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Total Synthesis of Vinigrol

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The total synthesis of the biologically significant diterpene vinigrol (**1**)[1] has stood for over two decades as a major unsolved challenge for organic synthesis.[2] The extreme difficulty in preparing this molecule stems from its unprecedented and highly congested decahydro-1,5-butanonaphthalene ring system containing eight contiguous stereocenters (shown in four different views in Figure 1A). In this Communication we report a solution to this longstanding problem in complex terpene synthesis.[3]

Last year we reported a short route to the core skeleton of **1**, featuring a simple sequence of classic transforms such as the Diels–Alder and Grob fragmentation, that proved to be capable of delivering structures similar to **2** (Figure 1B), albeit lacking the C-9 methyl group.[2w] In accord with the well-documented reluctance of late-stage intermediates to be converted to **1**,[2] many seemingly logical routes to **1** from **2** and related intermediates failed in our hands. The final route presented herein was formed from a detailed series of experiments.

The route to **1** commences from **3** (Scheme 1), an intermediate available in decagram quantities in seven steps from commercially available materials. The C-9 methyl group was installed by alkylation (LDA, MeI), and, following silyl group removal (TBAF), the adjacent alcohol stereochemistry was established using Evans's $Me_4NBH(OAc)_3$-mediated,[4] hydroxyl-directed reduction to deliver **4** as a single diastereomer in 72% yield over the three-step sequence. Nondirected reductions (i.e., DIBAL) afforded mainly the undesired alcohol diastereomer at C-11 due to the shielding effect of the C-9 methyl group. The correct stereochemistry is critical for the ensuing Grob fragmentation that furnished **2** (see Figure 1B for structure) after mesylation and treatment with KHMDS (85% yield over two steps).

Installation of the C-8 methyl and C-8a hydroxyl groups proved to be a challenge due to their *cis* orientation. The methyl group cannot arise from the simple hydrogenation of an exocyclic olefin because reagents approach from the less hindered (and wrong) diastereoface.[2] In essence, a hypothetical transform to achieve the *cis*-addition of the $-CH_3$ and $-OH$ groups of *methanol* across an olefin was required. After extensive exploration, the formal equivalent of such a reaction was developed. Thus, exposure of **2** to bromonitrile oxide[5] (generated *in situ* from dibromoformaldoxime and $KHCO_3$) resulted in a dipolar cycloaddition, leading to the formation of **5** as a single isomer in 88% yield on a gram scale. This cycloaddition proceeds with complete control over regio- and positional selectivity to produce a single diastereomer of **5** (verified by X-ray crystallography). Ketone reduction with DIBAL followed by directed olefin hydrogenation (20% Crabtree's catalyst, H_2, $B(O\text{-}iPr)_3$)[6] furnished **6** in 83% yield. It should be noted that olefin hydrogenation was confounded by the C-9 methyl and C-12 isopropyl groups flanking the disubstituted olefin on the face from which most hydrogenations would be expected to originate. In our hands this was the only intermediate and the only set of conditions that succeeded; dozens of hydrogenation conditions on several different intermediates failed.

Xanthate formation (NaH, CS_2, MeI) and subsequent Chugaev elimination (180 °C) furnished olefin **7** in 85% overall yield. The bromoisoxazole was unveiled to the desired tertiary alcohol **9** by the Saegusa deamination sequence:[7] (1) reduction with $LiAlH_4$ and immediate formylation of the crude amine, (2) dehydration to a primary isonitrile, and (3) treatment with Bu_3SnH in the presence of AIBN in 56% overall yield. The robustness of this overall route is evident from the fact that over 5 g of **9** has been easily prepared, and all the steps leading to this key intermediate have been conducted on a gram scale.

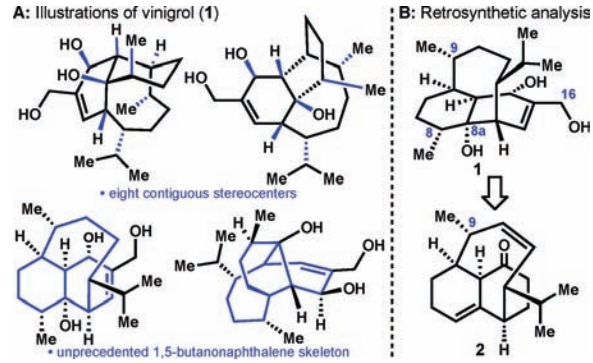

Figure 1. (A) Illustrations of vinigrol (**1**) and (B) retrosynthetic analysis.

Access to large quantities of key intermediates such as **9** was critical since, as alluded to above, we encountered a maze of unpredictable failures en route to **1**, a small sampling of which are shown in Figure 2. Thus, allylic oxidation of **9** led to **13**, which could not be productively functionalized further. Although olefin **9** reacted with bromonitrile oxide to furnish **14**, its downstream product **15** and related structures could not be converted to **1**. Finally, 2,3-dihydrovinigrol (**16**) and derivatives thereof could not be dehydrogenated to **1**.

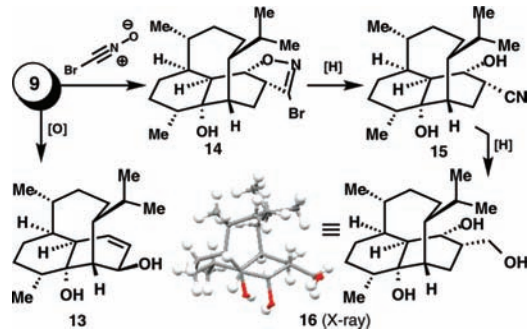

Figure 2. A small sampling of "dead-end" intermediates.

Ultimately, a simple route to **1** from **9** was developed. Thus, dihydroxylation of **9** with OsO_4 and chemoselective oxidation of the resulting diol (NaOCl, TEMPO)[8] led to α-hydroxy ketone **10** in 81% overall yield. A Shapiro reaction[9] via trisylhydrazone **11** took place presumably via the trianionic species **12** to deliver (±)-**1** (spectroscopically identical in all respects to a natural sample of **1**, with the exception of optical rotation).

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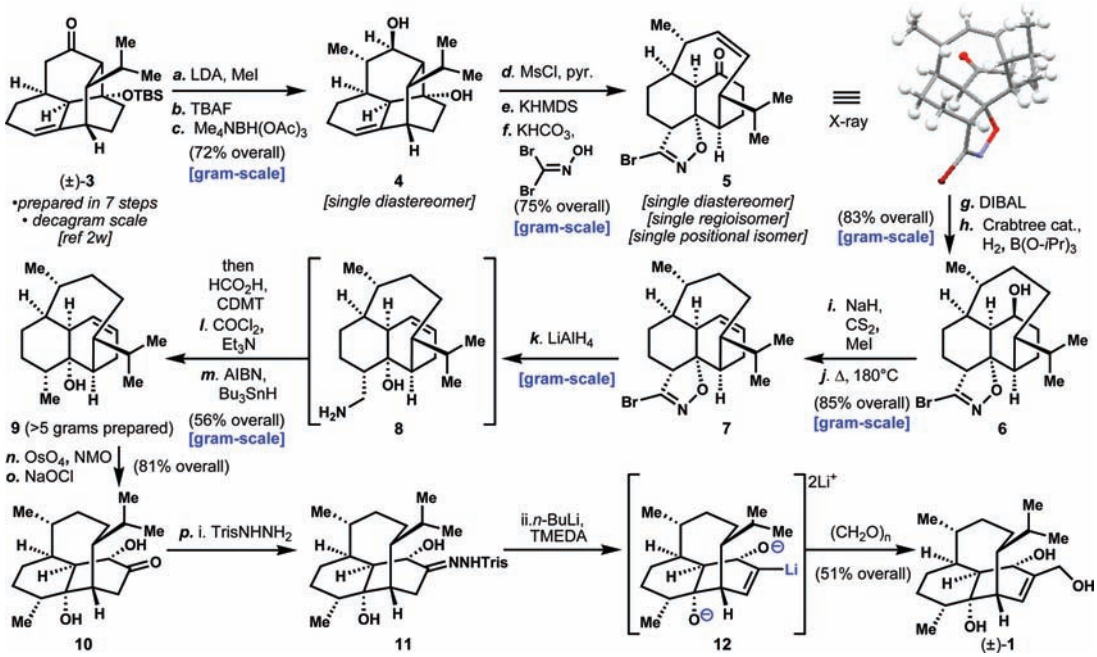
Scheme 1. Total Synthesis of Vinigrol (**1**)[a]



[a] Reagents and conditions: (a) LDA (1.3 equiv), MeI (1.6 equiv), THF, −78 to 0 °C, 3.3 h; (b) TBAF (3.2 equiv), THF, 50 °C, 3 h; (c) $Me_4NBH(OAc)_3$ (4.0 equiv, AcOH:MeCN:THF = 1:1:1, 23 °C, 1.5 h, 72% over three steps; (d) MsCl (1.2 equiv), pyridine, 0 °C, 2.5 h; (e) KHMDS (1.1 equiv), THF, 0 to 23 °C, 35 min, 85% over two steps; (f) $KHCO_3$ (3.0 equiv), $Br_2C{=}NOH$ (1.5 equiv), EtOAc, 23 °C, 45 min, 88%; (g) DIBAL (1.2 equiv), DCM, −78 °C, 1 h, 95%; (h) Crabtree's catalyst (0.2 equiv), B(O-*i*Pr)$_3$ (1.0 equiv), H_2 (1 atm), DCE, 80 °C, 8 h, 87%; (i) NaH (10 equiv), CS_2 (20 equiv), MeI (40 equiv), THF, 0 to 23 °C, 15 h, 88%; (j) *o*-DCB, 180 °C, 3 h, 96%; (k) $LiAlH_4$ (20 equiv), THF, 0 to 23 °C, 12 h; HCOOH (2.0 equiv), CDMT (2.1 equiv), NMM (2.2 equiv), DMAP (0.1 equiv), DCM, 23 °C, 1 h, 81%; (l) $COCl_2$ (1.0 equiv), Et_3N (15 equiv), DCM, −20 °C, 20 min, 76%; (m) AIBN (3.0 equiv), Bu_3SnH (9.8 equiv), toluene, 100 °C, 2.5 h, 91%; (n) OsO_4 (0.1 equiv), NMO (1.3 equiv), acetone:H_2O = 3:1, 23 °C, 12 h, 95%; (o) NaOCl (1.5 equiv), TEMPO (0.1 equiv), KBr (0.1 equiv), aq 5% $NaHCO_3$:DCM = 2:5, 0 °C, 1.5 h, 85%; (p) $TrisNHNH_2$ (2.0 equiv, DCM, 23 °C, 5 h; *n*-BuLi (4.0 equiv), $(CH_2O)_n$ (30 equiv), TMEDA:THF = 2:1, −78 to 23 °C, 3 h, 51% overall.

The venerable challenge posed by vinigrol (**1**) has been addressed by a 23-step route in 3% overall yield from commercially available materials. In addition to a minimal use of protecting group chemistry, nearly complete stereocontrol over all eight stereocenters, and the scalability of the route, notable aspects include (1) simple formation of the decahydro-1,5-butanonaphthalene ring system by way of inter- and intramolecular Diels−Alder reactions followed by Grob fragmentation, (2) highly selective functionalization of **2** by way of an unusual dipolar cycloaddition, and (3) a Shapiro reaction that takes place via trianion **12**. Obvious areas for refinement to the current route to **1** include a minimization of nonstrategic redox fluctuations and an enantioselective variant of the first step.

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Note Added after ASAP Publication. A correction was made in Figure 1A on November 6, 2009.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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