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A Novel Synthetic Approach to the Bicyclo[5.3.1]undecan-11-one Framework of Vinigrol

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The first synthetic attempt commencing from an eight-membered ring to approach the [5.3.1] bicyclic core of vinigrol has demonstrated the feasibility of taking advantage of the conformational bias of the cyclooctane-ring system to realize highly diastereoselective reactions. The synthetic potential of the newly disclosed access to *in/out* isomerism may stimulate broader interests.

The diterpenoid vinigrol (**1**) was isolated in 1987 by Hashimoto and co-workers from a fungus *Virgaria nigra*,[1] and exhibits interesting biological activities.[2] Structurally, vinigrol possesses a unique [4.4.4.0^{4a,8a}] tricyclic core harboring eight contiguous stereocenters. This exquisite formidable molecular architecture posed an unsurpassable barrier for two decades,[3] until being conquered by Baran in 2009,[4] and recently by Barriault [5] and Njardarson.[6] Noticeably, the [5.3.1] bicyclic framework is a privileged structure and also featured by paclitaxel (**2**).

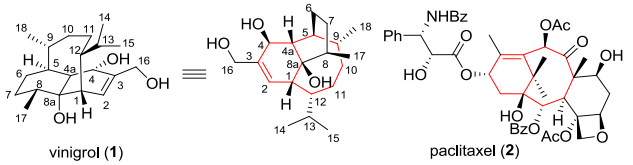
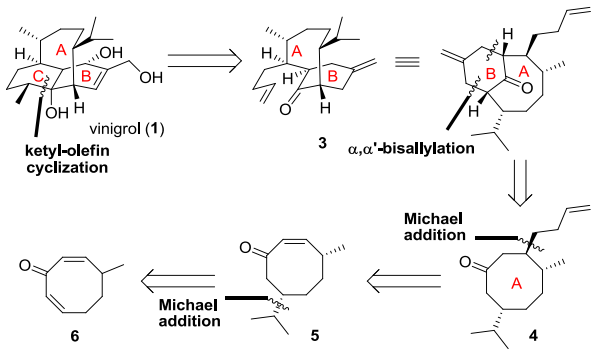


Figure 1. vinigrol (**1**) and paclitaxel (**2**).

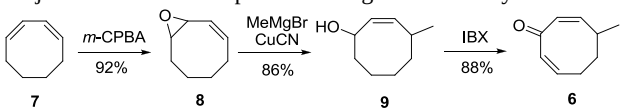
We have been fascinated by the structural exquisiteness and synthetic challenges demonstrated by vinigrol. Interestingly, all the preceding synthetic studies commenced with the six-membered ring(s) of the decalin moiety while choosing to construct the eight-membered ring at a later stage. We wondered if there was any possibility of this eight-membered ring being introduced first and the decalin system being fostered afterwards. This led to the emergence of a novel strategy. In this paper, we report the synthesis of the [5.3.1] bicyclic core of vinigrol in light of this strategy.

As depicted in Scheme 1, our retrosynthesis of vinigrol (**1**) was radically different from all the precedents by relying on the exploration of the inherent conformational bias of eight-membered ring.[7] We envisioned the functionalization of B-ring at the final stage, and the less functionalized C-ring from a ketyl-olefin cyclization, thus reducing the target to **3**. Central to our synthetic plan, diastereoselective α,α'-bisallylation reaction(s) and two stereoselective Michael addition reactions were imagined to transform cyclooctadienone **6** to **3** via the intermediary of **4** and **5**.



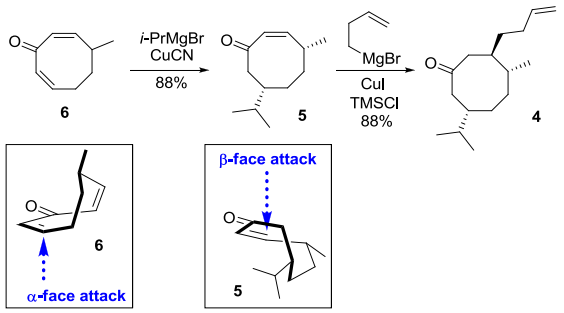
Scheme 1. Retrosynthesis of vinigrol (**1**)

The synthetic journey began with 1,3-cyclooctadiene (**7**) (Scheme 2). Compound **7** was treated with *m*-CPBA to furnish epoxide **8** followed by exposure to a S_N2' substitution reaction with MeMgBr/CuCN to give **9** in 86% yield along with minor amount of S_N2 substitution product.[8] The mixture was then subjected to Nicolaou's procedure to give **6** in 88% yield.[9]



Scheme 2. Synthesis of **6**

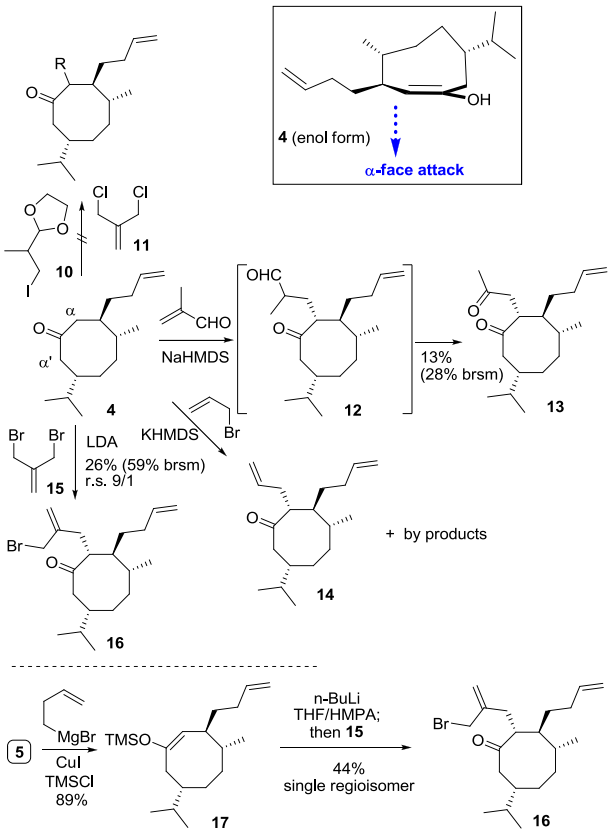
With **6** in hand, we began to explore the proposed substrate-controlled diastereoselective Michael addition reactions (Scheme 3). As depicted in Scheme 3, dienone **6** would favor a conformation in which the methyl substituent takes a pseudo-equatorial position to minimize the unfavorable steric interactions. Based on this conformation, we predicted that the Michael addition would selectively occurred on the α-face of the less hindered double bond of **6** (Scheme 3). Actually, when **6** was treated with *i*-PrMgBr (3.0 equiv) in the presence of CuCN (3.6 equiv) at -78 °C, a single product was isolated in 90% yield. According to the above analysis, the structure was tentatively assigned as **5**. Further optimization revealed that when 1.2 equiv *i*-PrMgBr/CuCN was employed, a similarly good yield (88%) could be obtained.



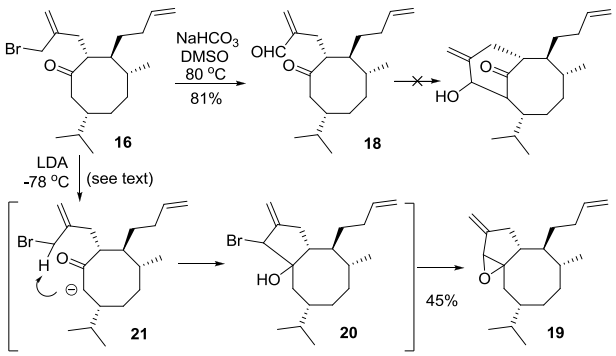
Scheme 3. Synthesis of **4** via diastereoselective Michael addition reactions

Encouraged by the above success, we moved on to the second Michael addition reaction. Molecule **5** should favor a conformation in which both the methyl and the isopropyl substituents position pseudo-equatorially, as depicted in Scheme 3. This conformational analysis of **5** led to the prediction that the Michael donor would selectively approach **5** from the less hindered β-face (Scheme 3). In practice, when **5** was exposed to but-3-enylmagnesium bromide in the presence of CuCN, a sluggish reaction was observed. Delightfully, by switching CuCN to CuI, a 50% conversion of the starting material was observed. Further optimization of the reaction involving addition of a Lewis acid such as BF_3 Et_2O or TMSCl significantly improved the yield to 88%. The product was tentatively assigned as **4** based on the above conformational analysis.

We next focused ourselves on the construction of the B-ring which, to our surprise, turned out to be extremely challenging. Our initial extensive explorations on Lu's α,α'-bisallylation protocol to realize the annulation in one event failed to give any alkylation product.[10] A stepwise alkylation-cyclization strategy was then pursued. Theoretically, to minimize the adverse interactions with **4**, the electrophile should approach the less hindered α-carbon of the carbonyl group and from the α-face of the corresponding enolate, thus leading to the anticipated regioselectivity and facial selectivity. With **4** being β,β'-disubstituted, the low reactivity of **4** was expected. Actually, initial experiments revealed that the low reactivity of the carbonyl group posed a big problem.[11] Attempted alkylation of **4** by iodide **10** or allylchloride **11** gave no reaction (Scheme 4). Interestingly, when the enolate was exposed to excess methacrolein, compound **13**, probably arising from oxidative cleavage of the precursor **12** by oxygen at the work-up stage, was isolated in a trace amount. This encouraging result suggested that reactive electrophiles could be viable alkylation reagents. Actually, alkylating **4** with allylbromide/KHMDS could generate **14** as a regioisomeric mixture as well as dialkylation and *O*-alkylation products. Accordingly, **4** was treated with LDA followed by addition of bromide **15** to provide a mixture with 9/1 regioselectivity in a combined yield of 26%. The major product was assigned as **16** according to the conformational analysis. Further, when **17** obtained from **5** in 89% yield was alkylated with **15**, compound **16** as a single regioisomer could be isolated in 44% yield (Scheme 4).



Scheme 4. Alkylation of **4** and **17**

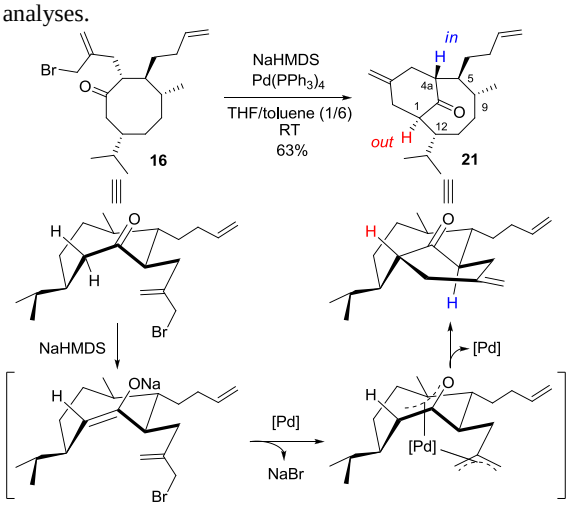


Scheme 5. Kornblum oxidation and Darzens-type reactions of **16**

The stage was now set for the cyclization. Bromide **16** was first converted to aldehyde **18** via Kornblum oxidation.[12] Attempted intramolecular aldol reaction of **18** turned out to be futile under various conditions. Interestingly, direct treatment of **16** with LDA in THF/HMPA, an unprecedented Darzens-type reaction occurred to give epoxide **19** in a yield of 45%. Noticeably, a minute amount of **20** could also be isolated. From a mechanistic viewpoint, compound **20** probably was derived from enolate **21** via an intramolecular proton transfer and the ensuing intramolecular nucleophilic addition reaction. Despite the little usefulness of compound **19** for our synthesis, we regarded the formative mechanism for **19** of high importance considering that the mechanistic rationale suggested the success of the initial deprotonation step and the difficulty of the subsequent

intramolecular alkylation. These findings encouraged us to explore further on the intramolecular α-allylation reaction.

The Tsuji-Trost allylation has gained significant attention from synthetic chemists despite the fact that the intramolecular Tsuji-Trost allylation has never been employed to approach a [5.3.1] bicyclic framework.[13] Nevertheless, compound **16** was treated with NaHMDS before being exposed to $Pd(PPh_3)_4$ (0.2 equiv) at room temperature. To our delight, after six hours a cyclization product, as evidenced by the NMR and MS analyses, was isolated in a yield of 63%, along with a minor amount of *O*-alkylation product (Scheme 6). In view of the fact that *out,out*-bicyclo[5.3.1]undecan-11-one is about 10 kcal/mol less strained than its *trans* isomer,[14] we expected formation of **3** from the cyclization of **16**. Surprisingly, the X-ray crystallographic analysis revealed the real structure of the cyclization product to be **21** (Figure 2).[15] Based on the stereochemistry of **21**, it is reckoned a kinetic product and the proposed stereochemical course of this reaction is depicted in Scheme 6. Among the five stereocenters of **21**, four (C4a, C5, C9, C12) possess the desired stereochemistry, and only the newly formed C1 stereocenter bears an undesirable configuration. But the unfavorable up/down atropisomerism of the bridging carbonyl group renders H-4a in an undesired *in* conformation.[16] Nevertheless, this settled the stereochemical issue and confirmed the preceding conformational analyses.



Scheme 6. Pd-catalyzed intramolecular α-allylation reaction of **16** and the proposed stereochemical course

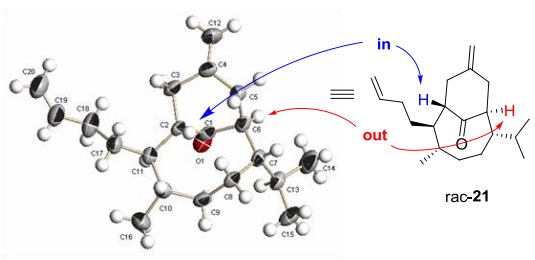
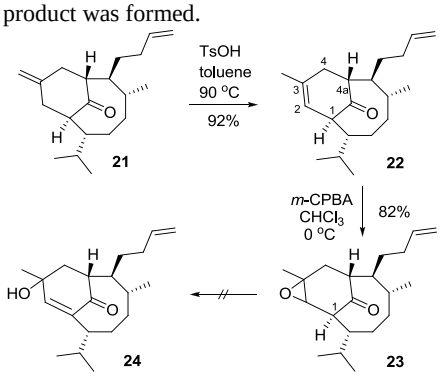


Figure 2. X-ray structure of **21**.

In view of the presence of the carbonyl group, endeavours were eventually made to epimerize the *in,out*-[5.3.1] bicyclic core.[17] Exposure of **21** to DBU in refluxing toluene resulted in nearly complete recovery of the starting material. Treatment of **21** with TsOH in heated toluene resulted in a 92% yield of a 6/1 mixture. In the ^{1}H NMR spectrum of the product, H-4a [3.24 (td, J_1 = 12.4 Hz, J_2 = 4.8 Hz, 1H)] only exhibited a minor change as compared to that in **21** [3.23 (td, J_1 =12.6 Hz, J_2 = 6.1 Hz, 1H)]. Based on this observation, the major product was determined to be **22**. The selective epoxidation of the endocyclic double bond in **22** could be realized with *m*-CPBA at 0 °C, furnishing **23** in a yield of 82%. The stereochemistry of **23** was not established. Subsequent efforts towards synthesizing **24** via eliminative opening of the epoxide were unsuccessful due to the steric hindrance as well as the low acidity of the proton at C1 (Scheme 7).[18] Exposure of **21** to SmI_2 delivered a mixture of products whose ^{1}H NMR spectrum showed that the monosubstituted terminal olefin remained intact, indicating no desired cyclization product was formed.



Scheme 7. Synthesis of **23** and **25**

Conclusions

In summary, a novel synthetic strategy has been realized to approach the [5.3.1] bicyclic core of vinigrol. The synthetic route features two highly diastereoselective Michael addition reactions, a regio- and diastereoselective alkylation, and an intramolecular Tsuji-Trost allylic alkylation reaction via the singly activated enolate. This represents the first synthetic attempt commencing from the eight-membered ring to approach vinigrol, which has enabled procurement of functionalized bicyclo[5.3.1]undecanone. The synthetic potential of the newly disclosed access to *in/out* stereoisomerism[19] featured by some complex natural products such as ingenol[20] may stimulate broader interests. Endeavours aiming at pinpointing a solution to the above *in,out* problem are currently pursued in our laboratory and will be reported in due course.

Acknowledgement

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experiments, characterization data and NMR spectra concerning the following compounds: **4**, **5**, **6**, **8**, **9**, **13**, **16**, **17**, **18**, **19**, **21**, **22**, **23**. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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