Thieme Chemistry Journal Awardees – Where are They Now? Efforts towards the Total Synthesis of Vinigrol

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Abstract: A strategy for the total synthesis of vinigrol is detailed with two key steps – oxidative dearomatization and intramolecular Diels–Alder cycloaddition – providing the *cis*-decalin core. A novel and mild means for the formation of *ortho*-quinone methides is also described.

Key words: vinigrol, oxidative dearomatization, cycloaddition, *ortho*-quinone methide, trichloroacetylisocyanate

Isolated from a fungus, *Virgaria nigra*, found at the foot of Mount Aso in Japan, the diterpenoid vinigrol (**1**, Figure 1) has attracted much interest due to a challenging and unique skeletal framework and potentially useful pharmacological properties. These latter include activity as an antihypertensive and platelet aggregation inhibitor,[1a,b] tumor necrosis factor antagonist,[1c] and nerve stem cell proliferation promoter.[1d] Yet despite work spanning more than 15 years from at least nine independent laboratories,[2] a total synthesis of this molecule has not been realized.

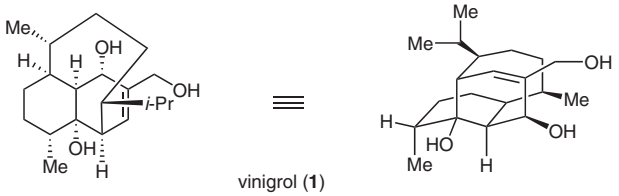
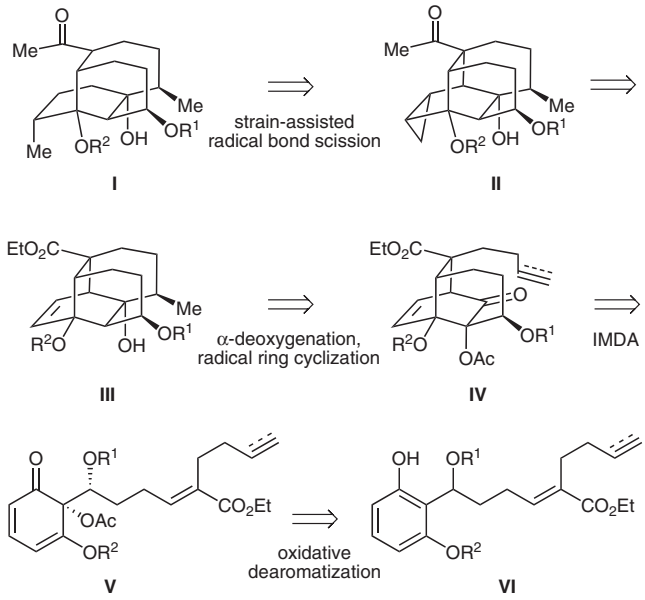


Figure 1 Representations of vinigrol

Our strategy for constructing an advanced vinigrol precursor such as **I** consists of four key operations (Scheme 1). As it has been well established that endgame closure of the eight-membered ring is infeasable,[2j–m] it is our belief that selective bond cleavage of a bicyclo[2.2.2]octane system such as **II** will 'unravel' the latent cyclooctane. Functional-group manipulation then leads us back to **III**, which we envision being generated from a 6-*exo*-trig or 6-*exo*-dig olefin reduction ring-closure protocol of **IV**. We imagine this bicyclic structure being produced in turn by the intramolecular Diels–Alder cycloaddition of a diene-containing *o*-benzoquinol **V**, itself generated via oxidative dearomatization of a suitably substituted phenol **VI**.

Jón T. Njarðarson was born and raised in the small town of Akranes, Iceland. After graduating from high school, he left his hometown and moved to Reykjavik to start his chemistry studies at the University of Iceland. During this time he worked in the laboratory of Professor Jón K. F. Geirsson. Jón then followed in the footsteps of his Icelandic ancestors and moved west, which brought him to New Haven Connecticut, where he chose to pursue a graduate career in Organic Chemistry at Yale University in the laboratories of Professor John L. Wood working on the total synthesis of CP-263,114. At the end of his graduate studies Jón was presented with the irresistible offer of moving to New York City and join the laboratory of Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center, where he worked on the total syntheses of the natural products epothilone 490 and migrastatin. Jón arrived in Ithaca in the summer of 2004 to start his independent career at Cornell University. His laboratory is focused on the development of useful new synthetic methods and the total synthesis of natural products.



Scheme 1 Retrosynthetic strategy

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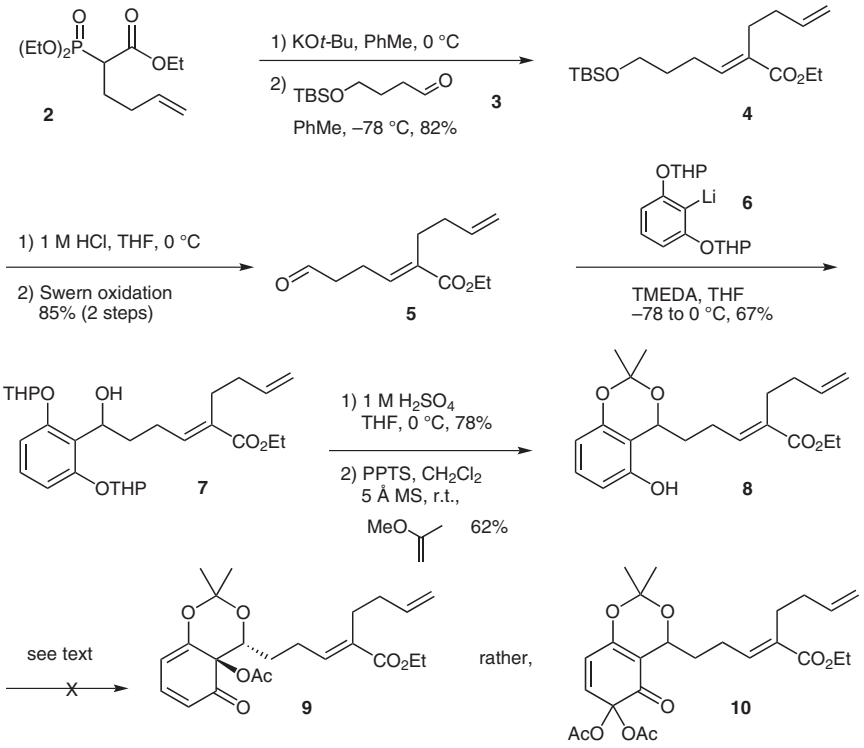
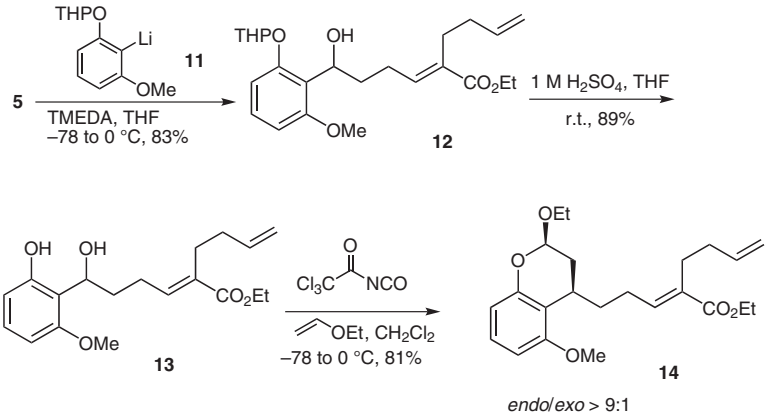


Scheme 2 First attempt at oxidative dearomatization

We initially focused on construction of the phenol **8** (Scheme 2) in the belief that, during oxidative dearomatization, the intramolecular acetonide tether would affect nucleophilic trapping from the opposite face as the large dienophile-bearing side chain. Furthermore, this acetonide would bring the dienophile into the proximity of the *o*-benzoquinol ring, facilitating the Diels–Alder cycloaddition. Towards this goal, a *Z*-selective Horner–Wadsworth–Emmons protocol[3,4] between phosphonate **2** and aldehyde **3**[5] generated the tribustituted olefin **4**. Formation of the *ortho*-lithiated[6] resorcinol derivative **6**[7] and electrophilic trapping with **3** then provided the benzylic alcohol **7**. Careful deprotection to the unstable triol and acetonide formation gave the desired **8**, and we were ready to attempt the first key step of our synthetic plan.

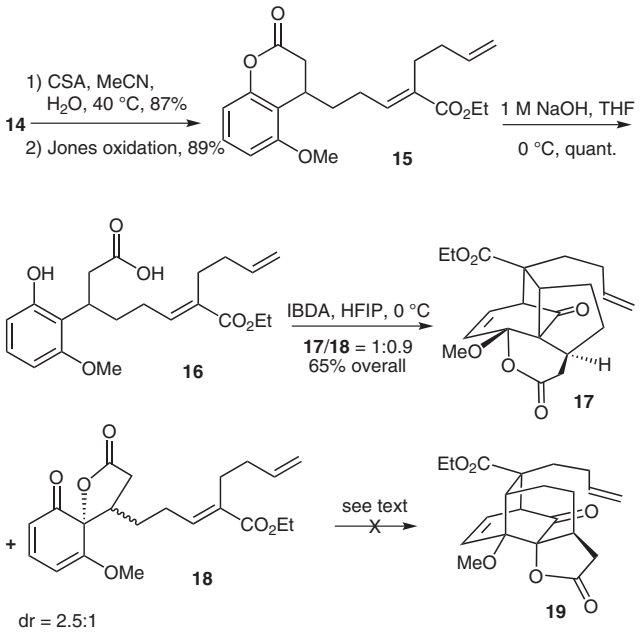
While the mechanism of oxidative dearomatization is dependent largely on the oxidant and conditions used, the Wessely oxidation, employing $Pb(OAc)_4$, generally provides selectivity for nucleophilic incorporation of acetate at the most electron-rich site *ortho* to the phenol.[8] We were thus disappointed to find that reaction of lead tetraacetate in CH_2Cl_2 with **8** gave no detectable quinol **9**, but rather only the undesired and readily hydrolyzed masked quinone **10** along with small amounts of its *para* isomer. Further efforts with other oxidants – LTA/$BF_3{\cdot}OEt_2$,[9] PIDA or PIFA,[10] benzeneseleninic anhydride,[11] and Cu(II)/morpholine/O_2[12] – were also unsuccessful in generating **9**.[13]

This failure in site selectivity led us to pursue a path (Scheme 3) in which use of an intramolecular nucleophile would enforce attack at the proper position. A carbamate



Scheme 3 *o*-Quinone methide-mediated hetero Diels–Alder reaction.

was chosen as an analogue to an amide, where the more electron-rich carbonyl oxygen is known to out-compete the nitrogen as nucleophile and hydrolysis of the resultant iminolactone provides the lactone.[14] Beginning with the same aldehyde **5** used in our first route, a similar nucleophilic addition with the *ortho*-lithiated resorcinol derivative **11** formed the benzylic alcohol **12** (Scheme 3). While it was possible to form various carbamates from this alcohol, successive deprotection of the THP moiety inevitably led to elimination through an *ortho*-quinone methide pathway and subsequent decomposition. In an effort to put this proclivity to good use, however, it was discovered that treatment of the diol **13** with trichloroacetylisocyanate[15] in ethyl vinyl ether and CH_2Cl_2 as co-solvents efficiently led to the hetero-Diels–Alder product **14** in one pot with good yield.[7,16]



Scheme 4 Formation of [5+2] product **17**

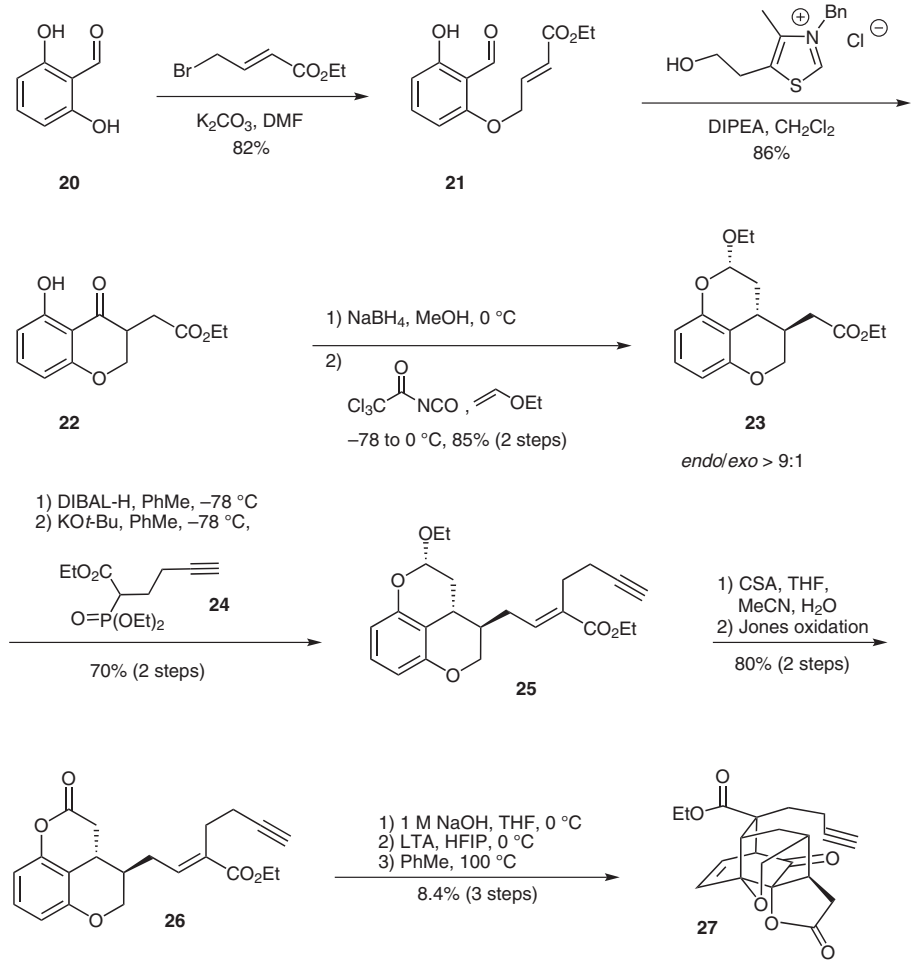
Intrigued by this mild means for the in situ formation of *ortho*-quinone methides,[17] we have tested this protocol with other 2-hydroxybenzylic alcohols and dienophiles, have found it to be quite general, and will report this work at a later time.

Continuing with our efforts towards vinigrol (Scheme 4), hydrolysis of the acetal **14** with camphorsulfonic acid (CSA), and subsequent Jones oxidation realized lactone **15**, which could be readily opened under alkaline conditions to the free acid **16**. Optimized oxidative dearomatization of **16** with iodobenzene diacetate (IBDA) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), however, resulted in three products: the unanticipated bicyclic adduct **17** and a nearly equal combined amount of the two spirobenzoquinol diastereomers **18** (dr = 2.5:1). The bicycle, whose structure was confirmed by X-ray crystallography of a pivaloate derivative,[18] probably results from a polar cationic [5+2] cycloaddition made possible by the electron-donating character of the methoxy substituent.[19] While separation of the spirobenzoquinol diastereomers **18** proved intractable, heating the mixture at reflux in benzene or toluene failed to afford any Diels–Alder adduct **19**, with more forcing or Lewis acidic conditions eventually leading only to decomposition.

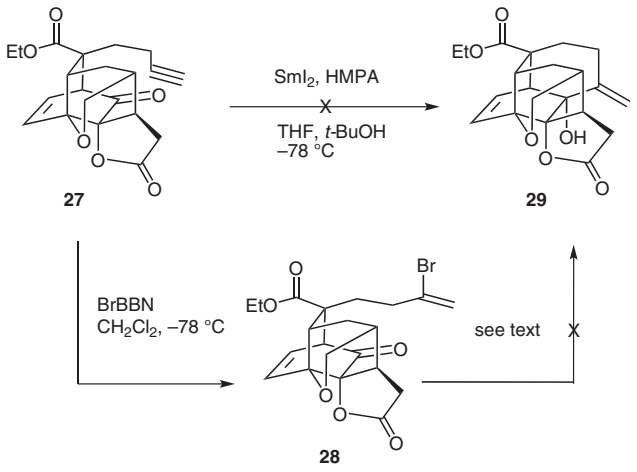
Altering the dienophile electronics might have enabled the Diels–Alder cyclization of **18**, but this would have no effect on the poor diastereoselectivity[20] of the oxidative dearomatization and the formation of **17** as a major byproduct. We thus sought to synthesize a construct which would exhibit both a predetermined stereoselectivity in the oxidative dearomatization and geometrical inhibition of the [5+2] adduct. To this end, the known benzaldehyde **20**[21] was monocrotonylated and engaged in an intramolecular Stetter reaction[22] to form the chromanone **22** (Scheme 5). Reduction with $NaBH_4$ led to the diol, after which use of our quinone methide-generating protocol yielded the adduct **23** with nearly complete facial diastereoselectivity.[23] Reduction to the aldehyde was accomplished with DIBAL-H, after which Horner–Wadsworth–Emmons olefination was employed to generate **25**. Deprotection to the lactol and Jones oxidation gave lactone **26**.

While opening to the free acid was again facile, the oxidative dearomatization proceeded in exceedingly poor yield despite extensive testing of oxidants, solvents, and temperature conditions. Reasons for this difficulty are unclear. Gratifyingly, however, the intramolecular Diels–Alder cycloaddition proceeded well, allowing us to indeed access the desired bicyclic structure **27**.[24]

With **27** in hand, it was then incumbent to affect closure of the posterior six-membered ring. We had initially envisioned a radical cyclization for this purpose (Scheme 6); however, employment of SmI_2 proved unsuccessful, giving only an intractable mixture of unidentified compounds. Changing tack, treatment of **27** with Br-9-BBN gave the vinyl bromide **28** with which we hoped to employ a 'top-down' cyclization approach. Unfortunately, efforts at transmetalation employing *t*-BuLi[25] and *n*-Bu_2CuLi[26] were unsuccessful in forming identifiable products, while Nozaki–Hiyama–Kishi[27] coupling conditions likewise failed to close the posterior six-membered ring. The difficulty might lie in the extreme steric crowding of the compact and rigid bicyclic ring systems preventing the incoming nucleophile from approaching the carbonyl at the requisite Bürgi–Dunitz trajectory.[28]



Scheme 5 Formation of the bicyclic adduct **27**



Scheme 6 Attempted posterior ring closure

Given the synthetically untenable yields for the transformation of **26** to the bicyclic adduct **27** and this unexpected difficulty in closing the posterior ring, we have ceased further efforts in this particular route. Instead, we are concentrating on a newer strategy for the synthesis of vinigrol, which still retains the four key ideas of our original retrosynthesis: oxidative dearomatization, intramolecular Diels–Alder cycloaddition, radical cyclization, and selective bond scission. This work will be communicated in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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