Natural Products

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A Concise Approach to Vinigrol**

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In 1987 Hashimoto and co-workers isolated the unusual diterpene vinigrol (**1**) from the fungal strain *Virgaria nigra* F-5408.[1] The promising biological properties[2] of **1** combined with its unique terpene framework has attracted significant attention from the synthetic community (17 publications and 4 dissertations on studies towards **1**, no total synthesis reported).[3] From a chemical standpoint, vinigrol provides a particularly difficult challenge, as it is the only natural product to contain the decahydro-1,5-butanonaphthalene carbon skeleton. As such, it holds a special place alongside other historically challenging diterpene systems such as the ingenanes, taxanes, and phomactins (see Figure 1).[4] Although **1** is

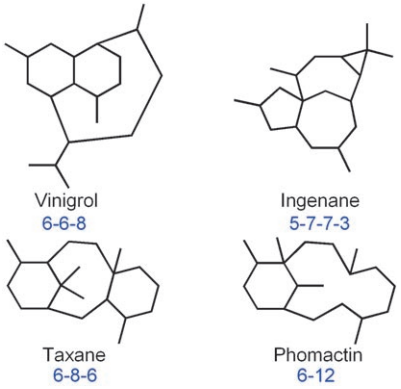
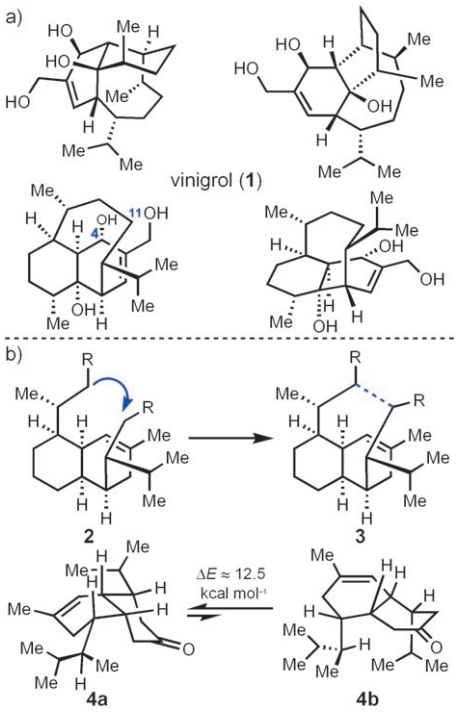


Figure 1. Historically challenging carbogenic ring systems in terpene synthesis.

relatively small in size (molecular weight < 325 Da), the presence of eight contiguous stereocenters and multiple sites of oxygenation make it a particularly challenging synthetic problem which can be analyzed from several seemingly different topological viewpoints (Scheme 1 a). Herein we posit a logical blueprint and the necessary empirical validation for an exceptionally concise total synthesis of **1**.

Continuous efforts by the Paquette group have vividly demonstrated the difficulty in forming the bridging eight-membered ring of vinigrol from a pre-existing *cis*-decalin framework (**2** to **3**) utilizing a variety of approaches (Scheme 1 b).[3a–d] Indeed, calculations by Paquette and co-workers on related model compound **4** point to a largely unfavorable equilibrium between two conformers (**4a** and **4b**, $\Delta E \approx 12.5$ kcal mol^{-1}), with the major conformer (**4a**) lacking the proximity needed for ring closure.



Scheme 1. a) Views of vinigrol (**1**). b) Inherent challenge of building the ring system of **1** from a *cis*-decalin as studied by Paquette et al.[3a–d]

In light of the unusually close proximity of C-4 and C-11 (vinigrol numbering, see Scheme 1 a) in **1**, we reasoned that the tricyclic carbon skeleton (**5**) could be formed by a Grob fragmentation of a more accessible tetracyclic ring system typified by construct **6** (Scheme 2). Our retrosynthetic blueprint (Scheme 2) of **1** incorporates this bond disconnection and offers a potentially rapid solution to the construction of the vinigrol carbon skeleton.[3e] Indeed, this key fragmentation step could be tested in short order from simple starting materials by using two sequential inter- and intramolecular Diels–Alder reactions.

Thus, (*E*)-methyl 4-methyl-2-pentenoate and diene **8** smoothly participated in an *endo*-selective Diels–Alder reaction to produce bicyclic ketone **9** in 65% yield (unoptimized, d.r. = 2:1) (Scheme 3).[5] Triflation of **9** and subsequent Stille coupling formed requisite diene **10** in 78% yield.[6] After an oxidation state adjustment, allyl magnesium bromide was added to the corresponding aldehyde (d.r. ≈ 6:1),

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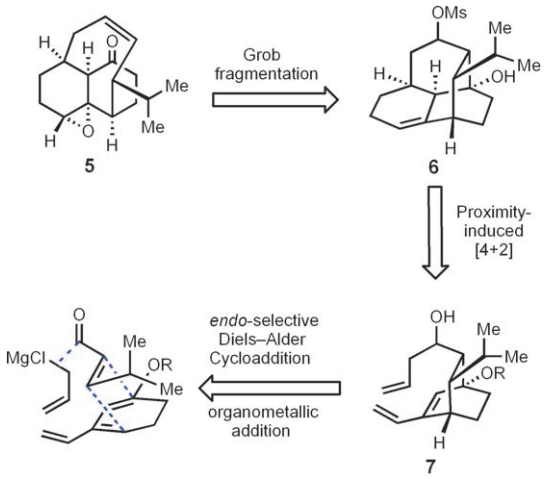
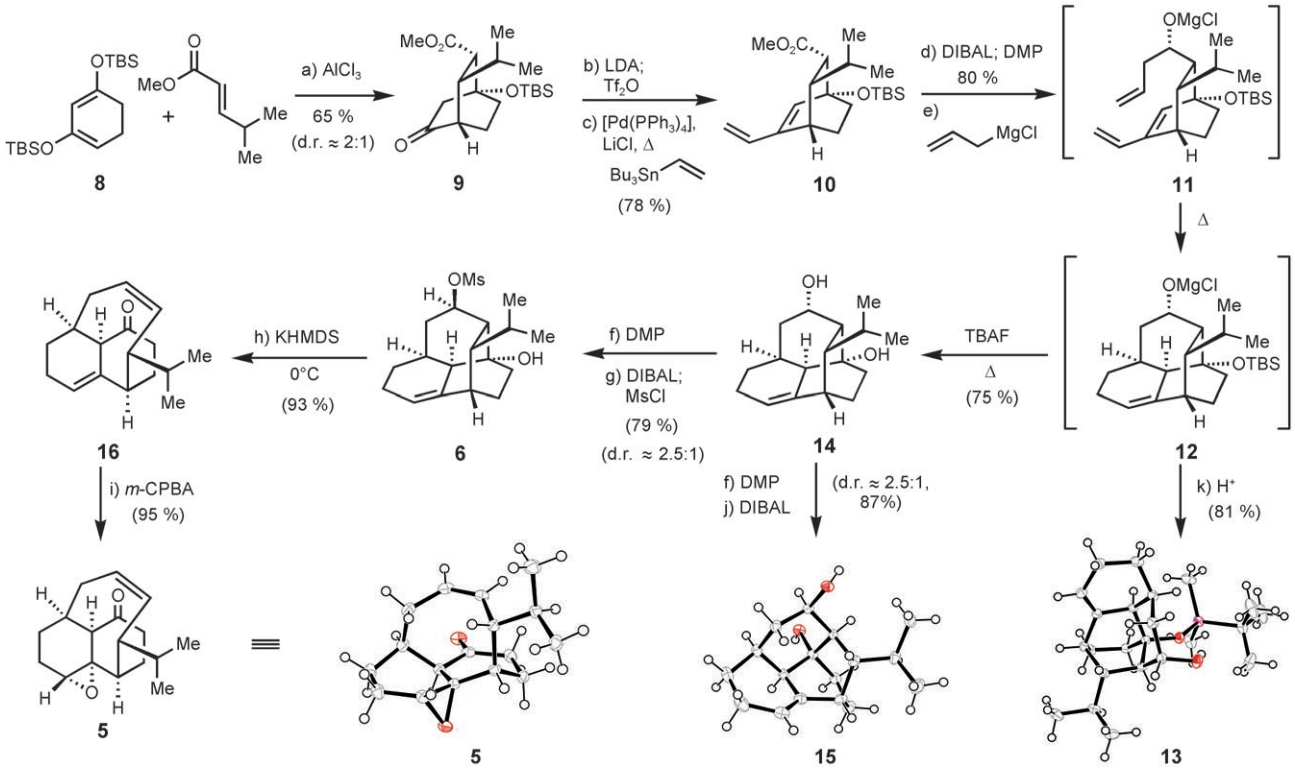


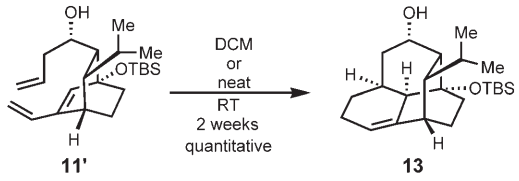
Scheme 2. Retrosynthetic analysis of the tricyclic carbon skeleton **5**.

producing an intermediate alkoxide **11** which was directly heated to 105 °C for 90 min followed by treatment of intermediate **12** with TBAF to furnish tetracycle **14** in 75% overall yield. The structure of **12** and all previous intermediates in this one-pot tandem reaction were confirmed unequivically by aqueous workup and X-ray crystallographic analysis of alcohol **13**. Although the olefinic units of **11** are not electronically complimentary for a Diels–Alder reaction, it was anticipated that a strong proximity effect would encourage bond formation to occur. Remarkably, this reaction even takes place at room temperature over the course of two weeks (Scheme 4). To the best of our knowledge, this is the only example of a completely electron-neutral diene and simple olefin taking part in a noncatalyzed cycloaddition at ambient temperature.[7]

Since alcohol **14** does not possess the correct antiperiplanar atomic arrangement required for Grob fragmentation[8] it was inverted by oxidation/reduction followed by mesylation to provide **6**. The stereochemistry of the intermediate alcohol (**15**) was verified by X-ray crystallography. Although the diastereoselectivity of the reduction step was modest (d.r. ≈2.5:1), the undesired alcohol isomer could be easily separated and reoxidized with almost no loss in material throughput. Deprotonation of **6** with KHMDS smoothly afforded the vinigrol core structure in high yield (93%). It should be noted that the conditions required (0 °C) are unusually mild for this type of bond cleavage. It is likely that



Scheme 3. Synthesis of the vinigrol core (**5**). a) (*E*)-methyl 4-methyl-2-pentenoate (1.0 equiv), diene **8** (2.0 equiv), $AlCl_3$ (1.5 equiv), DCM, −78 °C, 1 h, −45 °C, 3 h, 65% (d.r. ≈2:1); b) LDA (1.2 equiv), Tf_2O (1.3 equiv), THF, −78 °C→23 °C, 2 h, 87% (based on recovered starting material); c) vinyltributyl tin (1.2 equiv), LiCl (4.8 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), THF, reflux, 3 h, 90%; d) DIBAL (2.5 equiv), DCM, −78 °C, 30 min, then DMP (1.25 equiv), DCM, 23 °C, 30 min, 80% over two steps; e) allylmagnesium chloride (1.0 equiv), PhMe, −78 °C→105 °C, 90 min, then TBAF (4.8 equiv), 65 °C, 45 min, 75%; f) DMP (1.1 equiv), DCM, 23 °C, 30 min, 92%; g) DIBAL (3.2 equiv), DCM, −78 °C, 30 min, then MsCl (1.25 equiv), Et_3N (1.5 equiv), 23 °C, 20 min, 79% over two steps (d.r. ≈2.5:1); h) KHMDS (1.1 equiv), THF, 0 °C, 15 min, 93%; i) *m*-CPBA (1.5 equiv), $NaHCO_3$ (2.0 equiv), DCM, −15 °C, 45 min, 95%; j) DIBAL (3.2 equiv), DCM, −78 °C, 30 min, 96% (d.r. ≈2.5:1); k) aqueous NH_4Cl, 23 °C, 81% (d.r. ≈6:1). DCM = dichloromethane, LDA = lithium diisopropylamide, DIBAL = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, KHMDS = potassium hexamethyldisilazide, TBAF = tetrabutylammonium fluoride, *m*-CPBA = *meta*-chloroperoxybenzoic acid.



Scheme 4. A remarkable proximity-induced spontaneous Diels–Alder reaction.

strict enforcement of orbital alignment by the rigid bicyclic system greatly facilitates this process. A high-yielding (95%) chemo- and stereoselective epoxidation of the less hindered trisubstituted olefin in **16** completed the synthesis of **5** as confirmed by X-ray crystallography.

The concise, high-yielding (ca. 20% yield from **8**) route to **5** attests to the strength of the underlying logic of this synthesis plan. In particular, of the eight contiguous stereocenters in **1**, five have been partially addressed in compound **5**. A proximity-induced intramolecular Diels–Alder cycloaddition and mild Grob fragmentation make this rapid route possible. Approximately half of the steps in this approach either make C–C bonds or strategically break them. Careful sequence choreography and redox accounting in this nine-step sequence has led to a minimization of protecting group chemistry.[9] Efforts to streamline this sequence further and apply it to a total synthesis of **1** are well underway.[10]

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[10] Full characterization and experimental details can be found in Supporting Information. CCDC-675358, 675356, and 675357 (**5**, **13**, and **15**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

