Total Synthesis

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Fragmentation Enables Complexity in the First Total Synthesis of Vinigrol

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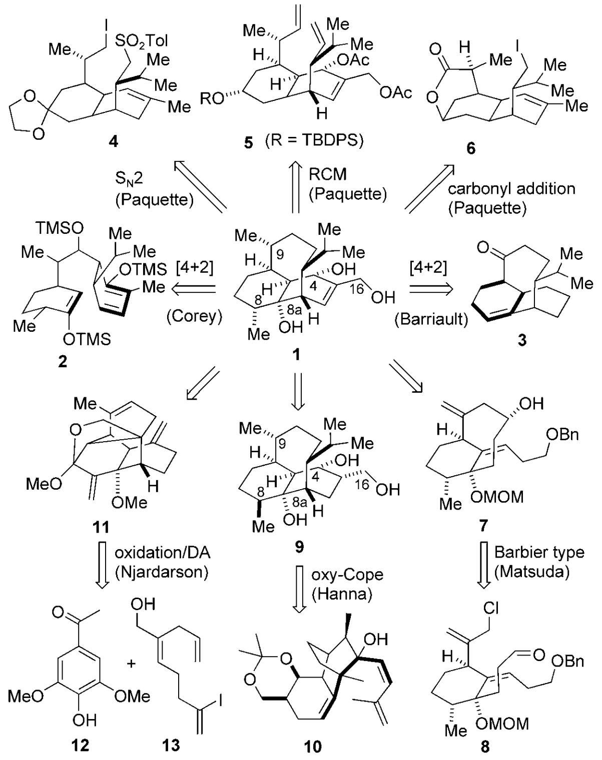
In a research field so rich in history, a number of natural products have for various reasons become mythical targets for total synthesis. Names such as quinine, erythromycin, palytoxin, taxol, ryanodol, azadirachtin, and palau'amine evoke passion amongst synthetic chemists. Vinigrol (**1**, Scheme 1) belongs to this group of venerable molecules.[1] It was isolated in 1987 from the fungal strain *Virgaria nigra* F-5408,[2a] and displays a host of biological activities including antihypertensive and platelet aggregation-inhibiting properties.[2b,c] Its unique diterpene framework, featuring a congested *cis*-fused tricyclic core with eight contiguous stereogenic centers, offers unprecedented structural challenges and has attracted significant attention from the synthetic community.



Scheme 1. Advanced synthetic intermediates toward vinigrol (**1**). Bn = benzyl, MOM = methoxymethyl, RCM = ring-closing metathesis, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, Tol = toluene.

A number of approaches have been established towards the total synthesis of vinigrol since its isolation.[1,3–9] These key achievements are summarized in Scheme 1. The Corey group attempted to reach the tricyclic core by a late stage intramolecular Diels–Alder (DA) reaction (**2**→**1**).[3] This approach was not met with success under various conditions and modifications on the diene. An alternative DA disconnection was devised by Barriault and co-workers in 2007.[4] Their strategy was to build up the tricyclic core **3** by planning the DA cycloaddition earlier in the anticipated sequence. However, despite the success of the key cycloaddition in a model study, a lack of functional groups in the tricycle **3** hampered its foray into vinigrol. With properly functionalized precursors, the potential of this expedient route is obvious. A similar DA approach to the tricycle core was also reported by Fallis and co-workers.[5] The Paquette group reported several attempts to construct the eight-membered ring of **1** on the basis of its decalin skeleton, mainly by intramolecular nucleophilic substitution (**4**) and ring-closing metathesis (**5**).[6a,b] Unfortunately, none of these pivotal transformations led to the desired tricyclic product. These failed attempts emphasize the perils associated with constructing the eight-membered ring of vinigrol. Indeed, ab initio calculations revealed the restricting factor to be a result of the diequatorial conformer, which is more favorable than the diaxial one (ca. 12.5 kcal mol^{-1}).[6a] Additional modification by making use of a lactone bridge (**6**) as a conformational lock was in vain.[6c] The Matsuda group synthesized the partial vinigrol skeleton **7** containing the requisite C8 and C8a functionalization through a SmI_2-promoted Barbier coupling as the key step (**8**→**7**),[7] but additional advances to vinigrol were not reported. Hanna and co-workers were the first team to assemble the decahydro-1,5-butanonaphthalene skeleton of vinigrol.[8a,b] Recently, this group completed the synthesis of epi-C8-dihydrovinigrol (**9**) using a remarkable oxy-Cope rearrangement of triene **10** as the key transformation leading to the tricyclic core.[8c] Njardarson and co-workers recently reported an elegant dearomatization/DA reaction cascade to construct the carbocyclic skeleton **11** from simple fragments **12** and **13**.[9]

These pioneering studies have focused primarily on the construction of the *cis* tricyclic core. The *cis* oriented C8 methyl and C8a hydroxy groups, and the late installation of

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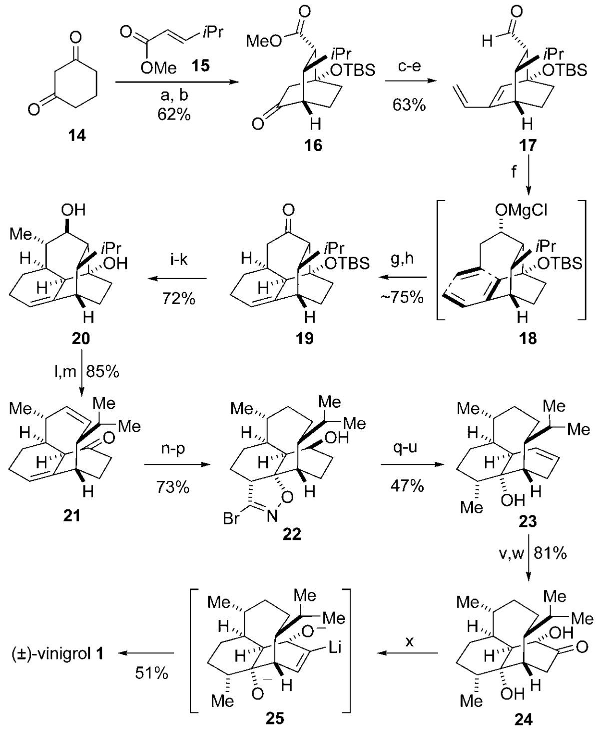
the C3 hydroxymethyl group still remained problematic. The recent completion of the vinigrol synthesis by the Baran group (Scheme 2) presents original solutions to these synthetic challenges.[10] Starting from the commercial diketone **14**, which was enolized to form a diene, subsequent fusion with dienophile **15** through a slightly *endo*-selective DA reaction delivered the advanced intermediate **16**. After enolate formation, Stille coupling, and adjustment of oxidation states (→**17**), the desired tetracyclic ketone **19** was secured by an intramolecular, thermal DA reaction via alkoxide intermediate **18** and subsequent alcohol oxidation. The ensuing sequence to prepare the *anti*-diol **20** comprised a stereoselective enolate methylation of C9 and a subsequent hydroxy-directed ketone reduction mediated by $Me_4NBH(OAc)_3$. This stereocontrolled reduction set up the desired Grob fragmentation (originally proposed by the Corey group)[3] that provided **21** under mild conditions. Thus, it is through the necessity of excising one ring and removing two stereogenic centers that the correct (minus C16) carbon skeleton of vinigrol was revealed. Installation of the *cis* oriented C8 methyl and C8a hydroxy groups was attempted using various approaches both in the earlier[3] and later stages of the sequence. Epoxide formation and subsequent ring-opening reactions were fruitless, as well as a pinacol formation/elimination/reduction sequence in which only the C8 epimer of vinigrol could be isolated.[8] After careful redesign and experimentation, Baran and co-workers found that the *cis* oriented methyl and hydroxy groups of the intermediate **23** could be installed efficiently by a dipolar cycloaddition and subsequent ketone reduction and olefin hydrogenation (**21**→**22**). Notably, the only successful set of olefin hydrogenation conditions required Crabtree's catalyst and a borate additive presumably to promote a hydroxy-directing effect. Then, from 23 a Chugaev elimination was performed, followed by reduction of the bromooxazole to the primary amine, in situ amidation, isonitrile formation, and a radical-promoted reductive C–N cleavage to elaborate the C8 methyl group of **23**. From **23**, various attempts to append the C3 hydroxymethyl group of **1**, including dipolar cycloaddition (similar to that previously used to install the *cis* C8 methyl and C8a hydroxy groups) and allylic oxidation, did not reward Baran and co-workers with a finale to vinigrol. Instead, the successful endgame elaboration (**24**→**1**) was realized using a Shapiro reaction via the proposed trianion intermediate **25**. The synthesis of racemic vinigrol (**1**) was thus completed after 23 steps in 3% overall yield.

As is often the case in the quest for targets of vinigrol's complexity, collective knowledge gathered on the feasibility of synthetic pathways and the reactivity of the molecule can be helpful to other chemists trying to achieve the same goal. In the end, however, solving the vinigrol puzzle required new and creative solutions to difficult issues of stereoselectivity and chemoselectivity created by the numerous functionalities that decorate its unusual tricyclic skeleton. This first total synthesis of vinigrol by Baran and co-workers provides a remarkable example of the unexpected obstacles that can surface during the completion of a complex target. Whereas the application of powerful methodologies such as the intramolecular Diels–Alder cycloaddition and the Grob fragmentation provided a fast and effective entry into the complex tricyclic skeleton of vinigrol, it was the endgame functionalization through creative use of a 1,3-dipolar cycloaddition and the Shapiro reaction that made the difference.



Scheme 2. Synthesis of vinigrol by Baran and co-workers:[10] a) TBSOTf, Et_3N, THF, 0 °C, 2 h; b) **15**, $AlCl_3$, CH_2Cl_2, −78→−45 °C, (d.r.≈2:1); c) LDA, Tf_2O, THF, −78→23 °C; d) tributylvinyltin, LiCl, $[Pd(PPh_3)_4]$, THF, reflux, 3 h; e) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, then DMP, CH_2Cl_2, 23 °C, 30 min; f) allylmagnesium chloride, toluene, −78→105 °C, 90 min; g) aq. NH_4Cl, 23 °C; h) DMP, CH_2Cl_2, 23 °C, 30 min; i) LDA, MeI, THF, −78→0 °C, 3.3 h; j) TBAF, THF, 50 °C, 3 h; k) $Me_4NBH(OAc)_3$, AcOH/MeCN/THF = 1:1:1, 23 °C, 1.5 h; l) MsCl, pyridine, 0 °C, 2.5 h; m) KHMDS, THF, 0→23 °C, 35 min; n) $KHCO_3$, $Br_2C{=}NOH$, EtOAc, 23 °C, 45 min; o) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; p) Crabtree's catalyst, $B(O\textit{i}Pr)_3$, H_2 (1 atm), $ClCH_2CH_2Cl$, 80 °C, 8 h; q) NaH, CS_2, MeI, THF, 0→23 °C, 15 h; r) *o*-DCB, 180 °C, 3 h; s) $LiAlH_4$, THF, 0→23 °C, 12 h; HCOOH, CDMT, NMM, DMAP, CH_2Cl_2, 23 °C, 1 h; t) $COCl_2$, Et_3N, CH_2Cl_2, −20 °C, 20 min; u) AIBN, Bu_3SnH, toluene, 100 °C, 2.5 h; v) OsO_4, NMO, acetone/H_2O = 3:1, 23 °C, 12 h; w) NaOCl, TEMPO, KBr, aq. 5% $NaHCO_3$/CH_2Cl_2 = 2:5, 0 °C, 1.5 h; x) TrisNHNH$_2$, CH_2Cl_2, 23 °C, 5 h; *n*BuLi, $(CH_2O)_n$, TMEDA/THF = 2:1, −78→23 °C, 3 h. AIBN = azobis(isobutyronitrile), CDMT = 2-chloro-4,6-dimethoxy.1,3,5-triazine, DCB = dichlorobenzene, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)-pyridine, DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl, NMM = *N*-methylmorpholine, NMO = *N*-methylmorpholine *N*-oxide, TBAF = tetra-n-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Tris = triisopropylbenzenesulfonyl hydradide.

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