenol and the adjacent hydroxy group protected in such a way that it was electronically deactivated to guide the oxidative dearomatization reaction towards the more hindered site and suppress unwanted opening of the intermediate acetal. These goals were accomplished by first treating **14** with DIBAL and then protecting the free phenol as β,β,β-trifluoroethyl ether (**15**). Dakin oxidation then converted **15** into the phenol **16**.[12]

After optimization of the oxidative dearomatization reaction, we were rewarded with high yields of intramolecular Diels–Alder cycloadduct **17** (Scheme 2). A Heck cyclization



Scheme 2. Synthesis of the carbocyclic core of vinigrol.

cascade afforded the carbocyclic core of vinigrol (**18**) in only two steps from **16**. During the Heck cyclization 11% of the product isomerized to a trisubstituted olefin isomer of **18**. This was inconsequential for the next step as both isomers were expected to afford **19** in the subsequent step. We next turned our attention to the installation of the congested C9 and C8 stereocenters. Hydrogenation of the carbocyclic cage predictably afforded the C9 methyl stereocenter (**19**). The C8 methyl stereocenter proved far more challenging to install. All attempts at converting the C8 ketone of **19** into a methylene group (**22**) using either direct olefination or addition/dehydration strategies failed. This problem was finally solved by first converting **19** into **20**, and derivatizing the resulting alcohol[13] as a xanthate (**21**) which was then subjected to Chugaev elimination (**22**). Unfortunately, when the *exo* olefin of **22** was subjected to classical heterogeneous hydrogenation conditions only the undesired C8 epimer was obtained. Remarkably, this problem could be solved by using iridium-catalyzed directed hydrogenation (**23**).[14] Presumably, the



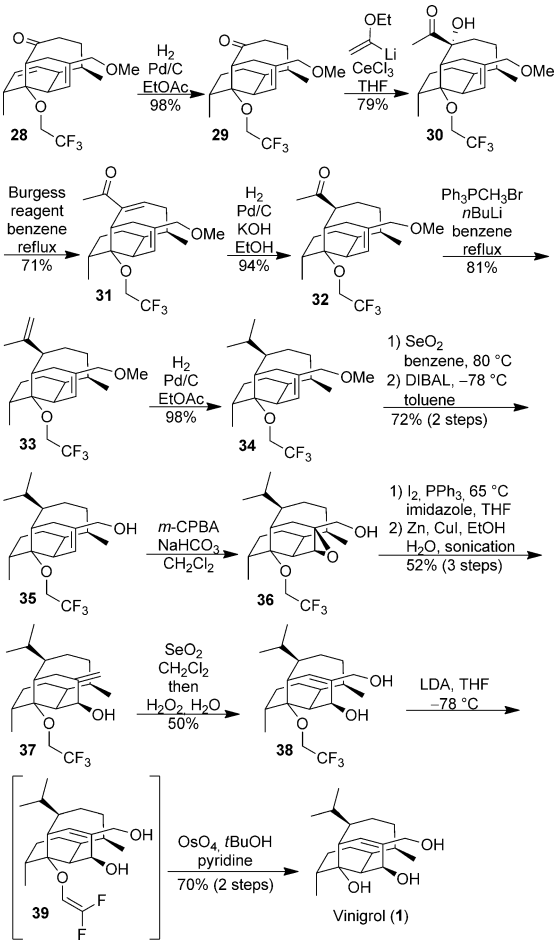
Scheme 3. Fragmentation—synthesis of the vinigrol core. DMP = Dess–Martin periodinane, *m*-CPBA = *meta*-chloroperbenzoic acid, Ms = methanesulfonyl.

iridium catalyst first coordinates to the furan oxygen atom prior to hydrogen transfer.

We next turned our attention to opening up the tetracyclic cage by fragmentation (Scheme 3). After a few unsuccessful attempts at carbanion fragmentation, we chose to pursue a Wharton fragmentation (**27**→**28**) strategy. Towards that end, the acetal **23** was opened and the resulting alcohol oxidized to an aldehyde (**24**), which we found could be oxidized selectively using a Baeyer–Villiger reaction and then exhaustively reduced (**25**). Although **25** is potentially competent for fragmentation, the C7 epimer would be better aligned. Inversion[15] and derivatization of the secondary alcohol as a mesylate (**27**) was straight forward. We were delighted to find that the desired Wharton fragmentation[16] reaction proceeded in high yield to produce the vinigrol core (**28**).

To complete the total synthesis of vinigrol we needed to address three final challenges: 1) convert the C12 ketone into an isopropyl group, 2) add the C4 hydroxy group, and 3) deprotect the C8a trifluoroethyl ether. We started our endgame journey by first tackling the C12 isopropyl group installation (Scheme 4).

After hydrogenation of **28**, we added a vinyl cerium reagent[17] to **29**. The complete selectivity in this addition step is the result of steric control. Deoxygenation or dehydration of the tertiary hydroxyl group in **30** proved tricky as unwanted Grob fragmentation of the trifluoromethyl ether proved quite facile. This problem was finally alleviated by employing Burgess' reagent for the dehydration (**31**).[18] Conjugate additions and reductions of the enone afforded primarily the undesired C12 epimer of the methyl ketone. By performing a hydrogenation in the presence of potassium hydroxide the desired thermodynamically more stable C12 epimer (**32**) could be accessed selectively.[19] After a Wittig olefination (**33**) and reduction the installation of the C12 isopropyl group was completed (**34**). We next turned out attention to the C4 hydroxy group. Removal of the methyl ether was accomplished using selenium dioxide (**35**),[20] and set the stage for substrate-controlled installation of the C4 hydoxy group by a directed epoxidation (**36**). Conversion of the primary alcohol into an iodide and subsequent reductive zinc-medi-



Scheme 4. Endgame—total synthesis of vinigrol. LDA = lithium diisopropylamide.

ated[21] opening of the epoxide yielded the allylic alcohol **37**. Isomerization of the allylic alcohol was challenging, but could be done forcefully with selenium dioxide and the aid of oxidative workup conditions. With trifluoroethyl ether protected vinigrol (**38**) in hand, the final challenge we were confronted with was deprotection of the C8a tertiary alcohol. With no reported examples of removing this stable protecting group, we needed to develop reaction conditions that were compatible with the rest of the vinigrol architecture. Finally, we found that we could convert **38** into **39** by treatment with LDA[22] and then selectively dihydroxylate[23] the difluorovinyl ether to afford vinigrol (**1**).[24]

In summary, a total synthesis of vinigrol has been accomplished. Our synthesis highlights the rapid complexity-generating power of a strategic oxidative dearomatization/Diels–Alder reaction, which coupled with a Heck cyclization cascade, affords the carbocyclic core of vinigrol in only two steps from a simple precursor. Efforts are underway to render the oxidative transformation asymmetric, which would provide access to vinigrol enantiomers. The synthesis features a number of notable transformations such as: 1) a directed hydrogenation in a very complex and hindered setting, 2) selenium-dioxide-mediated deprotection and olefin isomerization, 3) Wharton fragmentation, and 4) unique strategic applications and deprotection of a trifluoroethyl ether. We are currently using the lessons learned from this synthetic journey to streamline the synthesis.

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