VIP Natural Product Synthesis

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A Formal Synthesis of Vinigrol**

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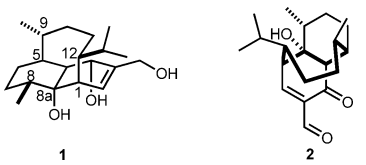
In memory of Keith Fagnou

In 1987, Hashimoto and co-workers isolated an unprecedented compact diterpene, vinigrol (**1**, Scheme 1), from the fungal strain *Virgaria nigra* F-5408, found at the foot of Mount Aso in the Kumamoto Prefecture in Japan.[1] The relative



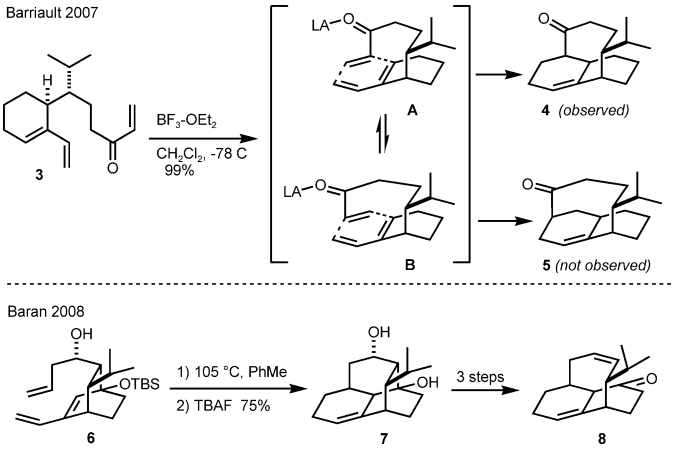
Scheme 1. Structure of vinigrol (**1**).

stereochemistry of the natural product was established by NMR and X-ray crystallographic analysis of the oxidized derivative **2**. Its tricyclic core is comprised of a *cis*-fused [4.4.0] system with a four-carbon bridge between C1 and C5 and features eight contiguous stereocenters. The rare boat half chair conformation of the eight-membered ring (highlighted in Scheme 1 in bold) makes vinigrol a unique structure among diterpenoids.

Biological testing of vinigrol (**1**) has revealed a number of interesting properties, including an influence on platelet aggregation[2] and tumor necrosis factor (TNF) antagonism.[3] These results prompted investigations into the application of vinigrol in medicine.[4,5] Not surprisingly, the impressive biological activities of vinigrol (**1**), combined with its unique and synthetically challenging structure, have resulted in considerable attention from the synthetic community.[6,7]

In 1993, Hanna et al. unveiled the first synthesis of the tricyclic core of vinigrol featuring an anionic oxy-Cope ring expansion.[6a] Subsequent investigations by our group and others,[6d,e,h,l–n] focused on a direct cyclization of the eight-membered ring (the ansa belt) of vinigrol from functionalized decalin precursors. Unfortunately, all such approaches were thwarted by an inability to find reaction conditions for the cyclization. The failure of these approaches can be attributed to an inability of the substrates to adopt the requisite conformation for direct cyclization to form the ansa belt.

We realized that an approach involving the generation of two rings in one step would avoid this fundamental cyclization problem. Specifically, we envisaged the formation of the vinigrol carbocyclic core **4** by a type 2 intramolecular Diels–Alder reaction[8] of triene **3** (Scheme 2), which should favor the less-strained transition state **A** over **B**, thus leading to the preferential formation of cycloadduct **4**. In early 2007, we



Scheme 2. IMDA approaches to synthesize the vinigrol core. LA = Lewis Acid, TBS = *tert*-butyldimethylsilyl.

reported a highly regioselective IMDA reaction of **3** to give **4** in high yield, thus validating our idea.[6p] Subsequent work from Baran and co-workers[6r] confirmed the effectiveness of the intramolecular Diels–Alder approach by converting triene **6** into tetracycle **7**, which was converted into the core of vinigrol (**8**) through a subsequent Grob fragmentation. In 2009, the same group extended the IMDA–Grob approach to the first total synthesis of vinigrol.[6w]

Herein, we report a sterecontrolled formal total synthesis of vinigrol that exploits the synthetic efficiency of our direct type 2 IMDA approach. Our retrosynthetic analysis, depicted in Scheme 3, takes advantage of the compact and conformationally restricted nature of IMDA adduct **11** to install the requisite functionalities of the natural product. Tricycle **11** is the result of an IMDA reaction of triene **12**. The latter could be readily prepared from ketone **13**, which in turn could be efficiently assembled through a Claisen rearrangement of **14**, which could be generated in situ from alcohol **15** and ketal **16**. A chair-like transition state would secure the correct relative stereochemistry at C1 and C12 in **13**.

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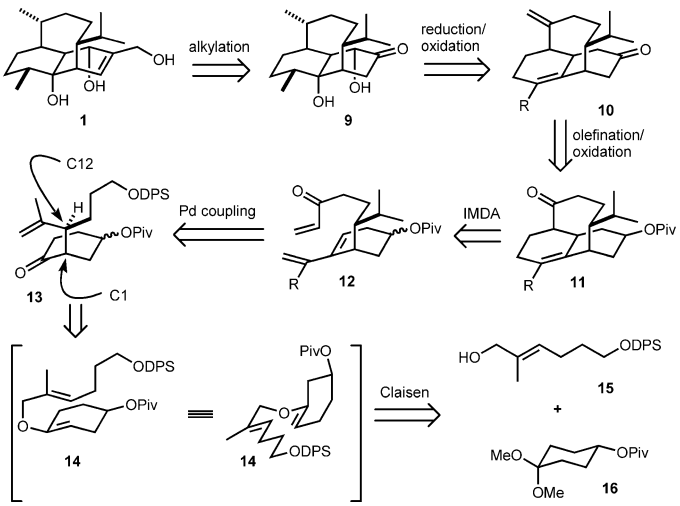
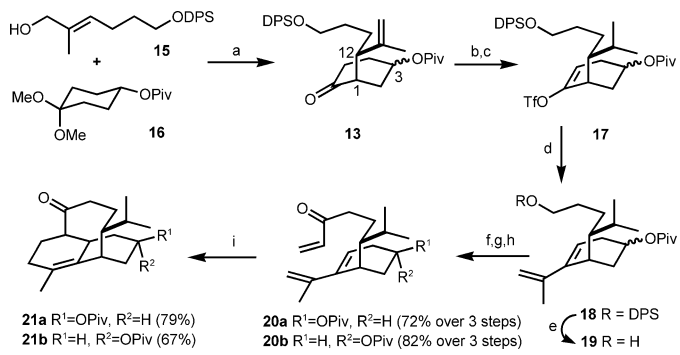


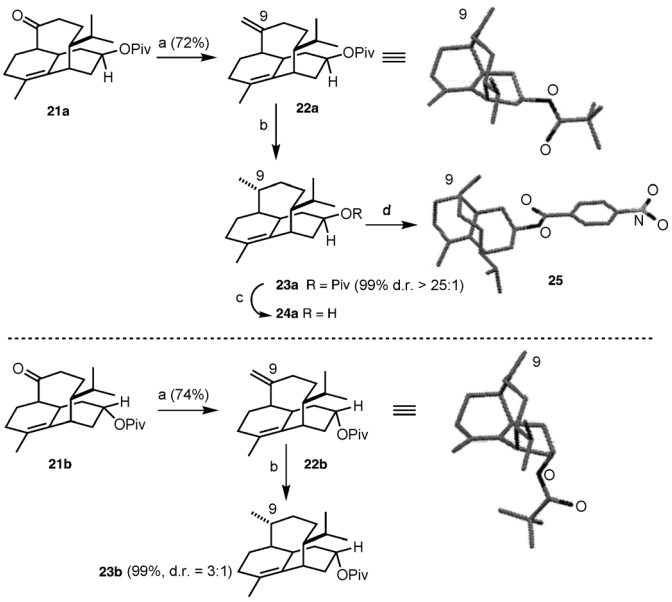
Scheme 3. Retrosynthetic analysis of vinigrol (**1**). DPS = *tert*-butyldiphenylsilyl, Piv = trimethylacetyl.

The synthesis began with a thermal Claisen rearrangement[9] of alcohol **15**[10] and ketal **16**[11] in the presence of propionic acid to give ketone **13** in 62% yield. The product possessed the required relative stereochemistry at C1 and C12 and was a 50:50 epimeric mixture at C3 (Scheme 4).[12] After PtO_2-catalyzed hydrogenation of the isopropenyl group, the ketone was converted into the enol triflate **17**. Next, a Kumada–Negishi coupling reaction with vinyl magnesium bromide[13] afforded the diene **18** in 93% yield.[14] Removal of the DPS group was achieved using TBAF to provide a 50:50 mixture of epimeric alcohols **19** in 68% yield. At this point, the epimers were separated and carried independently through the following steps. A sequence of oxidation, nucleophilic addition with vinyl magnesium bromide, and oxidation led to unstable enones **20a** and **20b** in 72% and 82% yields respectively. Enones **20a** and **20b** underwent a $SnCl_4$-mediated IMDA reaction in dichloromethane at −78 °C to give the desired vinigrol cores **21a** and **21b** as the sole isomers in 79% and 67% yield respectively.



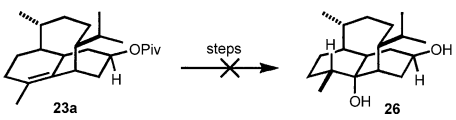
Scheme 4. Synthesis of the vinigrol skeleton (**21**). a) propionic acid, neat, 135 °C, 62%, (d.r. at C1–C12 > 25:1); b) PtO_2, H_2, EtOAc, 76%; c) KHMDS, THF, −78 °C then $PhNTf_2$, 99%; d) $CH_2{=}C(Me)MgBr$, $ZnBr_2$, $Pd(OAc)_2$, DPPB, THF, RT to 60 °C, 93%; e) nBu_4NF, THF, 68%; f) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to RT; g) $CH_2{=}CHMgBr$, PhMe, −78 °C; h) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to RT; i) $SnCl_4$, CH_2Cl_2, −78 °C. DPPB = diphenylphosphinobutane, KHMDS = potassium hexamethylsilazide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Wittig olefination of ketones **21a** and **21b** using Conia's conditions[15] afforded olefins **22a** and **22b** in 72% and 74% yield, respectively (Scheme 5). At this point, we envisaged a chemo- and diastereoselective hydrogenation of the exocyclic alkene to establish the C9 stereocenter and its associated methyl group. We had apprehensions about this transformation because poor stereoselectivity was reported in a similar reduction by Hanna et al.[6i] To our delight, the hydrogenation of epimer **22a** gave the desired product **23a** as the sole diastereomer (d.r. > 25:1) in quantitative yield. In contrast, an inseparable mixture of diastereomers at C9 was obtained for **22b**, with the desired isomer still being favored (d.r. = 3:1). Single-crystal X-ray analysis was employed to secure the stereochemistry of products in this sequence (Scheme 5). A crown conformation is adopted by the eight-membered ring in both **21a** and **21b**.



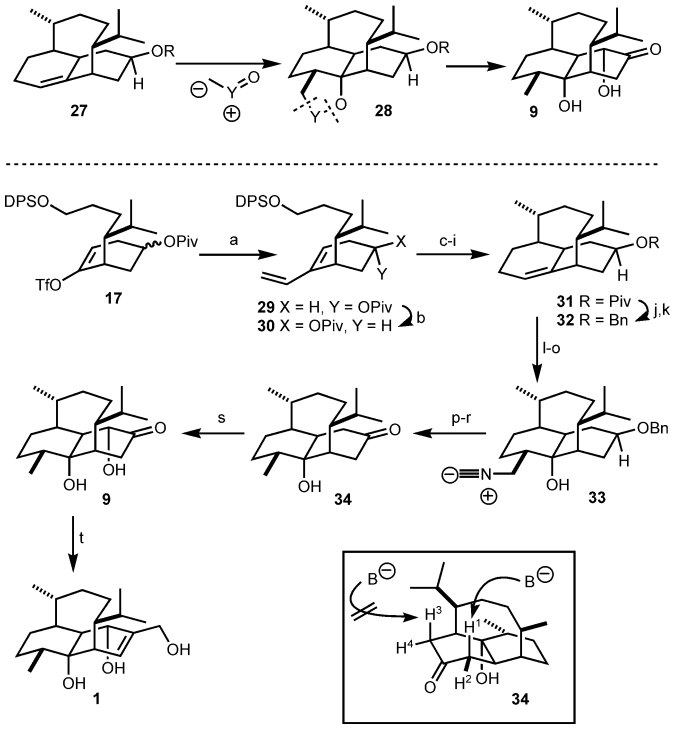
Scheme 5. Synthesis of vinigrol core **23**.[19] a) Ph_3PCH_3I, KO*t*Bu, PhMe; b) PtO_2, H_2, EtOAc; c) Dibal-H, CH_2Cl_2, −78 °C; d) *p*-$NO_2C_6H_4COCl$, Et_3N, CH_2Cl_2, RT, 56% over three steps. Dibal-H = diisobutylaluminum hydride.

With tricycle **23a** in hand, an overall *trans* hydration of the olefin to give diol **26** was necessary to place the C8 methyl and the C8a hydroxy groups in a *syn* orientation [Eq. (1)].



(1)

Frustratingly, our many attempts to bring about this transformation have thus far been unsuccessful.[16] The problem was solved through the synthesis of the des-methyl analogue of **23a**, tricycle **27** (Scheme 6), which would be the precursor for a regio- and stereoselective introduction of the C8 methyl



Scheme 6. Formal synthesis of vinigrol (**1**). a) $Bu_3SnCH{=}CH_2$, [Pd(PPh_3)$_4$] (10 mol%), LiCl, THF, 60°C (80%); b) i) Dibal-H, CH_2Cl_2, −78°C; ii) $pNO_2C_6H_4CO_2H$, DIAD, PPh_3, THF, 0°C; iii) NaOH, MeOH, RT; iv) PivCl, Et_3N, DMAP, CH_2Cl_2, RT (60% over 4 steps); c) nBu_4NF, THF, RT, (84%); d) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78°C then Et_3N, −78 to 0°C; e) $CH_2{=}CHMgBr$, toluene, −78°C; f) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78°C then Et_3N, −78 to 0°C; g) $SnCl_4$, CH_2Cl_2, −78°C, (65% over 4 steps); h) Ph_3PCH_3I, KO*t*Bu, THF/PhMe (1:1), RT (88%); i) PtO_2, H_2, EtOAc, 0°C (99%, d.r. > 25:1); j) Dibal-H, CH_2Cl_2, −78°C; k) NaH, BnBr, $Bu_4N^+I^-$, DMF, 0°C to RT (90% over 2 steps); l) $Br_2C{=}NOH$, $KHCO_3$, wet EtOAC, RT (71%), m) LAH (10 equiv), 4 Å MS, THF, 0°C to RT; n) HCO_2H, CDMT, NMM, DMAP, CH_2Cl_2, RT, (83% over 2 steps); o) $COCl_2$, Et_3N, CH_2Cl_2, −10°C (71%); p) AIBN, Bu_3SnH, PhMe, 120°C (91%); q) Li, naphthalene, THF, 0°C, (83%); r) TEMPO, KBr, NaOCl, CH_2Cl_2/$NaHCO_{3(aq)}$, RT (94%); s) KHMDS (6 equiv), Davis' oxaziridine, −78 to 0°C, THF, (40%, 65% brsm); t) see Ref. [6w] (two steps). AIBN = 2,2′-azobis(2-methylpropionitrile), Bn = benzyl, brsm = based on recovered starting material, CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, LAH = lithium aluminum hydride, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

and the C8a hydroxy groups. Specifically, a cycloaddition reaction between **27** and a suitable dipole would give cycloadduct **28**. The latter intermediate could be then converted into diol **9** through reductive ring opening and functional-group removal.

In the event, a Stille reaction between advanced intermediate **17** and vinyltributylstannane gave a mixture dienes **29** and **30** in 80% yield. The material was consolidated as a single diastereomer at this stage through conversion of α-epimer **29** into β-epimer diene **30** by a Mitsunobu reaction. By a similar synthetic route to that described earlier (Scheme 4), a sizeable quantity (> 2 g) of tricycle **31** was readily prepared in six steps from diene **30**. Drawing inspiration from the work of Baran and co-workers,[6w] the pivaloyl ester **31** was transformed into the benzyl ether **32** in readiness for an overall *syn* addition of methyl and hydroxy moieties to the trisubstituted olefin. Thus, the tricyclic alkene **32** was converted into isocyanate **33** by a [3+2] cycloaddition of bromonitrile oxide and subsequent hydride reduction.[17] A Saegusa deamination[18] and removal of the benzyl group revealed diol **26** in 76% yield over two steps. TEMPO oxidation of the secondary alcohol to ketone **34** was achieved in 94% yield. As expected, the conformationally restricted nature of **34** favored the regioselective α-oxygenation at C4 to afford diol **9** in 40% yield (65% based on recovered starting material). The manipulation of the ketone functionality of **9** into the allylic alcohol of vinigrol (**1**) has been realized in two steps by Baran and co-workers.[6w] The interception of a late-stage intermediate in the Baran synthesis thus completes the formal total synthesis of the natural product.

In conclusion, a formal synthesis of vinigrol (**1**) was achieved in 24 steps from commercially available starting materials. A unique strategic feature of our synthesis involves the construction of the vinigrol carbocyclic core in only 12 steps through a sequence involving a sterecontrolled Claisen rearrangement and an intramolecular Diels–Alder reaction as key steps. This work serves as a platform for further synthetic and biological studies with this unique and important natural product.[19]

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