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Synthetic Studies Inspired by Vinigrol

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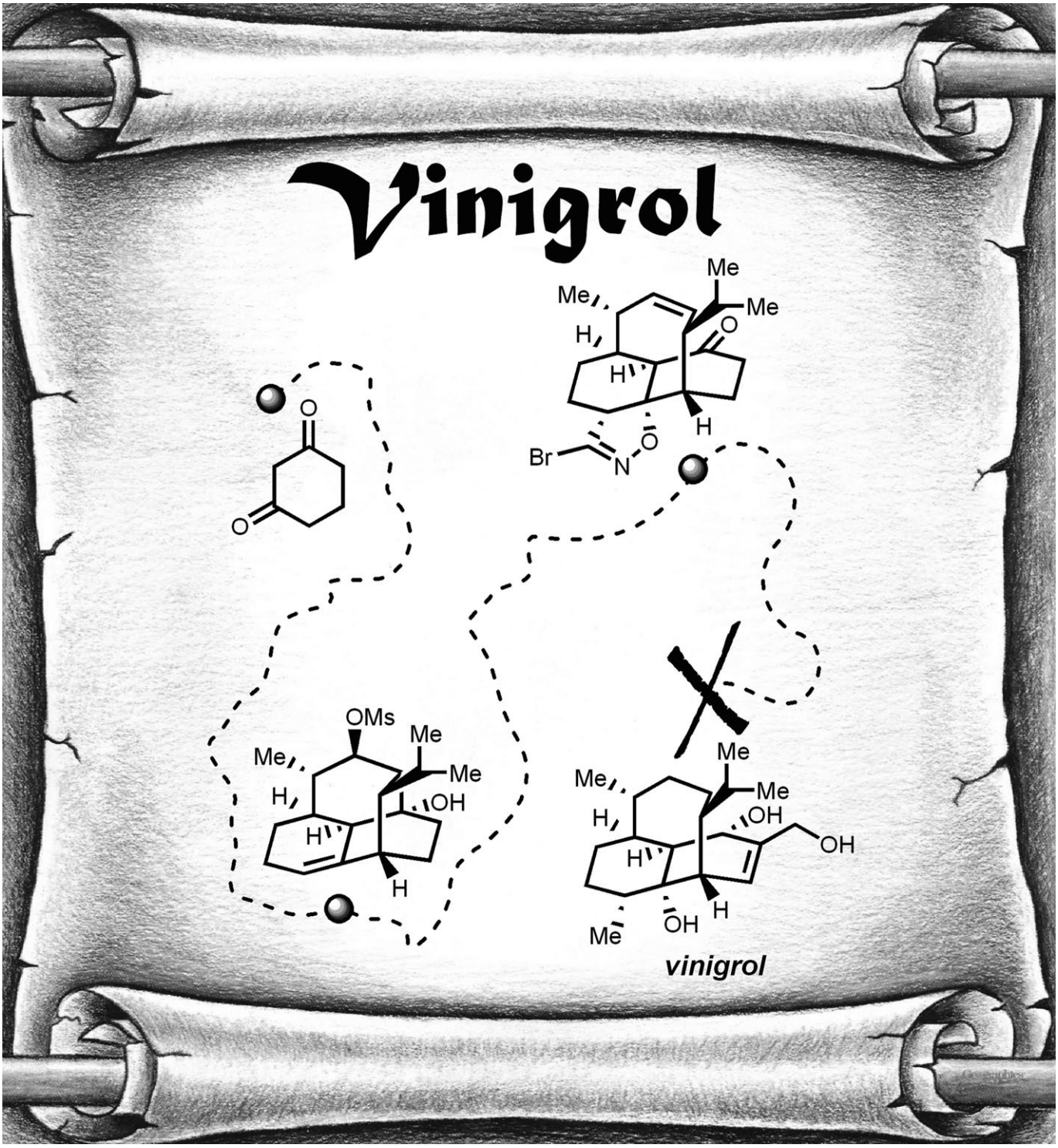
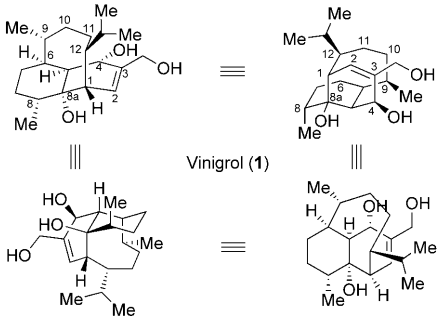


Abstract: Vinigrol, a diterpene natural product, has been a fascinating target for total synthesis for over two decades. This minireview describes recent synthetic studies that have ultimately allowed access to the coveted vinigrol scaffold. Barriault's synthesis of the vinigrol core is described, in addition to the elegant strategies disclosed by Njarđarson and Hanna. The first total synthesis of vinigrol, reported by Baran in 2009, is also highlighted. This review showcases the fundamental role that natural products play in spawning innovations in synthetic chemistry.

Keywords: natural products · pericyclic reaction · terpenoids · total synthesis · vinigrol

Introduction

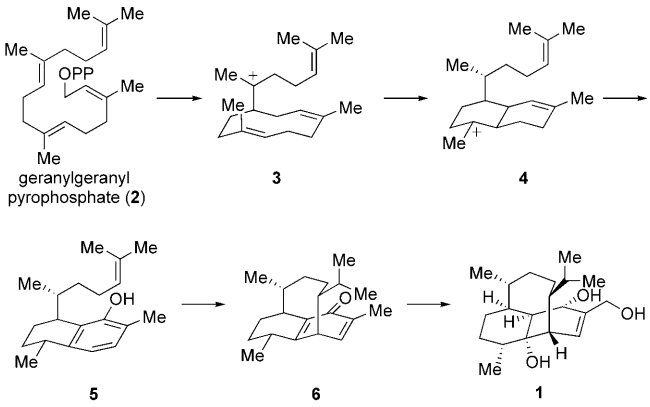
The diterpene natural product vinigrol (**1**, Scheme 1) was first isolated in 1987 by Hashimoto, Ando and co-workers from the cultured mycelium of a fungus, *Virgaria nigra* F-



Scheme 1. Vinigrol (**1**).

5408.[1] Since then, diterpene **1** has been a subject of fascination particularly amongst synthetic chemists. The provocative structure of **1** features an unprecedented 1,5-butanodecahydronaphthalene core that is not found in any other natural product. The core of **1** is decorated with eight contiguous stereogenic centers, ultimately providing a daunting challenge for total synthesis.

It has been proposed that **1** arises biosynthetically from the common diterpene building block geranylgeranyl pyrophosphate (**2**) following the sequence shown in Scheme 2.[2] The pyrophosphate **2** is believed to undergo an enzyme-assisted cyclization to arrive at the ten-membered ring intermediate **3**. Subsequent hydride shift and cyclization yields compound **4**. Oxidation of **4** provides phenol derivative **5**, which in turn, undergoes oxidative cyclization to install the final ring and provide tricycle **6**.[3] Additional oxidation state adjustments of tricycle **6** ultimately give rise to **1**.



Scheme 2. Proposed biosynthesis of **1**.

The promising biological profile of **1** has furthered its appeal as a synthetic target. Vinigrol was initially found to decrease mean arterial blood pressure in spontaneously hypertensive rats in a dose-dependant manner, and later shown to inhibit human platelet aggregation induced by epinephrine ($IC_{50}=52$ nM) and platelet-activating factor ($IC_{50}=33$ nM).[1b] Furthermore, vinigrol was shown to function as a potential tumor necrosis factor (TNF) antagonist agent,[4] and could therefore be useful for the treatment of inflammation and a host of autoimmune disease responses. Moreover, TNF antagonists are thought to slow the progression of AIDS, and are therefore considered especially valuable.[5]

The daunting structure of **1**, coupled with its promising biological profile, has sparked the interest of chemists worldwide. Over the past 23 years, more than 20 papers and six doctoral dissertations describing synthetic efforts towards **1** have been published. At least ten laboratories have pursued the total synthesis of **1**, with key studies reported by Hanna,[6] Paquette,[7] Matsuda,[8] Mehta,[9] Corey,[2] Barriault,[10] Fallis,[11] Njarđarson,[12] and Baran.[13] A comprehensive review describing synthetic progress toward **1** prior to 2007 is available.[10e] This minireview focuses primarily on the subsequent synthetic efforts that have led to the construction of advanced intermediates, in addition to the completed total synthesis reported by Baran in 2009.[14]

Early Synthetic Efforts

Before surveying the most recent studies toward **1**, it is worthwhile to consider some of the earlier efforts that reveal the challenges associated with accessing the vinigrol

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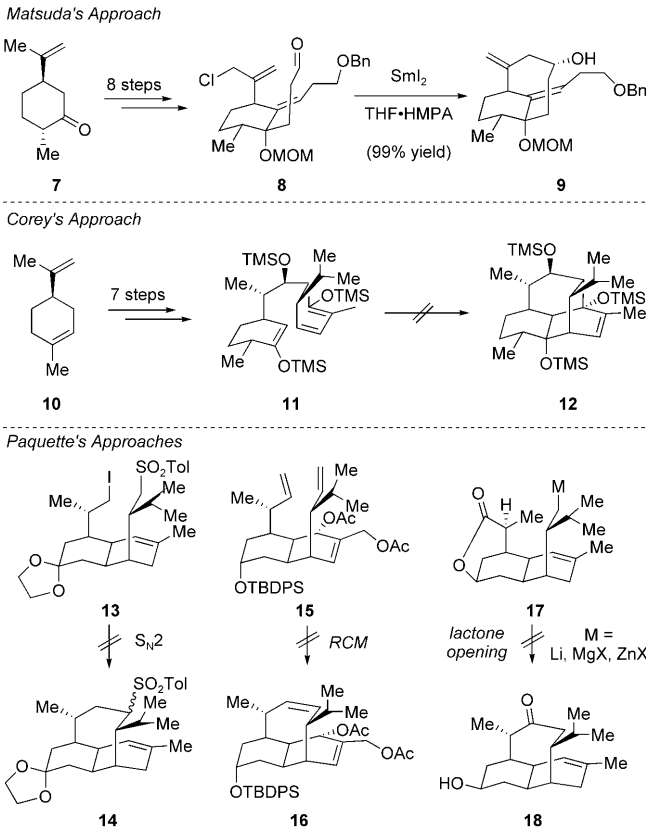
core scaffold. Several prior approaches to **1** are shown in Scheme 3 and can be summarized as follows: 1) The Matsuda group planned to construct the 6–8 ring system present in the natural product by using a SmI_2-mediated Barbier-type



Scheme 3. Early synthetic efforts towards **1**; HMPA = hexamethylphosphoramide, Bn = benzyl, MOM = methoxymethyl, TMS = trimethylsilyl, Tol = tolyl, TBDPS = *tert*-butyldiphenylsilyl.

ring closure.[8] The substrate for this transformation, aldehyde **8**, was prepared from dihydrocarvone (**7**) in eight steps. Upon treatment of **8** with SmI_2, bicycle **9** was obtained in 99% yield. However, the elaboration of **9** to a compound containing the polycyclic vinigrol core has remained elusive. 2) The Corey group aimed to assemble the framework of **1** by employing an intramolecular Diels–Alder cycloaddition.[2] To this end, (*R*)-limonene (**10**) was elaborated to triene **11** over seven steps. However, numerous attempts to implement the key Diels–Alder cycloaddition were unsuccessful. 3) Finally, the Paquette group has explored several routes to the vinigrol core.[7] In each case, it was envisioned that a readily accessible *cis*-decalin derivative, with suitable functional group handles, would be elaborated to a product containing the necessary eight-membered ring of the natural product. Unfortunately, strategies involving S_N2 displacement (**13**→**14**), ring-closing metathesis (**15**→**16**), and lactone opening (**17**→**18**) were deemed ineffective. The sum of these studies clearly indicates the inherent difficulty in assembling the polycyclic core of **1**.

Recent Studies Toward the Total Synthesis of Vinigrol

Over the past five years, several research groups have made breakthrough discoveries that ultimately allow access to the coveted vinigrol core. These studies include: 1) Barriault's assembly of a vinigrol model system by using an intramolecular Diels–Alder reaction,[10] 2) Njardarson's rapid construction of the vinigrol scaffold featuring an oxidative dearomatization/Diels–Alder reaction sequence,[12] 3) Hanna's synthesis of *epi*-C8-dihydrovinigrol by using an anionic oxy-Cope rearrangement,[6] and 4) Baran's total synthesis of **1**, which features a proximity-driven intramolecular Diels–Alder reaction and Grob fragmentation.[13] This section describes each of these efforts in detail, and ultimately highlights the inspirational role natural products play in spawning innovations in synthetic design.

Barriault's route

Retrosynthetic analysis of a model system target: Barriault's strategy for assembling a tricyclic vinigrol model system is shown in Scheme 4.[10] It was envisioned that the tricyclic core **19** could be formed through an intramolecular Diels–

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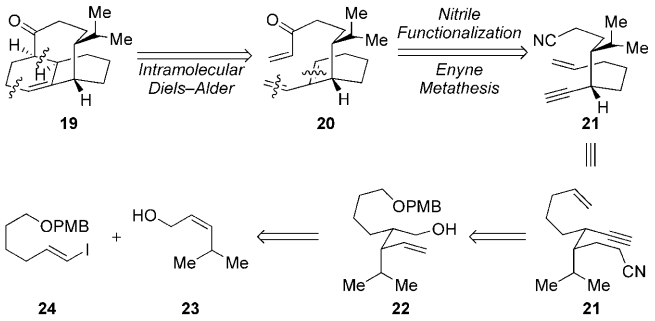
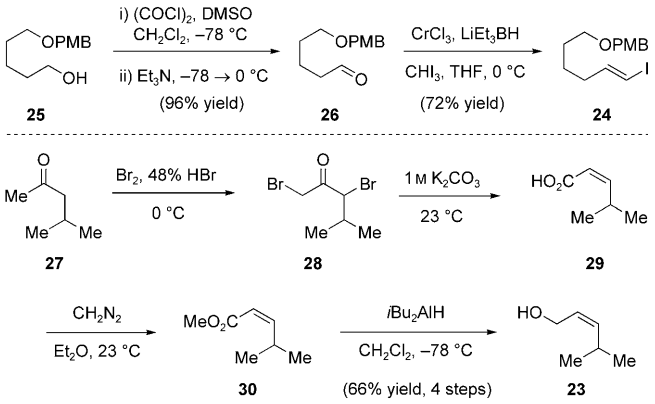


Scheme 4. Barriault's retrosynthesis of model system target **19**; PMB = *para*-methoxybenzyl.

Alder (IMDA) reaction of triene **20**.[15] This bold approach would provide the vinigrol skeleton from a considerably simpler cyclohexane derivative. In turn, triene **20** would be prepared from enyne **21**. In the forward sense, this conversion would proceed through an enyne metathesis reaction[16] to install the diene component, followed by functionalization of the nitrile to introduce the requisite dienophile. The enyne **21** could be prepared from alcohol **22**, an intermediate accessible from two basic fragments: allylic alcohol **23** and vinyl iodide **24**.

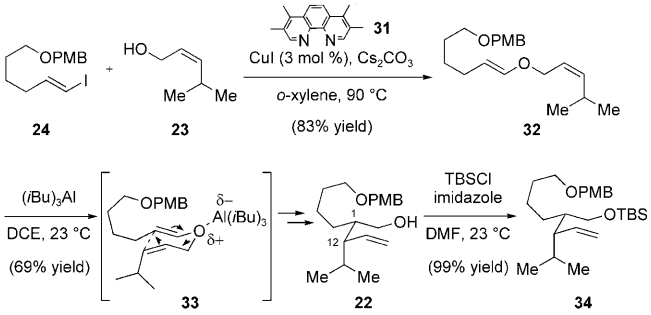
*Synthesis of acyclic intermediate **21***: The two requisite building blocks, **23** and **24**, were prepared using the routes shown in Scheme 5. To synthesize the vinyl iodide fragment **24**, 1,5-pentanediol derivative **25** underwent oxidation under Swern



Scheme 5. Synthesis of coupling fragments **23** and **24**.

conditions to afford aldehyde **26**. Aldehyde **26** was then converted to the *E*-vinyl iodide **24** through a Takai olefination reaction.[17] The allylic alcohol fragment **23** was synthesized by using a high-yielding four-step sequence beginning from 4-methyl-pentane-2-one (**27**). Ketone **27** was treated with bromine and aqueous hydrobromic acid to provide dibromoketone **28**. Subjection of **28** to aqueous K_2CO_3 at ambient temperature promoted a Favorskii rearrangement to form α,β-unsaturated acid **29**.[18] The carboxylic acid was then converted to α,β-unsaturated ester **30** upon treatment with diazomethane. Finally, reduction of **30** with iBu$_2$AlH gave the desired allylic alcohol **23**.

With straightforward access to **23** and **24**, Barriault turned to coupling these fragments and installing the C1–C12 vicinal stereogenic centers present in intermediate **22** (Scheme 6). Using methodology developed by Buchwald,[19]

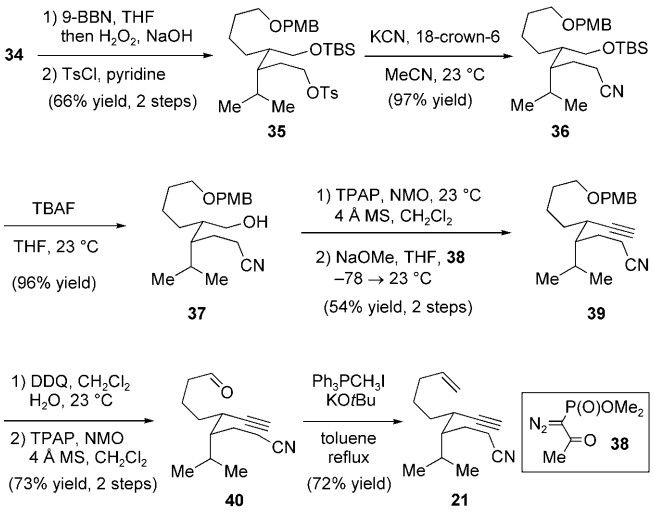


Scheme 6. Installation of the C1–C12 vicinal stereocenters; DCE = 1,2-dichloroethane.

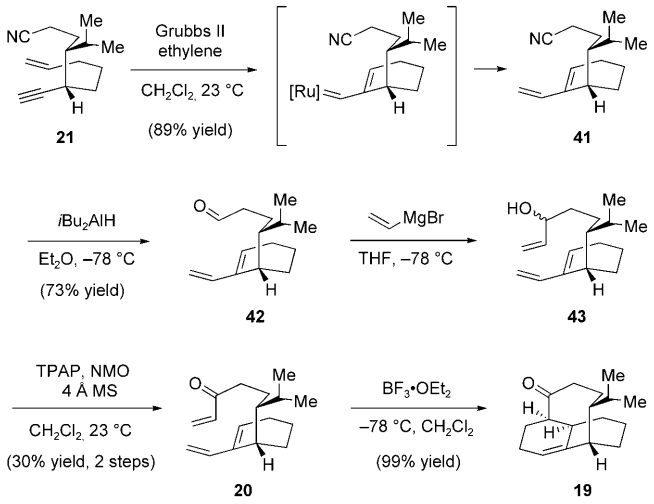
fragments **23** and **24** were coupled upon treatment with catalytic copper iodide and 3,4,7,8-tetramethylphenanthroline (**31**) to afford allylic vinyl ether **32**. It was anticipated that substrate **32** would be prone to undergo a Claisen rearrangement. Indeed, treatment of **32** with triisobutylaluminum effected the desired [3,3] sigmatropic rearrangement (see transition structure **33**), with in situ aldehyde reduction to give alcohol **22**. The conversion of **32**→**22** occurred in 69% yield and provides the C1 and C12 stereocenters, both of which would be present in the natural product. Alcohol **22** was subsequently converted to the TBS ether **34** by using standard protection conditions.

As detailed in the retrosynthetic analysis (see Scheme 4), Barriault intended to assemble the first ring of **1** through an enyne metathesis reaction. It was thus necessary to elaborate alkene **34** to enyne **21**, which was ultimately achieved using the process shown in Scheme 7. Alkene **34** was first converted to tosylate **35** through a two-step sequence involving hydroboration/oxidation, followed by tosylation of the intermediate alcohol. The tosylate was then displaced with potassium cyanide to deliver nitrile **36**, which, in turn, underwent smooth TBAF-promoted desilylation to generate alcohol **37**. Ley oxidation[20] provided an intermediate aldehyde, which was then converted to alkyne **39** through a modification of Ohira's protocol.[21] Finally, a sequence involving cleavage of the PMB group and oxidation (**39**→**40**), and Conia–Wittig olefination[22] gave the desired enyne **21**.

*Assembly of tricycle **19***: With enyne **21** in hand, attention was directed toward testing the key Diels–Alder reaction and assembling the vinigrol core (Scheme 8). To prepare the necessary substrate, enyne **21** was subjected to the Grubbs second-generation catalyst under an atmosphere of ethylene to afford cyclic diene **41**. To install the dienophilic unit of the Diels–Alder substrate, the nitrile was first reduced with iBu$_2$AlH to afford aldehyde **42**. Subsequent addition of vinylmagnesium bromide provided allylic alcohol **43**, which was then oxidized under Ley conditions to deliver triene **20**.



Scheme 7. Synthesis of enyne **21**; 9-BBN = 9-borabicyclo[3.3.1]nonane, Ts = tosyl, TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

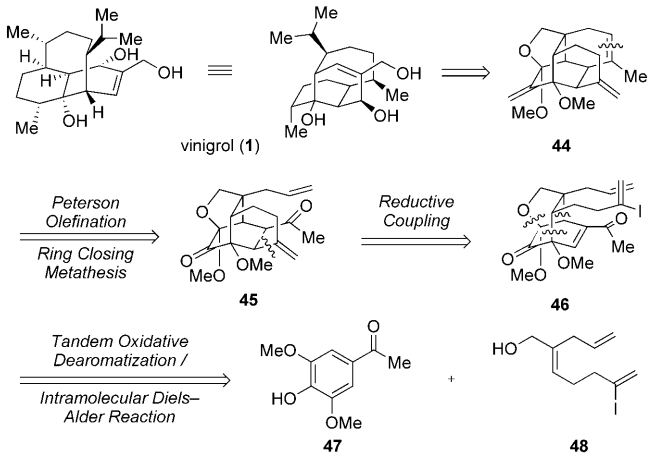


Scheme 8. Construction of tricycle **19**.

Impressively, submission of triene **20** to BF_3•OEt_2 promoted the anticipated intramolecular Diels–Alder reaction and delivered **19** in 99% yield. With this result, Barriault and coworkers have demonstrated the feasibility of assembling the elusive vinigrol core using their ambitious strategy.

Njarđarson's Approach

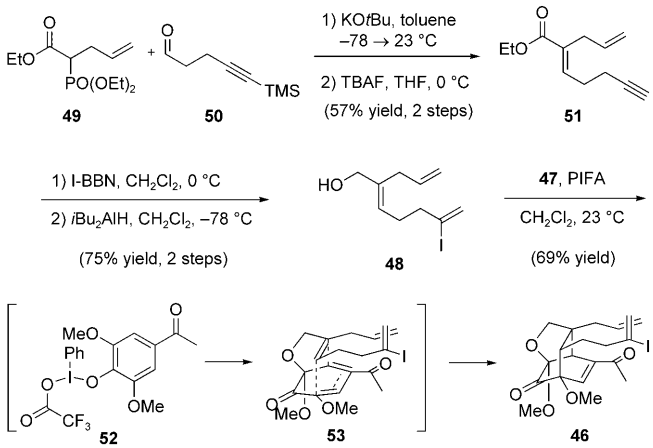
Retrosynthetic analysis of vinigrol: Njarđarson's strategy for the preparation of **1** is depicted in Scheme 9, in retrosynthetic fashion.[12] It was anticipated that **1** could be accessed through late-stage functionalization of polycyclic intermediate **44**. In turn, this intermediate could be derived from dienedione **45**, carried out in the forward sense through a Peterson olefination of the dione followed by ring-closing metathesis. Dienedione **45** would be prepared from vinyl



Scheme 9. Njarđarson's retrosynthetic analysis of **1**.

iodide **46**. Finally, in the key complexity-generating step, polycycle **46** would be derived from pyrogallol derivative **47** and allylic alcohol **48** by way of a tandem oxidative dearomatization[23]/Diels–Alder reaction.

Oxidative dearomatization to assemble the carbon framework of vinigrol: As shown in Scheme 10, Njarđarson and co-workers developed an efficient route to access allylic alcohol **48** en route to testing the planned Adler–Becker oxidative dearomatization/Diels–Alder reaction sequence. Phosphonate ester **49** and aldehyde **50** underwent Horner–Wadsworth–Emmons olefination to afford an intermediate olefin possessing the desired *trans* configuration. Treatment of this intermediate with TBAF afforded alkyne **51**, which was then converted to allylic alcohol **48** by using an efficient two-step iodination/reduction sequence.

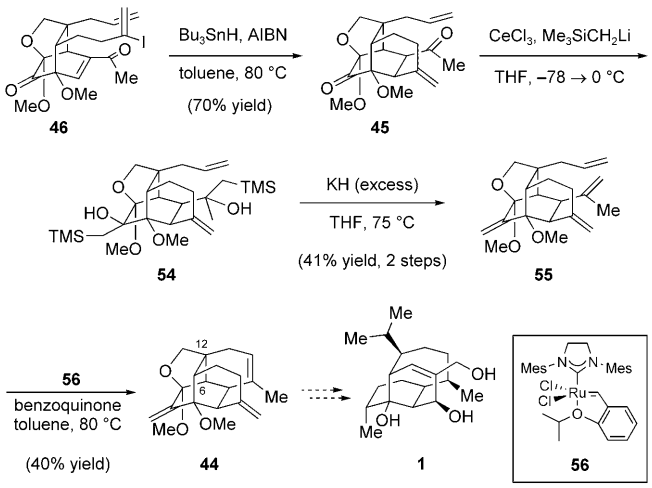


Scheme 10. Assembly of vinigrol carbon framework.

With straightforward access to allylic alcohol **48**, the crucial Adler–Becker oxidative dearomatization/Diels–Alder reaction was examined. Reaction of allylic alcohol **48** with commercially available pyrogallol derivative **47** in the presence of phenyliodo(bis)trifluoroacetate (PIFA) indeed pro-

vided vinyl iodoenone **46** in 69% yield. The transformation is thought to proceed through an initial displacement of a trifluoroacetate ligand from PIFA to afford **52**, followed by hypervalent iodine-mediated oxidation to arrive at Diels–Alder precursor **53**. This intermediate, perfectly poised for the planned [4+2] cycloaddition, underwent smooth in situ conversion to the polycyclic product **46**. This powerful process introduces five new stereogenic centers (three of which would be needed in the natural product), ultimately beginning from simple achiral starting materials. Moreover, this impressive transformation introduces 17 of the 20 carbon atoms of the natural product, and sets the stage for introduction of the remaining rings of the vinigrol core.

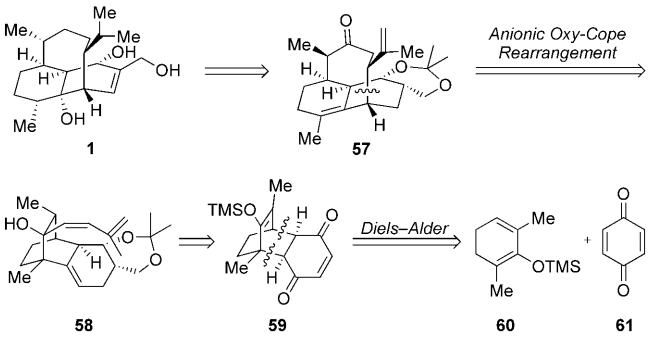
*Elaboration of **46** to advanced intermediate **44***: The elaboration of iodoenone **46** to an advanced intermediate containing the vinigrol core is depicted in Scheme 11. An intramolecular reductive coupling of the vinyl iodide and enone functionalities of **46** facilitated by Bu_3SnH and azobisisobutyronitrile (AIBN) delivered diketone **45**. With one of the rings assembled, **45** was olefinated using Peterson conditions[24] to afford tetraene **55**. Finally, ring-closing metathesis of tetraene **55**, catalyzed by the Grubbs–Hoveyda second-generation catalyst[25] (**56**), gave the polycyclic intermediate **44**, containing the core of **1**. Although steps remain to elaborate **44** to **1**, including fragmentation of the C6–C12 bond, the route is strikingly concise (8 steps to intermediate **44**) and provides an innovative means to build the intricate vinigrol scaffold.



Scheme 11. Elaboration of **46** to vinigrol core.

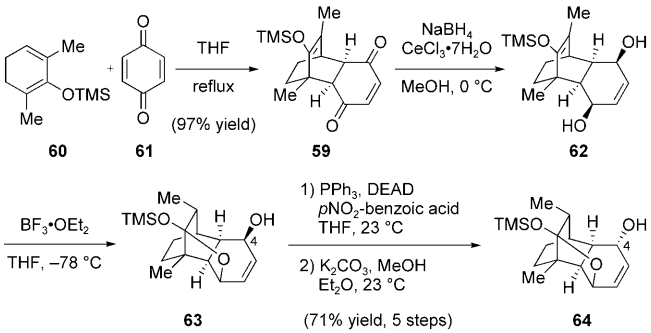
Hanna's Strategy

Retrosynthetic analysis of vinigrol: Hanna's strategy for the total synthesis of **1** is represented in Scheme 12.[6] It was expected that **1** could be accessed from tricycle **57**. In turn, tricycle **57** would arise from allylic alcohol **58** through an anionic oxy-Cope rearrangement.[26] By employing this strategy, the complex vinigrol core would be generated from a more accessible decalin ring system. Allylic alcohol **58** could ultimately be derived from dihydroquinone **59**, the product of an intermolecular Diels–Alder reaction between silyloxydiene **60** and quinone (**61**).



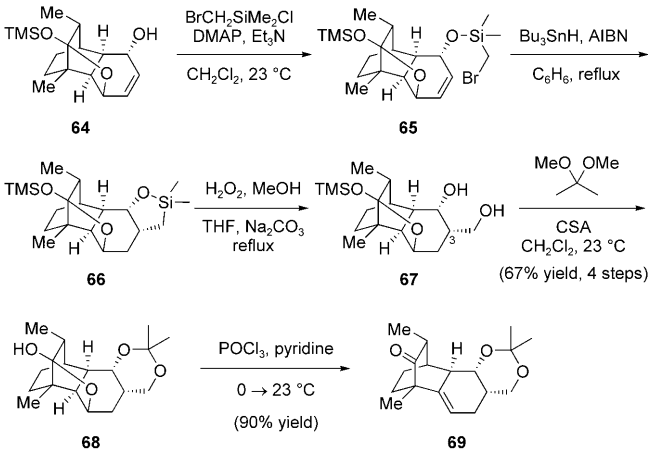
Scheme 12. Hanna's retrosynthetic analysis of **1**.

Anionic oxy-Cope rearrangement to assemble the tricyclic core: With the ultimate goal of preparing allylic alcohol **58** (see Scheme 12) for the key anionic oxy-Cope rearrangement, the necessary decalin ring system was generated (Scheme 13). Upon heating a mixture of silyloxydiene **60** and quinone (**61**), an *endo*-selective Diels–Alder reaction took place to provide adduct **59**. The resulting dihydroquinone **59** was reduced under Luche conditions to give *cis*-diol **62**. Treatment of **62** with $BF_3{\cdot}OEt_2$ catalyzed the formation of silyl ketal **63**, leaving the C4 alcohol exposed. Stereochemical inversion at C4, was achieved under modified Mitsunobu conditions developed by Dodge and Martin[27] to afford alcohol **64**. Notably, alcohol **64** possesses the necessary C4 configuration present in **1**, in addition to the decalin ring system.



Scheme 13. Synthesis of allylic alcohol **64**; DEAD = diethyl azodicarboxylate.

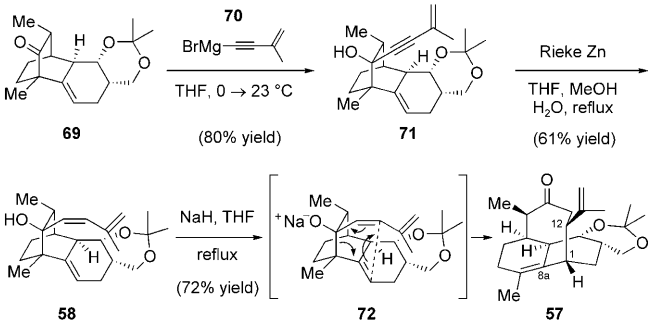
Alcohol **64** was further elaborated by using the sequence shown in Scheme 14. Following silylation of alcohol **64** with bromomethyldimethylsilyl chloride, reductive cyclization of **65** with Bu_3SnH and AIBN afforded silyl ether **66**. Tamao oxidation of **66** produced diol **67**, thus introducing the C3 hydroxymethyl group.[28] Reaction of **67** with 2,2-dimethoxy-



Scheme 14. Conversion of alcohol **64** to ketoalkene **69**; DMAP = 4-dimethylaminopyridine, CSA = camphorsulfonic acid.

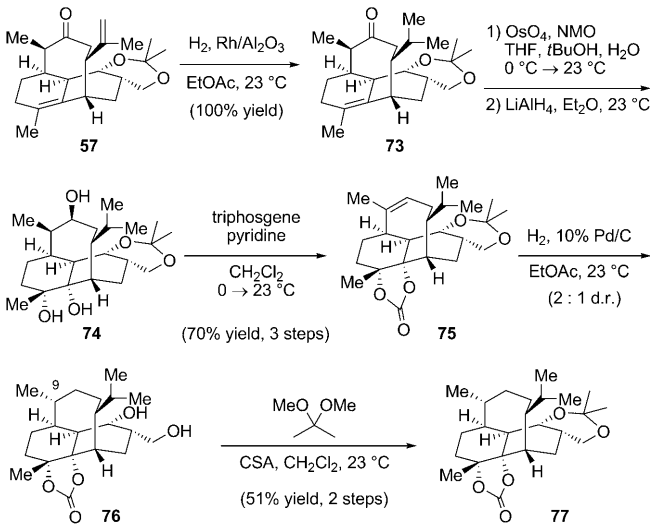
propane and catalytic camphor sulfonic acid resulted in acetonide formation with concomitant silyl group cleavage to afford hemiacetal **68**. Dehydration of hemiacetal **68** with $POCl_3$ delivered ketoalkene **69** in 90% yield.

With intermediate **69** in hand, the key substrate for the anionic oxy-Cope rearrangement was prepared in two steps (Scheme 15). Treatment of ketoalkene **69** with Grignard reagent **70** afforded propargylic alcohol **71**. Alkyne reduction to the corresponding *Z* olefin was achieved by using Rieke zinc,[29] thus providing allylic alcohol **58**. In the key step, exposure of intermediate **58** to sodium hydride under refluxing conditions delivered tricyclic ketone **57** in 72% yield through the planned anionic oxy-Cope rearrangement (see transition state **72**). This transformation is particularly significant since it allows for introduction of the C1 and C12 stereocenters, provides a functional group handle for the C8a hydroxyl group, and generates the evasive vinigrol core.



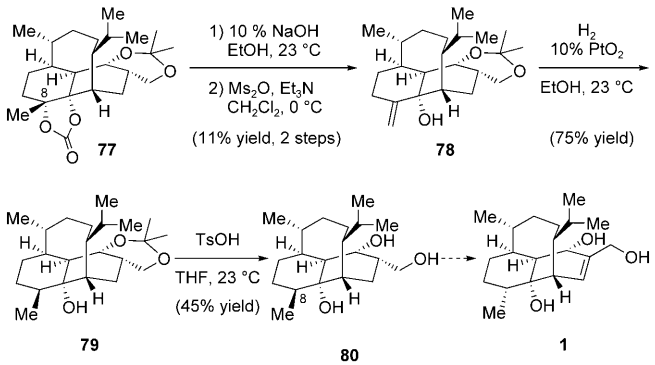
Scheme 15. Anionic oxy-Cope to assemble the tricyclic core.

Synthesis of epi-*C8-dihydrovinigrol*: With tricyclic ketone **57** available, the authors attempted to complete the natural product synthesis. Scheme 16 depicts the efforts toward this end, which largely involve functional group manipulations. The isopropylidene of **57** was first hydrogenated with Rh/Al_2O_3 and H_2 to afford the reduced product **73**. Next, the tetrasubstituted alkene of **73** was dihydroxylated with OsO_4. Subsequent ketone reduction with $LiAlH_4$ occurred diastereoselectively to give triol **74**. Treatment of triol **74** with triphosgene and pyridine led to dehydration of the secondary alcohol, with concomitant protection of the 1,2-diol as the cyclic carbonate. The resulting product, **75**, was hydrogenated to afford the reduced products **76** as a 2:1 mixture of diastereomers, favoring the desired C9 stereoisomer shown. Since the acetonide underwent cleavage under the hydrogenation conditions, this diol protecting group was re-introduced and ultimately enabled the diastereomers to be separated. Thus, acetonide **77** was isolated as a single diastereomer in 51% yield over two steps.



Scheme 16. Further elaboration of tricycle **57**.

From intermediate **77**, a total synthesis of **1** appeared within reach. However, the elaboration of **77** to the natural product proved challenging. In the final efforts reported by Hanna, deprotection of the cyclic carbonate of **77** in the presence of 10% sodium hydroxide produced a diol intermediate (Scheme 17). This intermediate was subjected to mesylation conditions to ultimately eliminate the C8 hydroxyl group and generate the evasive vinigrol core.

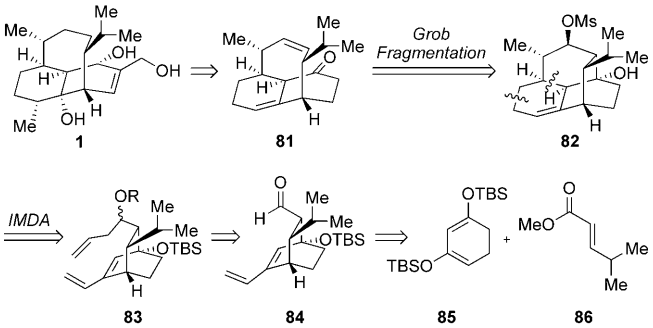


Scheme 17. Synthesis of *epi*-C8-dihydrovinigrol (**80**); Ms = methanesulfonyl.

droxyl and afford allylic alcohol **78**. Competing side-reactions and alternative elimination pathways are likely to be responsible for the modest yields obtained in this transformation. Unfortunately, attempts to reduce the exocyclic olefin of **78** and install the C8 stereocenter were met with difficulty. In fact, only the undesired C8 epimer **79** could be obtained with PtO_2, providing **79** in good yield. Deprotection of acetonide **79** gave *epi*-C8-dihydrovinigrol (**80**), an unnatural derivative of the desired natural product. Hanna's preparation of **80** represents the most advanced progress toward **1** to date, with the exception of Baran's recent total synthesis of the natural product (see below).

Baran's Total Synthesis of Vinigrol

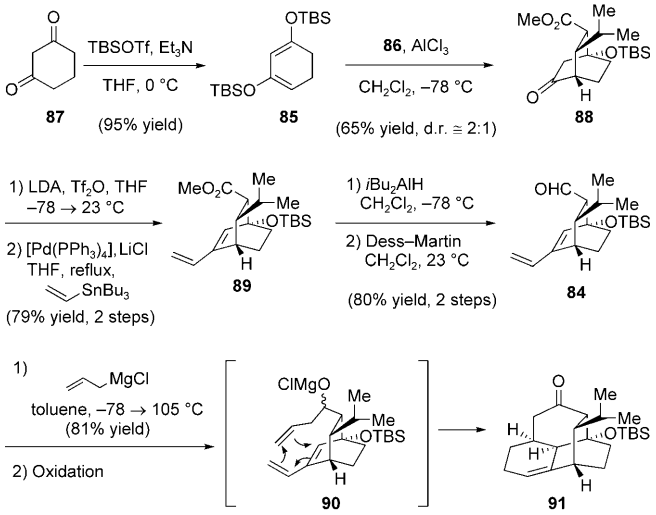
Retrosynthetic analysis of vinigrol: Baran's retrosynthetic analysis of **1** is highlighted in Scheme 18.[13] It was envisioned that **1** could be accessed through late-stage functionalization of tricycle **81**, which, in turn, would arise from a



Scheme 18. Baran's retrosynthetic analysis of **1**.

Grob fragmentation[30] of tetracyclic mesylate **82**.[31] The Grob fragmentation substrate **82** could be prepared from triene **83** through an intramolecular Diels–Alder reaction (IMDA) and functional group manipulations. Retrosynthetic disconnection of triene **83** revealed aldehyde **84**, which would ultimately be derived from the Diels–Alder partners diene **85** and dienophile **86**. Thus, Baran's ambitious approach would take advantage of sequential cycloaddition reactions to assemble much of vinigrol's carbon skeleton in an impressively concise fashion.

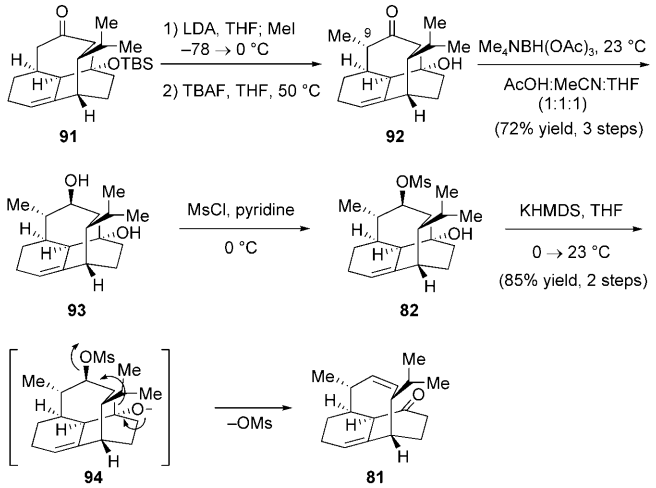
*Intramolecular Diels–Alder to assemble tetracycle **91***: The initial steps of Baran's total synthesis of **1** are shown in Scheme 19. 1,3-cyclohexadione (**87**) was treated with TBSOTf and Et_3N to give the bis(silyloxy)diene **85**. Exposure of this diene to dienophile **86** in the presence of $AlCl_3$ afforded Diels–Alder product **88**, favoring the desired *endo* adduct as a 2:1 mixture of diastereomers. To examine the key IMDA, it was necessary to install both diene and dienophilic components. The diene unit was introduced by conversion of ketone **88** to the corresponding enol triflate, which, in turn, was cross-coupled with tributylvinylstannane to produce diene **89**. The necessary dienophilic olefin was installed



Scheme 19. Baran's assembly of tetracycle **91**; Tf = trifluoromethanesulfonyl.

upon conversion of ester **89** to aldehyde **84** by using a standard two-step sequence, followed by addition of allylmagnesium chloride. Remarkably, the intermediate alkoxide underwent a thermal Diels–Alder reaction (see transition structure **90**) to assemble the desired tetracyclic framework. Following alcohol oxidation, tetracycle **91** was obtained in high yield. It should be noted that the Diels–Alder reaction proceeds smoothly despite the fact that neither the diene nor the dienophile are electronically activated.

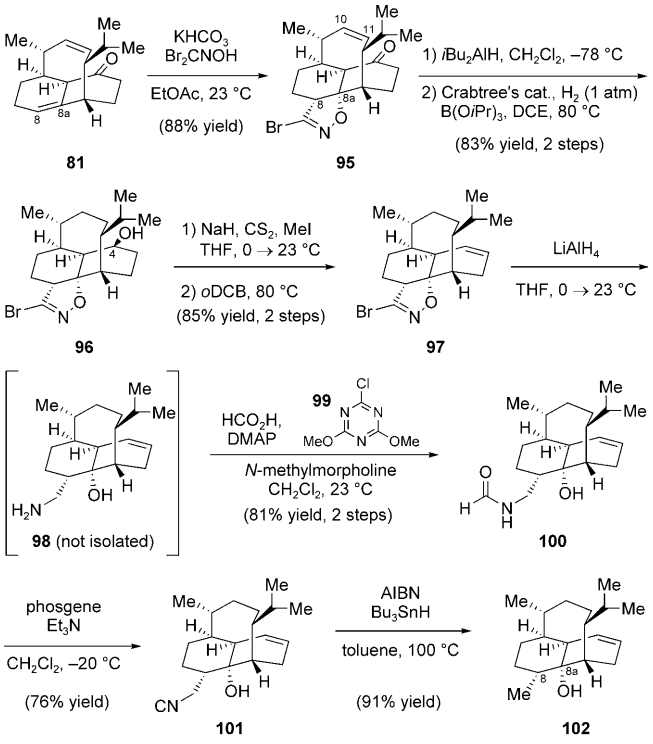
Grob fragmentation to generate the vinigrol core: With access to tetracyclic ketone **91**, efforts shifted toward installing the C9 methyl group and executing the key Grob fragmentation (Scheme 20). Thus, ketone **91** was treated sequentially with lithium diisopropylamide (LDA) and methyl iodide to install the necessary methyl substituent in a diastereoselective fashion. Subsequent desilylation afforded ke-



Scheme 20. Grob fragmentation to access tricycle **81**.

toalcohol **92**. Reduction of ketoalcohol **92** by the action of $Me_4NBH(OAc)_3$ delivered the *anti*-diol **93**.[32] Selective mesylation of the secondary alcohol provided the desired Grob fragmentation substrate **82**. Indeed, treatment of mesylate **82** with potassium hexamethyldisilazide (KHMDS) generated alkoxide intermediate **94**, which underwent carbon–carbon bond cleavage (see transition structure **94**) to afford tricyclic ketone **81**. Tricycle **81**, prepared in short order from commercially available materials, possesses the coveted vinigrol core. Moreover, tricycle **81** contains sufficient functional group handles that could ultimately enable the total synthesis of **1**.

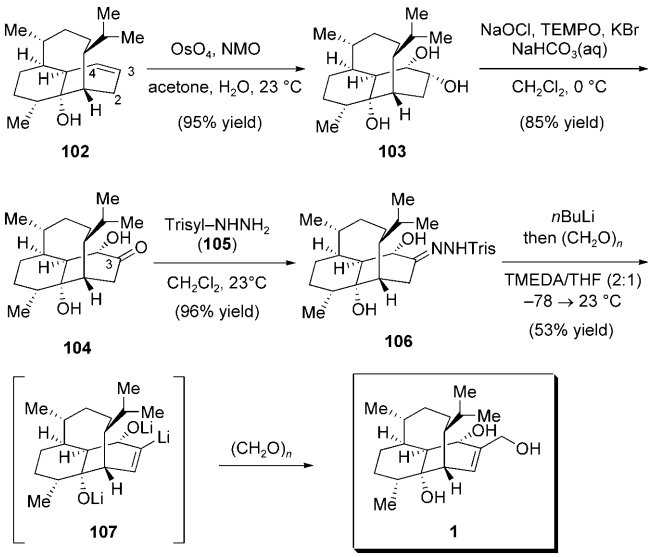
Completion of the total synthesis: With the core of **1** in hand, the next challenge was to install the C8 methyl and C8a hydroxyl groups. As initial direct attempts to introduce these units were unsuccessful, Baran turned to the stepwise approach summarized in Scheme 21. Diene **81** was treated



Scheme 21. Elaboration of tricycle **81** to late-stage intermediate **102**; *o*DCB = ortho-dichlorobenzene.

with $KHCO_3$ and dibromoformaldooxime to give bromoisoxazoline **95** in 88% yield. The transformation is thought to proceed by the in situ generation of bromonitrile oxide, which undergoes a diastereo-, regio-, and chemoselective 1,3-dipolar cycloaddition.[33] The cycloadduct **95** now possessed suitable C8 and C8a functional groups that would be manipulated shortly. Prior to this, however, **95** underwent ketone reduction and directed hydrogenation to provide alcohol **96**.[34] Although this sequence led to reduction of the C10=C11 double bond (needed for the total synthesis), the C4 alcohol present in **96** is epimeric relative to the desired natural product **1**. Thus, a Chugaev elimination was carried out to ablate the C4 stereocenter and convert alcohol **96** to alkene **97**. Returning to the task of installing the necessary C8 and C8a substituents, bromoisoxazoline **97** was treated with an excess of lithium aluminum hydride to afford intermediate amino alcohol **98**. Intermediate **98** was not isolated, but rather was directly formylated by using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **99**) as the coupling reagent.[35] Dehydration of formamide **100** delivered isonitrile **101**, which, in turn, was reduced using Saegusa's deamination protocol[36] to arrive at late-stage intermediate **102**.

The final steps of Baran's total synthesis of **1** are shown in Scheme 22. With the aim of properly substituting C2, C3, and C4, alkene **102** was diastereoselectively dihydroxylated to afford triol **103**. Subsequent oxidation of the most sterically accessible secondary alcohol delivered α-hydroxy ketone **104**.[37] Next, it was envisioned that a Shapiro reaction[38] could be used to install the hydroxymethyl unit at C3. To this end, trisylhydrazine (**105**) was condensed with ketone **104** to afford intermediate trisylhydrazone **106**. Treatment of **106** with an excess of *n*BuLi (**106**→**107**), followed by quenching with paraformaldehyde, provided **1**. The total synthesis of **1** by the Baran group proceeds in only 23 steps from commercially available starting materials in a 3% overall yield. Moreover, this study remains the only completed total synthesis of **1** to date.



Scheme 22. Completion of the total synthesis of **1**; TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide, Tris = triisopropybenzenesulfonyl, TMEDA = tetramethylethylenediamine.

Conclusion

The diterpene natural product vinigrol (**1**) has been a fascinating target for total synthesis for more than two decades. Although assembly of the polycyclic vinigrol core has proved challenging, several research groups have now devel-

oped synthetic strategies that overcome the challenges of accessing this complex molecular scaffold. Innovative synthetic tactics used en route to **1** include: 1) an intramolecular Diels–Alder reaction to assemble a vinigrol model system (Barriault),[10] 2) an oxidative dearomatization/Diels–Alder reaction sequence to rapidly construct the vinigrol scaffold (Njarđarson),[12] 3) an anionic oxy-Cope rearrangement for the synthesis of *epi*-C8-dihydrovinigrol (Hanna),[6] and 4) a proximity-driven intramolecular Diels–Alder reaction and Grob fragmentation to achieve the total synthesis of **1** (Baran).[13] The recently disclosed approaches by Barriault, Njarđarson, and Hanna hold much promise for future total syntheses of **1**. Baran's first total synthesis of **1**, however, will surely be considered a landmark achievement in natural product synthesis for many years to come.

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