Published in final edited form as:

Tetrahedron. 2015 June 10; 71(23): 3775–3793. doi:10.1016/j.tet.2015.04.073.

Synthetic Approaches and Total Syntheses of Vinigrol, a Unique Diterpenoid

Cristian Draghici and Jon T. Njardarson

University of Arizona, Department of Chemistry and Biochemistry, 1306 E. University Blvd., Tucson, AZ 85716, USA

Jon T. Njardarson: njardarson@gmail.com

Abstract

This review summarizes all published total and formal syntheses as well as synthetic approaches towards vinigrol. The content is divided into sections, which are focused on each research groups contributions and how far each approach was advanced towards vinigrol. Graphical summaries of all the published vinigrol structural perspectives, starting materials used for each routes and a discussion of preferred or privileged reactions employed is also presented.

Graphical Abstract

Keywords

vinigrol; total synthesis; diterpenoid; Diels-Alder; fragmentation

Introduction

The aim of this review is to present a detailed account of all published total syntheses and synthetic approaches toward the unique diterpenoid natural product vinigrol. We have chosen to summarize the efforts of each paper by graphically detailing the synthesis, and associated reaction details, of only the most advanced intermediate each research team made. This review¹ omits contributions only reported in graduate student theses. The

© 2015 Published by Elsevier Ltd.

Correspondence to: Jon T. Njardarson, njardarson@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

remarkable structure of vinigrol, which is most simply described as a densely decorated *cis*-decalin core with a diaxial four carbon bridge connecting the two cyclohexyl rings, was first reported in 1987.² Vinigrol contains seven challenging stereocenters and is decorated with only three heteroatoms in the form of hydroxyl groups (primary, secondary and tertiary) all of which are located on one of the two cyclohexyl rings. Vinigrol has been reported to exhibit a promising biological profile, most notably in the areas of cancer and HIV.³ Shown in Scheme 1 is a compilation of all the vinigrol structural perspectives reported to date by the research teams whose efforts are summarized in the following sections. Each one of these perspectives will appear in later schemes as we utilize each authors chosen vinigrol perspective to highlight (with color) how far their synthetic efforts advanced.

Summarized in Scheme 2 is a structural taste of the synthetic journeys you the reader are about to embark on. Shown are the structures of all the starting materials used by these research teams in their investigations towards vinigrol. It is evident that there are preferred structural patterns as all these approaches can be represented by only five structural types: a) cyclohexanones (Mehta, Baran, Matsuda, Crowe, Hanna and Barriault), b) phenols (Njardarson and Liao), c) cyclic 1,3-dienes (Sun and Barriault), d) acyclic diols (Fallis and Barriault) and e) Evans auxiliary (Paquette and Kaliappan). What does this mean? It is not an easy question to answer, but as we summarize the key reaction types used in each one of these routes later in the review it becomes clear that certain key reactions are preferred as well and they might be one of the key reasons for the starting material choices. There are of course much simpler explanations such as the fact that vinigrol has two fused cyclohexyl rings, which quite reasonably calls for a six membered ring starting materials, which is indeed the preferred choice.

Although the contents of this review can be organized in several ways we decided to focus each section of the review on authors and to present within these sections all of the author's contributions to date. Furthermore, we selected to arrange these sections in order of the timeline of the first disclosure by each author. We have tried our best to faithfully recreate each author's chosen structural perspective. Key transformative reactions are highlighted with instructive names in orange boxes. The final structure of each sequence is then compared with vinigrol and atom, bond forming and stereochemical accomplishments highlighted in blue.

1. Hanna's Approaches to Vinigrol

The first vinigrol approach (1993)⁴ was reported by Professor Hanna and coworkers (Scheme 3). A Diels-Alder union between the silyl enol ether (**2**) of cyclohexenone (**1**) and *para*-quinone (**3**) affords a cyclohexyl fused [2.2.2] adduct **4**. Following a sequence of Luche reduction, protection, deprotection and elimination the stage is set for selective reduction of a 1,3-cyclohexadiene moiety (**7**). This reduction challenge was accomplished with hydrogen in the presence of Wilkinson's catalyst. Deprotection of the MOM-protecting group is followed by selective addition of a vinyl magnesium chloride reagent to the less hindered face of the ketone sets the stage for the key step in Hanna's proposed route, a Cope-rearrangement to form vinigrol's carbocyclic core. Hanna and his team demonstrated that by employing oxy-anionic Cope rearrangement conditions in refluxing tetrahydrofuran

in the presence of the appropriate crown ether, they could indeed access the vinigrol core (**11**) in excellent yield from **10**. Thus, in only ten steps from **1**, vinigrol core (**11**) is rapidly accessed.

Few years later, Hanna reported a short report which highlighted some of the challenges they would be facing in the coming years in trying to realize the success of their model system towards the actual target (vinigrol).⁵ Protection of **11** (Scheme 4), reduction of the ketone and protection as a methyl ether (**12**) set the stage for evaluating double hydration approaches. Interestingly, they learned that structures like **12** underwent a very facile acid catalyzed cascade to form fused tricyclic products like **13** instead of any desired hydrated products. Undeterred, Hanna's team marched forward towards a synthetic solution.

Only a year later, an olefin hydration solution was identified by Hanna's team (Scheme 5).⁶ They demonstrated that alcohol **14** could be hydrated in such a way to afford triol **15** in modest yield. This was a significant achievement as it completed the critical *cis*-decalin ring fusion of vinigrol. With enough quantities of **15** in hand they turned their attention toward installing some additional functional groups. The unprotected secondary alcohol was removed using a xanthate radical reduction approach (**17**) and the remaining secondary alcohol was oxidized using Dess-Martin periodinane to ketone **19**. Installation of the methylene hydroxyl group (**20**) of vinigrol was accomplished in moderate yield by first forming a silylenol ether and then trapping it with formaldehyde with the aid of a lanthanide catalysts. With the decalin challenges mostly solved, Professor Hanna turned his attention to the four carbon bridge and its two chiral centers.

Hanna next turned his attention to employing a more complex nucleophile in the addition step to the ketone to enable introduction of the two four carbon bridge substituents (Scheme 6).⁷ Towards that end, by starting with a slightly more complex cyclohexadiene (**22**) in the Diels-Alder reaction he was able to bring in the methyl group needed in the bridge. Following Luche reduction, a Mitsunobo inversion reaction was needed to set the correct vinigrol secondary alcohol stereocenter (**25**). With the secondary alcohol stereochemistry set a new approach was needed to install the methylene alcohol functionality. A creative solution was identified in the form of a silyl tethered radical cyclization (**27**) followed by peroxide mediated oxidation of the C-Si bond (**28**). Following standard protection and dehydration steps the stage was set for introduction of a more complex Grignard nucleophile (**31**) to afford propargylic alcohol **32**. Syn reduction of the alkyne group with Rieke zinc afforded *Z*-olefin **33**, which was essential for setting the appropriate stereochemistry of the isopropyl bridge stereocenter in the key oxy-anionic Cope rearrangement step (**34**). Unfortunately the methyl group stereocenter on the bridge was incorrect, which is why a three step solution involving reduction, dehydration (**35** to **36**) and substrate controlled hydrogenation (**37** to **38**) was needed. Advanced intermediate **38** has all the necessary vinigrol carbon atoms but it lacks a double bond and the ability to selectively reduce one of the oxirane C-O bonds to reach vinigrol.

In Hanna's final attempt to reach vinigrol he needed to find a way to hydrate the tetrasubstituted olefin achieving a net anti addition (Scheme 7).⁸ Dihydroxylation with osmium tetroxide achieved the first part of his task, the introduction of a hydroxyl group

(**39**) at the decalin ring fusion. Before turning his attention toward how to reduce the other C-O bond, he first needed to flip the methyl stereochemistry using the substrate controlled olefin reduction logic described in Scheme 6 (**41**). This was accomplished by first protecting the 1,2-diol as a carbonate, followed by hydrogenation of the trisubstituted olefin and reprotection of the 1,3-diol group. Following carbonate group removal, diol **43** was functionalized as the *mono*-mesylate with the aim of eliminating it to form exocyclic olefin **44** exclusively. This non-trivial activation-elimination task was only achieved in dismal 11% yield, which is perhaps not surprising as both alcohols can react, or be mesylated and then eliminated in a variety of ways. All hopes were squashed when they realized that reduction of this exocyclic olefin only afforded the incorrect stereoisomer (**45**). Their most advanced intermediate (**46**) is only one double bond away from vinigrol in addition to being epimeric at one of the stereocenters.

2. Mehta's Vinigrol Approach

Professor Mehta⁹ reported a model study toward vinigrol soon after that of Professor Hanna's (Scheme 8). The study commences with a Robinson annulation to build **50**, which was then bis alkylated (**50**) and subjected to an addition of a vinyl magnesium bromide to afford allylic alcohol **52**. As vinigrol contains a [5.3.1] bridged bicyclic core, similar to that of Taxol, within its structure, Professor Mehta postulated that an oxy-Cope rearrangement could be used to convert **52** into **53** and rapidly reveal this bicyclic core. Interestingly, oxy-anion accelerated Cope rearrangement conditions failed for **52** and the best results were achieved by heating **52** in the absence of solvent to very high temperatures. These harsh thermal oxy-Cope rearrangement conditions afforded the expected product **53** as well as substantial amount of **54**, which is the product of an alternate intramolecular ene-reaction.

3. Matsuda's Vinigrol Approaches

Professor Matsuda's group was next in reporting their synthetic strategy towards vinigrol (Scheme 9).¹⁰ His approach commenced with an aldol union between dihydrocarvone (**55**) and aldehyde **56**. The resulting aldol product was then dehydrated (**58**) and the enone subjected to a Luche reduction. Vanadium directed epoxidation of allylic alcohol **59** afforded oxirane **60**. Following a Swern oxidation, samarium diiodide was employed as a reducing agent to break one of the oxirane C-O bonds via ketyl radical intermediate and protonation of the resulting enolate (**62**). Acylation of the secondary alcohol then set the stage for establishing the feasibility of the proposed key *6-exo-trig* ketyl radical cyclization. Samarium diiodide turned out to be the optimal reagent for forming *cis*-decalin **64**, which contains all but one of the necessary *cis*-decalin substituents found in vinigrol.

In his second approach (Scheme 10). Matsuda focused his attention on accessing the [5.3.1] bicyclic core Professor Mehta had shown could be built using an oxy-Cope rearrangement strategy.¹¹ Again, starting from dihydrocarvone an aldol reaction was followed by a dehydration step to form **68**. This time around, an allylmagnesium Grignard reagent was added to the ketone and the resulting allylic alcohol (**69**) protected as a MOM-ether (**70**). Hydroboration of the mono-substituted olefin and oxidation of the primary alcohol product with Dess-Martin periodinane afforded aldehyde **72**. In this proposal, Professor Matsuda hoped to bring together the aldehyde and an allyl chloride in a samarium mediated reductive

coupling reaction to form [5.3.1] bridged bicyclic core **73**. This was indeed shown to be feasible using samarium(II) diiodide in the presence of HMPA as co-solvent.

4. Paquette's Vinigrol Approaches

With only several approaches towards vinigrol synthesis reported in the 1990's, contributions from numerous laboratories starting emerging in the 21st century. The first such contribution came in 2003 from the laboratory of Professor Paquette.¹² All his routes (Schemes 11–13) focus on building a fully functionalized *cis*-decalin precursor and then evaluate cyclization approaches to form the four carbon bridge. Synthesis of the common *cis*-decalin precursor and the first cyclization substrate are shown in Scheme 11. Evan's asymmetric alkylation was used to set the first chiral center (the isopropyl stereocenter), and after standard redox manipulations, aldehyde **77** was then subjected to a Robinson annulation sequence to afford enone **78** (DB-18-Cr-6 = Dibenzo-18-Crown-6). An anionic double Michael addition cascade between enone **79** and a vinyl sulfoxide provided access to [2.2.2] bicyclic product **80** in a suboptimal 27% yield. Grignard reagent derived from vinyl iodide **81** was used to form allylic alcohol **82**, which then underwent the key oxy-anionic Cope rearrangement to yield densely substituted *cis*-decalin product **83**. Protection of the newly formed ketone as a cyclic ketal allowed selective manipulations of the two protected primary alcohol groups to take place to eventually afford pre-cyclization precursor **86**. Unfortunately, all attempts to displace the sulfonate leaving group intramolecularly with the anion derived from the sulfone failed.

In their second cyclization attempt, their goal was to use a carbanion or a ketyl radical to attack a more proximal and rigid strained lactone electrophile (Scheme 12).¹³ Their routes commenced with intermediate **83**, which was advanced through a series of standard redox and protection-deprotection steps to lactones **89** and **92**. The low yielding lactone steps are a testament to how difficult these bridge bicyclic lactones are to make. Sadly again, no productive cyclization was observed from either substrate.

Still undeterred, the Paquette group decided to use their advanced intermediate to evaluate a host of other cyclization approaches, including a ring closing metathesis, Ramberg-Bäcklund and Lactam-Sulfoxide ring contraction reactions (Scheme 13).¹⁴ All cyclization substrates were made using standard manipulations from common intermediate **83**. Sadly, ring closing metathesis substrates **93–95** failed, as did lactam-sulfoxide ring contraction substrates **96–98**, Ramberg-Bäcklund substrate **99** and reductive cyclization substrate **100**. With these *cis*-decalin cyclization failures, no more advances towards vinigrol were made.

5. Barriault's Approaches and Total Synthesis of Vinigrol

Professor Barriault has pursued several creative approaches towards vinigrol, which finally culminated in a total synthesis in 2012. His first approach, reported in 2004, was focused on employing an ingenious pericyclic cascade (Scheme 14).¹⁵ Cyclohexadiene **101** served as his starting material for his model studies. Following standard oxidative manipulations, oxirane **103** was desymmetrized using isopropenyl magnesium bromide to afford cyclohexyl triol **104**. Protection of the vicinal alcohols and oxidation of the remaining secondary alcohol furnished ketone **105**, which was then converted into propargylic alcohol **106**.

Allylation of the tertiary alcohol provided requisite substrate (**107**) for the pericyclic reaction studies. Impressively, when ene-yne **107** was heated to high temperatures in toluene it underwent the proposed oxy-Cope/Claisen/Ene-rearrangement cascade to afford *cis*-decalin **108** in excellent yields. Unfortunately, this remarkable pericyclic cascade did not proceed when the olefin terminus was substituted, which ended efforts to further advance this route.

Professor Barriault's second vinigrol attempt also aimed at employing a key pericyclic reaction (Claisen rearrangement) to form the four carbon decalin-bridge (Scheme 15).¹⁶ The substrate (**116**) needed for this key step was assembled from cyclohexenone **1**. After vinylation of **1**, enone **109** was reduced and the resulting diene subjected to a magnesium-directed Diels-Alder cycloaddition reaction to afford **110**. Standard redox and protection/deprotection manipulations then advanced **110** to alcohol **113**. Oxidation of the free alcohol, addition of a vinyl cerium nucleophile and deprotection furnished diol **114**. Treatment of **114** with Ley oxidation conditions yielded lactone **115**, which was readily converted into Claisen rearrangement substrate **116** using Tebbe's olefination. Regrettably, enol ether **116** did not undergo the expected Claisen rearrangement.

Barriault and co-workers used the same decalin intermediates to also evaluate additional cyclization approaches. Shown in Scheme 16 is their approach towards ring closing metathesis substrate **122**, whose precursor was also a candidate for a McMurry cyclization. Grignard addition of **118** to ketone **117** was followed by protection and elimination to afford trisubstituted olefin **120**. High pressure ruthenium catalyzed reduction of olefin **120** afforded **121**. Removal of both silyl groups with tetrabutylammonium fluoride followed by Ley oxidation furnished a *bis*-aldehyde, which did not cyclize when subjected to the requisite titanium reagents and conditions most commonly employed in McMurry type cyclizations. Olefination of the *bis*-aldehyde was easily accomplished under standard Wittig olefination conditions. Sadly, the resulting diene (**122**) did not undergo the expected ring closing metathesis reaction to form the vinigrol carbocyclic core.

The Barriault group evaluated an alternative Claisen rearrangement strategy as well to form the vingirol core (Scheme 17). Towards that end, 1,4-butanediol was converted into enal **125** and then subjected to Weiler addition reaction conditions, which yielded alcohol **127**. Directed reduction was then followed by acid mediated lactonization conditions (**128**) and the ensuing lactone carbonyl group was next converted into a diene (**129**) via a four step protocol. The diene was then reacted with benzyl protected maleimide in a Lewis acid directed Diels-Alder cycloaddition reaction to afford decalin **130**. Following silyl protection of the alcohol, Barriault and his team were rewarded with a successful Claisen rearrangement under microwave heating conditions to afford the much desired vinigrol carbocyclic core **131**.

Despite the success of the Claisen rearrangement in their 2005 approach, the Barriault group decided to go back to the drawing board and pursue a new synthetic approach (Scheme 18).¹⁷ Starting from 1,4-butanediol they rapidly form vinyl iodide **133**, which is subjected to copper catalyzed etherification with allylic alcohol **134** to afford Claisen rearrangement precursor **135**. Claisen rearrangement proceeded smoothly in the presence of a Lewis acid,

which also served the critical role of rapidly reducing the sensitive aldehyde product. Standard redox and homologation procedures then advanced **136** to aldehyde **138**, which was subjected to the Bestman-Ohira alkylation conditions to afford alkyne **140**. Deprotection of the primary alcohol was then followed by Ley oxidation and a Wittig olefination to yield **142**, which underwent a high yielding intramolecular ene-yne metathesis cyclization reaction in the presence of Grubb's second generation ruthenium catalyst. The nitrile of the ene-yne product (**143**) was converted into a vinyl ketone (**144**) using standard procedures. This triene underwent a remarkably mild and near quantitative intramolecular Diels-Alder cycloaddition reaction to form the vinigrol carbocyclic core (**145**). Following this excellent success, the Barriault group turned their attention toward completing the total synthesis.

With an exciting synthetic blueprint established, Professor Barriault and his team set out to complete the total synthesis of vinigrol (Scheme 19).¹⁸ Following basic diol (**123**) manipulations, allylic alcohol **146** was reacted with cyclohexyl ketal **147** under Johnson-Claisen rearrangement conditions to afford ketone **148**. Reduction of the propene moiety was followed by triflate formation (**149**) and a Stille coupling of the resulting enol triflate with vinyl tributyltin (**150**). The undesired of the two pivaloate isomers was subjected to a four step sequence to funnel all of the material to pivaloate **151**. After silyl deprotection the primary alcohol was converted into enone **152**, which was subjected to the facile intramolecular Diels-Alder cycloaddition to deliver the vinigrol carbocyclic core (**153**). Wittig olefination and platinum catalyzed hydrogenation then ensured installation of a key stereocenter (**154**). At this point, the alcohol protecting group was swapped and the trisubstituted olefin converted in a five step sequence to a methyl group and a tertiary alcohol. This is a slight variation of a cycloaddition solution designed by Professor Baran in his vinigrol synthesis (Scheme 22). Following reductive removal of the benzyl group and oxidation with TEMPO, ketone **157** was obtained. The enolate of ketone **157** was treated with an electrophilic oxygen source in the form of Davis oxaziridine to install the final vinigrol stereocenter (**158**). Shapiro reaction conditions, as described by Baran,²¹ were then used to convert **158** into vinigrol.

6. Fallis's Vinigrol Approach

Professor Fallis from the University of Ottawa reported a Diels-Alder focused approach towards vinigrol (Scheme 20).¹⁹ His route commenced with conversion of 1,3-propanediol to aldehyde **160**, which was treated with diene bromide **161** in the presence of indium metal. The resulting alcohol (**162**) was then dehydrated in two steps to yield triene alcohol **164**, which underwent a magnesium directed Diels-Alder cycloaddition reaction with N-methyl maleimide. Cycloaddition product **165** was then oxidized (**166**) and homologated to alkyne **167**. Deprotonation of the alkyne and trapping with dimethylformamide (DMF) afforded ynal **168**, which following a Lindlar reduction (producing **169**) was treated with vinyl magnesium bromide (**170**). Upon mild manganese dioxide oxidation of divinyl alcohol **170**, the resulting ketone (**171**) underwent an efficient intramolecular Diels-Alder reaction with the aid of gentle heating to form cycloadduct **172**, which contains the carbocyclic vinigrol core.

7. Baran's Approach and Total Synthesis of Vinigrol

Professor Phil Baran model approach to the vinigrol carbocyclic core is summarized in Scheme 21.²⁰ Bis-silylated diene **176**, obtained from 1,3-cyclohexadione (**173**), was reacted with enoate **175** in a Diels-Alder reaction. Cycloadduct **176**, was then homologated via vinyl triflate **177** to 1,3-diene **178**. Reduction of the ester afforded a primary alcohol (**179**), which was oxidized with Dess-Martin periodinane to aldehyde **180**. Remarkably, addition of allyl magnesium bromide in toluene afforded intramolecular Diels-Alder cycloadduct **181** in one pot and excellent yield. In collaboration with Professor Houk further experimental and computational follow up studies have been performed in an attempt to explain the remarkably facile nature of this Diels-Alder reaction.²¹ Deprotection of the silyl group was followed by oxidation and reduction of the resulting ketone to set up the necessary orbital alignment needed for the key ring expansion reaction. Mono-mesylation of diol **184** afforded **185**, which gratifyingly underwent a mild and high yielding Grob fragmentation reaction to reveal the vinigrol carbocyclic core (**186**). Substrate controlled epoxidation of the trisubstituted olefin demonstrated that the tertiary C-O bond could be installed, which is where model efforts ended and total synthesis plans began (Scheme 22).

To complete the first total synthesis of vinigrol, Baran and his team were able to take advantage of advanced intermediate **188** from their model studies (Scheme 22).²² Ketone **188** was used to install the four carbon bridge methyl group stereocenter in a substrate controlled manner (**189**) after which the Grob fragmentation was successfully executed to unravel the vinigrol core (**190**). At this point, Professor Baran and his coworkers were faced with solving a non-trivial challenge, the controlled conversion of the *tri*-substituted olefin into a tertiary alcohol and a secondary methyl group stereocenter with a *syn*-relationship. They solved this problem with a remarkable cycloaddition reaction, which afforded heterocycle **191** containing both groups with the necessary stereochemical relationships albeit with some additional redox manipulations needed to unravel the desired native vinigrol functionality. Before tackling the heteocycle, the remaining double bond and ketone were reduced (**192**) and the resulting secondary alcohol subjected to a Chugaev elimination reaction (**193**). Reduction and activation of **193** afforded formamide **194**, which could be reduced in two steps to a methyl group (**195**). Substrate controlled dihydroxylation of olefin **195** afforded a diol whose less hindered secondary alcohol could be selectively oxidized to α -hydroxy ketone **196**. Ketone **196** was then condensed to hydrazone **197**, which was converted in one step to vinigrol using the Shapiro reaction conditions and formaldehyde as the vinyl anion trapping agent. This remarkable final step proceeds without any hydroxyl protecting groups.

8. Njardarson's Approaches and Total Synthesis of Vinigrol

Professor Njardarson and coworkers have pursued vinigrol using several approaches all of which employ a strategic oxidative dearomatization/Diels-Alder reaction and a late stage fragmentation step. Their first published route, which focuses on the Wessely oxidation, is shown in Scheme 23.²³ Alkylation of resorcinol aldehyde **198** with bromoenolate **199** afforded **200**, which was cyclized with an organocatalyst (**201**) using the Stetter reaction. Sodium borohydride reduction of ketone **202** afforded benzylic alcohol **203**. The Njardarson

group devised a remarkably mild method for forming a quinone methide *in situ* and trapping it with ethyl vinyl ether to afford **204** as a single diastereomer. Selective reduction of the ester to an aldehyde and homologation with phosphonate **205** afforded enoate **206** in a high overall yield. Ethyl acetal **206** was hydrolyzed in the presence of camphorsulfonic acid and the resulting lactol oxidized to lactone **207** using Jones oxidation conditions. Careful hydrolysis of the lactone afforded a sensitive phenol-acid product, which was subjected to an extensive range of Wessely oxidation conditions. This turned out to be most challenging and it was finally revealed that in the presence of lead(IV) acetate (LTA) in hexafluoroisopropanal (HFIP), small amounts of the desired intramolecular Wessely oxidation products could be obtained. This intermediate ortho-quinone spiro lactone underwent a near quantitative intramolecular Diels-Alder cycloaddition to afford **208**. The incredibly low overall 8% yield for these three steps is exclusively the result of the Wessely oxidation step. Although gratifying as a proof of concept result, the miserably low yielding dearomatization step required a redesign.

The Njardarson group's second vinigrol approach was also focused on trapping a reactive dearomatized phenol intermediate with an adjacent nucleophile followed by an intramolecular Diels-Alder reaction (Scheme 24).²⁴ This time, the Adler-Becker reaction served as the oxidative dearomatization platform. Exhaustive alkylation of ketone **209** followed by palladium mediated deprotection of the unwanted allyl ether afforded *bis*-allylated ketone product **210**. Reduction of the ketone yielded phenol alcohol **211**, which was shown to be an excellent Adler-Becker oxidation substrate. Dearomatized quinone *spiro*-epoxide **212** underwent an intramolecular Diels-Alder cycloaddition to furnish **213** in excellent yield. Despite these promising results, more highly substituted substrates did not fair as well and a redesign was required.

The Njardarson group's third approach centered on realizing an oxidative dearomatization of a pyrogallol precursor to generate a reactive quinone intermediate capable of undergoing the intramolecular Diels-Alder reaction in the same pot (Scheme 25).²⁵ Horner-Wadsworth-Emmons condensation between phosphonate **214** and aldehyde **215** afforded enoate **216**. The terminal alkyne group was then converted into a vinyl iodide and the ester group reduced with diisobutylaluminum hydride to allylic alcohol **217**. Remarkably, the oxidative dearomatization union between **217** and commercially available pyrogallol **218** afforded the proposed [2.2.2] bicyclic product **219** in one pot at room temperature. Vinyl iodide **219** was then converted to **220** via a *6-exo-trig* radical cyclization. The two ketones were then treated with a cerium nucleophile and the resulting adducts reacted with potassium hydride to facilitate a base mediated Peterson type elimination and formation of tetraene **221**. Ring closing metathesis using the Grubbs-Hoveyda second generation catalyst (**222**) in the presence of benzoquinone to suppress unwanted olefin migration converted **221** to tetracyclic cage **223**, which contains the pre-fragmented vinigrol carbocyclic core.

The clues from the Njardarson group pyrogallol model system motivated an adjustment, which culminated in the second total synthesis of vinigrol being accomplished (Schemes 26–27).²⁶ Etherification of phenol **224** with alcohol **225** afforded **226**, whose lactone was reduced and the resulting free phenol strategically protected with a trifluoroethylether, whose role was also to deactivate and guide the pending dearomatization to the more

electron rich ether. Dakin oxidation of aryl aldehyde **227** yielded phenol **228**, which underwent the proposed oxidative dearomatization-Diels-Alder to form cycloadduct **229**. A tandem *6-exo-trig/6-exo-dig* palladium cyclization completed the *pre*-fragmentation vinigrol core (**230**) in only two steps from the flat aromatic precursor **228**. Installation of the methyl group stereocenter on the four carbon bridge was easily accomplished using a substrate controlled hydrogenation. Olefination of ketone **231** proved tricky, but was eventually realized via an addition/Chugaev elimination sequence. Substrate controlled hydrogenation of **232** only afforded the incorrect methyl diastereomer, which is why an iridium catalyzed (**233**) directed homogeneous hydrogenation conditions were required to form **234**. Mild acetal deprotection using lithium tetrafluoroborate and oxidation to aldehyde **235** set the stage for a remarkably selective and mild Baeyer-Villiger oxidation, which afforded diol **236** after reduction with diisobutylaluminum hydride. Diol **236** was converted to *pre*-fragmentation mesylate **238** using a directed reduction as the key step.

Mesylate **238** underwent a mild Grob fragmentation to form vinigrol core **239** in excellent yield (Scheme 27). Interestingly, the mesylate derived from diol **236** (i.e. the product of direct mesylation of the secondary alcohol of **236**) also underwent the fragmentation despite having much poorer orbital overlap. Following hydrogenation of the newly formed double bond, ketone **240** was converted to α -hydroxy ketone **241**. Dehydration of this alcohol turned out to be remarkably challenging and revealed an unforeseen and unwanted Grob fragmentation wherein the trifluoroethyl ether served the role of a leaving group. Finally, a solution was realized employing the Burgess dehydrating agent. Reduction of the enone under basic conditions set the stereochemistry required for the isopropyl stereocenter, which was then completed using a two step Wittig olefination/reduction sequence (**243**). Deprotection of the allyl methyl ether was accomplished in an unusual way with selenium dioxide and a reduction of the resulting enal. Directed epoxidation afforded oxirane **245**, which was then strategically ring opened to allylic alcohol **246** with the help of a primary iodide and zinc. A remarkable interrupted selenium dioxide allylic oxidation not only oxidized olefin **246** but also transposed it to the thermodynamically more stable allylic alcohol **247**. The final step required removal of a new and stable protecting group, trifluoroethyl ether, from the tertiary alcohol. By taking advantage of the high acidity of the α -trifluoromethyl methylene protons, enol ether **248** could be formed *in situ* upon treatment with lithium diisopropyl amide (LDA). This surprisingly stable enol ether was then oxidatively cleaved with osmium tetroxide to liberate vinigrol.

9. Wang's Vinigrol Approach

Professor's Wang and Crowe have evaluated an intramolecular alkylation approach to construct parts of the vinigrol skeleton (Scheme 28).²⁷ Enone **249** is converted to [3.3.1] bicyclic product **250** upon treatment with methyl acetoacetate and base via a Michael/Aldol addition cascade. Methylation of the β -keto ester followed by decarboxylation affords ketone **252**, which is then temporarily protected as silylenol ether to allow a hydroboration-oxidation to be performed on the terminal olefin. Deprotection and iodination yielded iodide **256**, whose desired epimer underwent the proposed (**257**) intramolecular enolate alkylation with the help of a lithium tetramethylpiperidide (LiTMP) base.

10. Sun's Vinigrol Approach

Professor Sun evaluated an alternative intramolecular alkylation approach to form the [5.3.1] bridged bicyclic part of vinigrol (Scheme 29).²⁸ Cyclooctene monoxide **259** was ring opened with methyl cuprate and the resulting alcohol oxidized with IBX to dienone **261**. Conjugate addition of isopropyl cuprate afforded primarily diastereomer **262**, which then underwent a second substrate controlled cuprate addition in the presence of trimethyl silyl chloride (TMSCl) activator. Alkylation of silyl enol ether **264** then set the stage for the key intramolecular alkylation, which unfortunately did not afford any of **267**, but instead provided fused oxirane **268**. Interestingly, when ketone **266** was subjected to palladium mediated alkylation conditions inside-out ring system **269** was obtained in high yield.

11. Kaliappan's Formal Total Synthesis of Vinigrol

Professor Kaliappan most recently completed a nice formal total synthesis of vinigrol (Scheme 30).²⁹ Evans auxiliary based reagent **270** set the stage for the introduction of the first two stereocenters via Michael-alkylation sequence. Removal of the auxiliary and reduction then afforded aldehyde **275**, which was homologated using the Corey-Fuchs reaction protocol to alkyne **277**. Oxidative cleavage of the terminal olefin followed by addition of chiral Brown's allylation reagent then yielded **280**, which was then promptly deprotected (silyl group and MOM-ether) and strategically reprotected with a silyl and a pivalate group to afford, after silyl deprotection, alcohol **285**. Swern oxidation was followed by addition of vinyl magnesium bromide and another Swern oxidation to furnish enone **288**. This enone then underwent a clever one pot intramolecular ene-yne ring closing metathesis followed by a facile intramolecular Diels-Alder cycloaddition with the aid of Grubb's second generation catalyst and tin(IV) tetrachloride. Wittig olefination of vinigrol core **289** afforded an olefin (**290**), which could be selectively hydrogenated with a platinum catalyst to afford **291**, which is an intermediate in Professor Barriault's¹⁸ total synthesis of vinigrol.

12. Liao's Vinigrol Approach

Professor Liao has recently demonstrated a nice oxidative dearomatization approach towards vinigrol (Scheme 31).³⁰ Dearomatization of phenol **292** in the presence of allylic alcohol **293** affords cycloadduct **294** in excellent yield. After a Stille coupling reaction a vinyl nucleophile was added to ketone **295** to form triene **296**. Microwave mediate intermolecular Diels-Alder union between **296** and methyl vinyl ketone in dimethylformamide (DMF) then delivered **297**. Following protection of ketone **297** as a cyclic ketal the stage was set to test the key oxy-anionic Cope rearrangement step. Gratifyingly, in the presence of potassium base and crown ether in refluxing tetrahydrofuran, the proposed rearrangement proceeded to form **300** in high yield. Interestingly, a thermal oxy-Cope rearrangement of **299** affords none of the desired product.

It is instructive to compare and analyze the key reactions utilized by the twelve research groups approaches towards vinigrol featured in this review. For example, 50% (6/12) of these groups employ a Diels-Alder reaction as a key step while 33% (4/12) use an anionic-oxy Cope rearrangement and 25% (3/12) a metathesis reaction. Other classic reactions

playing a key role in these approaches are the Grob fragmentation, Claisen rearrangement and Robinson type annulations. Clearly the “classic” reaction types are holding their own and still playing a vital role in supporting the assembly of complex diterpenoid natural products like vinigrol.

Acknowledgments

We gratefully acknowledge the NIH-NIGMS for their support of our natural product synthetic program (R01 GM086584).

References

1. Early vinigrol synthetic contributions have been reviewed: Tessier G, Barriault L. *Org Prep Proc Int*. 2007; 37:313–353. Harmata M, Calkins NL. *Chemtracts*. 2009; 22:205–209. Lu JY, Hall DG. *Angew Chem Int Ed*. 2010; 49:2286–2288. Hutters AD, Garg NK. *Chem Eur J*. 2010; 16:8586–8595. [PubMed: 20602369]
2. Uchida I, Ando T, Fukami N, Yoshida K, Hashimoto M, Tada T, Koda S, Morimoto Y. *J Org Chem*. 1987; 52:5292–5293.
3. a) Ando T, Tsurumi Y, Ohata N, Uchida I, Yoshida K, Okahura M. *J Antibiot*. 1988; 41:25–30. [PubMed: 3346190] b) Ando T, Yoshida K, Okahura M. *J Antibiot*. 1998; 41:31–35. [PubMed: 2831182] c) Norris, DB.; Depledge, P.; Jackson, AP. *PCT Int Appl WO*. 9107 953. 1991. d) Nakajima, H.; Yamamoto, N.; Kaizu, T.; Kino, T. *Jpn Kokai Tokkyo Koho JP*. 07206668. 1995. e) Keane, JT. *PCT Int Appl WO*. 20011000229. 2001. f) Onodera, H.; Ichimura, M.; Sakurada, K.; Kawabata, A.; Ota, T. *PCT Int Appl WO*. 2006077954. 2006. g) Onodera, H.; Ichimura, M.; Sakurada, K.; Kawabata, A.; Ota, T. *PCT Int Appl WO*. 2006077954.
4. a) Devaux JF, Hanna I, Lallemant JY. *J Org Chem*. 1993; 58:2349–2350. b) Devaux JF, Hanna I, Fraise P, Lallemant JY. *Tetrahedron Lett*. 1995; 36:9471–9474.
5. Devaux J-F, Hanna I, Lallemant J-Y, Prange T. *J Chem Res Synth*. 1996:32–33.
6. Devaux JF, Hanna I, Lallemant JY. *J Org Chem*. 1997; 62:5062–5068.
7. a) Gentric L, Hanna I, Ricard L. *Org Lett*. 2003; 5:1139–1142. [PubMed: 12659593] b) Gentric L, Hanna I, Huboux A, Zaghdoudi R. *Org Lett*. 2003; 5:3631–3634. [PubMed: 14507190]
8. Gentric L, Le Goff X, Ricard L, Hanna I. *J Org Chem*. 2009; 74:9337–9344. [PubMed: 19911847]
9. Mehta G, Reddy KS. *Synlett*. 1996:625–627.
10. Kito M, Sakai T, Haruta N, Shirahama H, Matsuda F. *Synlett*. 1996:1057–1060.
11. a) Kito M, Sakai T, Shirahama H, Miyashita M, Matsuda F. *Synlett*. 1997:219–220. b) Matsuda F, Kito M, Sakai T, Okada N, Miyashita M, Shirahama H. *Tetrahedron*. 1999; 55:14369–14380.
12. Paquette LA, Guevel R, Sakamoto S, Kim IH, Crawford J. *J Org Chem*. 2003; 68:6096–6107. [PubMed: 12895037]
13. Paquette LA, Efremov I. *J Org Chem*. 2005; 70:510–513. [PubMed: 15651794]
14. a) Paquette LA, Efremov I, Liu Z. *J Org Chem*. 2005; 70:505–509. [PubMed: 15651793] b) Paquette LA, Liu Z, Efremov I. *J Org Chem*. 2005; 70:514–518. [PubMed: 15651795]
15. Morency L, Barriault L. *Tetrahedron Lett*. 2004; 45:6105–6107.
16. Morency L, Barriault L. *J Org Chem*. 2005; 70:8841–8853. [PubMed: 16238317]
17. Grise CM, Tessier G, Barriault L. *Org Lett*. 2007; 9:1545–1548. [PubMed: 17362025]
18. Poulin J, Grise-Bard CM, Barriault L. *Angew Chem Int Ed*. 2012; 51:2111–2114.
19. Souweha MS, Enright GD, Fallis AG. *Org Lett*. 2007; 9:5163–5166. [PubMed: 17999510]
20. Maimone TJ, Voica AF, Baran PS. *Angew Chem Int Ed*. 2008; 47:3054–3056.
21. Krenke EH, Perry EW, Jerome SV, Maimone TJ, Baran PS, Houk KN. *Org Lett*. 2012; 14:3016–3019. [PubMed: 22630569]
22. Maimone TJ, Shi J, Ashida S, Baran PS. *J Am Chem Soc*. 2009; 131:17066–17067. [PubMed: 19877628]
23. Morton JGM, Kwon LD, Freeman J, Njardarson JT. *Synlett*. 2009:23–27.

24. Morton JGM, Kwon LD, Freeman J, Njardarson JT. *Tetrahedron Lett.* 2009; 50:1684–1686.
25. Morton JGM, Draghici C, Kwon LD, Njardarson JT. *Org Lett.* 2009; 11:4492–4495. [PubMed: 19728692]
26. a) Yang Q, Njardarson JT, Draghici C, Li F. *Angew Chem Int Ed.* 2013; 52:8648–8651. b) Yang Q, Draghici C, Njardarson JT, Li F, Smith BR, Das P. *Org Biomol Chem.* 2014; 12:330–344. [PubMed: 24258093]
27. a) Wang D, Crowe WE. *Org Lett.* 2010; 12:1232–1235. [PubMed: 20180523] b) Wang D, Crowe WE. *Chinese Chem Lett.* 2015; 26:238–242.
28. Wang XL, Lu YY, Wang J, Wang X, Yao HQ, Lin GQ, Sun BF. *Org Biomol Chem.* 2014; 12:3562–3566. [PubMed: 24676561]
29. Betkekar VV, Sayyad AA, Kaliappan KP. *Org Lett.* 2014; 16:5540–5543. [PubMed: 25310274]
30. Lu YB, Hsu DS, Liao CC. *Tetrahedron Lett.* 2014; 55:5315–5318.

Biographies

Jón was born and raised in the small town of Akranes, Iceland. After graduation, he left his hometown and moved to Reykjavik to start his studies at the University of Iceland. Jon then followed in the footsteps of his Icelandic ancestors and moved west, to America. This journey brought him to New Haven Connecticut, where he chose to pursue a graduate career in Organic Chemistry at Yale University. While at Yale, he joined the research group of a newly hired assistant professor, John L. Wood, after becoming affected by his enthusiasm, energy and exciting new research program. During his doctoral studies Jon worked on the total synthesis of the nonadride natural products CP-225,917 CP-263,114. At the end of his graduate studies Jon was presented with the irresistible offer of moving to New York City to work in the laboratory of Professor Samuel J. Danishefsky the Memorial Sloan-Kettering Cancer Center (MSKCC). While in the Danishefsky group, as a General Motors Cancer Research Scholar, he worked on the total syntheses of the natural products epothilone 490 and migrastatin. Jon moved to Ithaca in 2004 to start his independent career at Cornell University, where he launched a research program focused on natural products and the development of new methods. In 2010 Jon and his group loaded the wagons, journeyed across the continent, and settled in Tucson where he is currently an associate professor of chemistry at the University of Arizona.

Cristian was born in the Moldovian hills of northeast Romania, and for 18 years after that never even contemplated the thought of becoming a chemist. After moving to the US everything changed. He first graduated from Western Connecticut State University with a B.A. in chemistry/biochemistry, and then began his doctoral studies at the University of Vermont, working for his first two years on radical additions to hydrazones in Gregory Friestad's lab and the latter three under the supervision of Matthias Brewer, developing synthetic methodology for the fragmentation of cyclic C-C bonds. Cristian began his postdoctoral studies in Jon T. Njardarson's labs at both Cornell University and The University of Arizona, working on the total synthesis of vinigrol. After the Sonoran desert adventure Cristian made the move back east and continued his postdoctoral studies at Yale in Professor Spiegel's group. There he focused his efforts on the synthesis and evaluation of the most prevalent cross-linking type advanced glycation end product, glucosepane. He still sometimes wonders: why chemistry?... but not for too long.

Scheme 1.
Reported Vinigrol Structural Perspectives.

Scheme 2.

Starting Materials Used for Published Vinigrol Approaches and Total Syntheses.

Scheme 3.

I. Hanna's **1993** Approach Toward the Vinigrol Core.

Scheme 4.

I. Hanna's **1996** Vinigrol Core Rearrangement Observations.

Scheme 5.

I. Hanna's **1997** Decalin Functionalization Explorations.

Scheme 6.
I. Hanna's 2003 Approach Toward Vinigrol.

Scheme 7.

I. Hanna's **2009** Approach Toward Vinigrol – Almost there!

Scheme 8.

G. Mehta's 1996 oxy-Cope Rearrangement Approach Toward Vinigrol.

Scheme 9.F. Matsuda's **1996** Ketyl Radical Cyclization Approach Toward Vinigrol.

Scheme 10.
F. Matsuda's **1997** Approach Toward Vinigrol.

Scheme 11.

L. A. Paquette's **2003** Vinigrol Approach.

Scheme 12.

L. A. Paquette's **2005** Vinigrol Eight Membered Ring Cyclization Studies I.

Scheme 13.

L. A. Paquette's **2005** Vinigrol Eight Membered Ring Cyclization Studies II.

Scheme 14.
L. Barriault's **2004** Approach Toward Vinigrol.

Scheme 15.

L. Barriault's 2005 Claisen Rearrangement Approach Toward Vinigrol.

Scheme 16.

L. Barriault's **2005** Ring Closing Metathesis Approach Toward Vinigrol.

L. Barriault's **2005** Second Claisen Rearrangement Approach Toward Vinigrol.

Scheme 18.L. Barriault's **2007** Intramolecular Diels-Alder Approach Toward Vinigrol.

Scheme 19.

L. Barriault's 2012 Formal Total Synthesis of Vinigrol.

Scheme 20.

A. G. Fallis's 2007 Vinigrol Approach.

Scheme 21.

P. S. Baran's **2008** Vinigrol Approach.

Scheme 22.

P. S. Baran's 2009 Vinigrol Total Synthesis.

Scheme 23.

J. T. Njardarson's 2009 Vinigrol Wessely Oxidation Approach.

Scheme 24.

J. T. Njardarson's **2009** Vinigrol Adler-Becker Oxidation Approach.

Scheme 25.

J. T. Njardarson's **2009** Vinigrol Pyrogallol Oxidation Approach.

Scheme 26.

J. T. Njardarson's 2013 Vinigrol Total Synthesis (Part I).

Scheme 27.

J. T. Njardarson's **2013** Vinigrol Total Synthesis (Part II).

Scheme 28.

D. Wang's 2014 Vinigrol Approach.

Scheme 29.
B.-F. Sun's 2014 Vinigrol Approach.

Scheme 30.

K. P. Kaliappan's 2014 Vinigrol Formal Total Synthesis.

Scheme 31.
C. C. Liao's 2014 Vinigrol Approach.