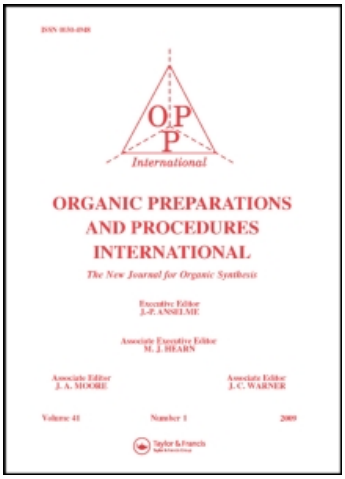

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THE CONQUEST OF VINIGROL. CREATIVITY, FRUSTRATIONS, AND HOPE

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THE CONQUEST OF VINIGROL. CREATIVITY, FRUSTRATIONS, AND HOPE

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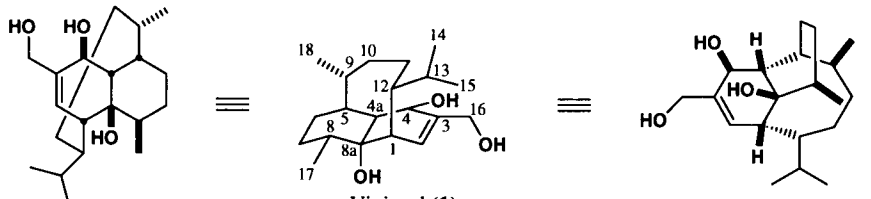
INTRODUCTION

The real voyage of discovery consists not in seeking new landscapes, but in having new eyes (Marcel Proust). Ever since its discovery in 1987, several research groups have attempted the synthesis of vinigrol (**1**) using various approaches, but the total synthesis of vinigrol (**1**) has not been reported yet. The synthesis of this molecule featuring an unusual architecture is still an ongoing challenge for the synthetic community. Herein, the progress achieved towards the synthesis of vinigrol (**1**) will be reviewed.

I. DISCOVERY AND STRUCTURE OF VINIGROL

Vinigrol (**1**) is a novel diterpenoid first isolated by Ando and coworkers from *Virgaria nigra* F-5408,[1] a fungus strain found at the foot of Mount Aso, in Kumamoto Prefecture in Japan (*Fig. 1*). Its tricyclic core contains a *cis*-fused [4.4.0] system bridged by an eight-membered ring and features eight contiguous stereocenters. Vinigrol was first extracted from the cultured mycelium and purified by solvent extraction followed by repeated silica gel chromatography. It was isolated as colorless prisms (mp 108°C and $[a]_D$ = -96.2°C (*c* 1.05, $CHCl_3$)) which are

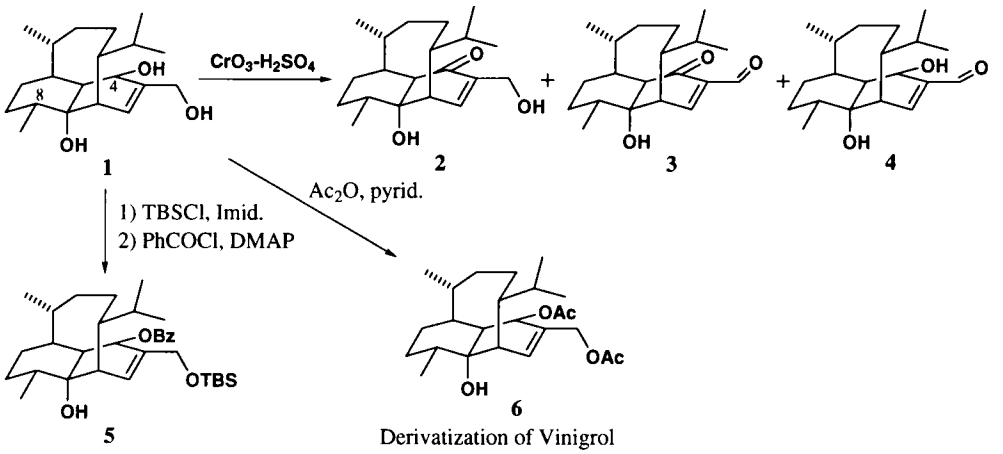


Vinigrol (**1**) Vinigrol (**1**) Vinigrol (**1**)

Fig. 1

soluble in chloroform, ethyl acetate, methanol and insoluble in water. Since attempts to determine the structure of vinigrol using chemical derivatization, IR, MS, ^1H and ^{13}C NMR spec-

troscopy (*Scheme 1*) proved unsuccessful; X-ray crystal analysis of vinigrol and its derivatives



Derivatization of Vinigrol

Scheme 1

was performed. It was determined that crystals of the oxidation product **3** were optimum for this purpose and its structure was established. Determination of the relative configuration of C-4 was achieved by analysis of ^{1}H NMR data. The absence of proton coupling between 4-Hs and 4a-Hs in **1** and **6** indicated that the dihedral angle was close to 90°C and therefore were *trans* to each other. This assumption was further supported by NOESY analysis of **6**. The absolute structure of **1** was assessed using the CD allylic benzoate method.[2] The absolute configuration at C-4 was established to be *S* owing to the fact that the circular dichroism spectrum of **5** exhibited a negative Cotton effect (De - 14.0 at 230 nm in MeOH). This indicated an anti-clockwise relationship between the endocyclic olefinic bond and the benzoate group at C-4.

From these data, the absolute stereochemistry of vinigrol was deduced to be as shown in **1**. It is important to point out that the decahydro-1,5-butanonaphthalene skeleton of vinigrol is unique among diterpenoids and its total synthesis represents an exceptional challenge in organic synthesis. When conceiving a retrosynthetic plan of **1**, one must account for the several stereochemical and steric issues of the vinigrol structure and also select chemical transformations that can be performed in a congested and rigid environment. This is especially true at the late stage of the synthesis.

II. BIOLOGICAL ACTIVITY

Vinigrol first isolated in 1988 became of interest because of its antihypertensive and platelet aggregation inhibition properties.[3] It was discovered that intravenous injections of vinigrol in anesthetized normotensive rats decreased arterial blood pressure by 20% at a dose of 100 mg/kg. Given orally to spontaneously hypertensive rats (SHR), a 15% blood pressure reduction was observed at 2 mg/kg and the effect lasted over 6 hours.[4] It was also found that vinigrol induced the contraction of rat aortic smooth muscle strips. A comparison study for the sensitivity

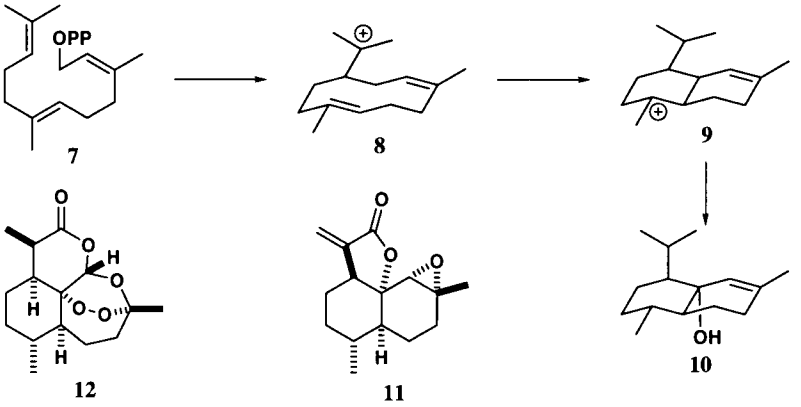
of vinigrol to different vasodilators such as nilvadipine (Ca^{2+} blocker), prazosin (a_1 blocker) and yohimbine (a_2 blocker)[4] showed that vinigrol exhibits a Ca^{2+} agonist activity similar to the one of KCl on smooth muscles preparation. It was also reported that vinigrol shows no affinity for both a_1 and a_2-adrenoreceptors of rat brain membrane. The same group reported that vinigrol (**1**) has an effect on rabbit and human platelet aggregation triggered by epinephrine or by a phospholipid activator (PAF) at low concentration.[3] The IC_{50} values are 1.7×10^{-8} M and 4.4×10^{-7} M on rabbit platelet and 5.2×10^{-8} M and 3.3×10^{-8} M for human platelet for epinephrine and PAF, respectively. However at high concentration, vinigrol induces aggregation. No inhibitory activity was detected on adenosine diphosphate (ADP), thrombin or collagen- induced rabbit platelet aggregation nor on ADP induced human platelet aggregation.

A patent filed by Norris and coworkers revealed that vinigrol was identified as a tumor necrosis factor (TNF) antagonist.[5] TNF is a protein which induces necrosis of tumor cells and acts as a mediator in the immune system. Blocking the action of TNF with vinigrol could therefore treat endotoxic shock, inflammation, muscle atrophy (cachexia) or arrest the progression from AIDS-related complex to AIDS. In *in-vitro* binding studies on HL60 cells, vinigrol at a concentration of 310 mM displayed 100% inhibition of [^{125}I]-TNF binding at 2.1 nM. A significant reduction of TNF-induced cytotoxicity on L929 cells by vinigrol is also described.[5] This discovery stimulated further investigations on vinigrol applications and Fujisawa Pharmaceutical Company Limited disclosed that vinigrol could be used as an alternative therapy for the treatment of HIV infectious diseases.[6] Vinigrol is also reported to have a 50% and 90% effective concentration (EC_{50} and EC_{90}) of 0.092 mM and 0.38mM respectively for its antiviral activity on HIV-infected MT-4 cells while azidothymidine (AZT) shows a EC_{50} of 0.2 nM in the same experiment. Also, concentration at which vinigrol showed 50% cytotoxicity (CC_{50}) for non-infected MT-4 cells was found to be higher than the CC_{50} of AZT (91.15 mM and 24.85 mM respectively). A patent filed by Guglielmotti and coworkers claims that vinigrol could be used as an anti-inflammatory drug capable of suppressing the cytokines production in a pharmaceutical composition comprising a cytokine-suppressive anti-inflammatory drug (CSAID), an immunosuppressant and a pharmaceutically acceptable excipient.[7] Such a mixture could provide a method of treating autoimmune diseases which include rheumatoid arthritis, glomerulonephritis (autoimmune renal disease), Hashimoto's thyroiditis, systemic lupus erythematosus, myasthenia gravis (neuromuscular disease), autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, autoimmune disorders and type 1 diabetes. Also, a recent study revealed that combination of vinigrol with COX-2 inhibitors has a potential in the prevention or treatment of inflammatory diseases and arthritic disorders.[8]

III. BIOSYNTHESIS

Corey and Goodman proposed a biogenesis of vinigrol (**1**) based on the well-studied arteannuin **11** and artemisinin **12** biosyntheses (*Scheme 2*).[9] It has been proposed that the artean-

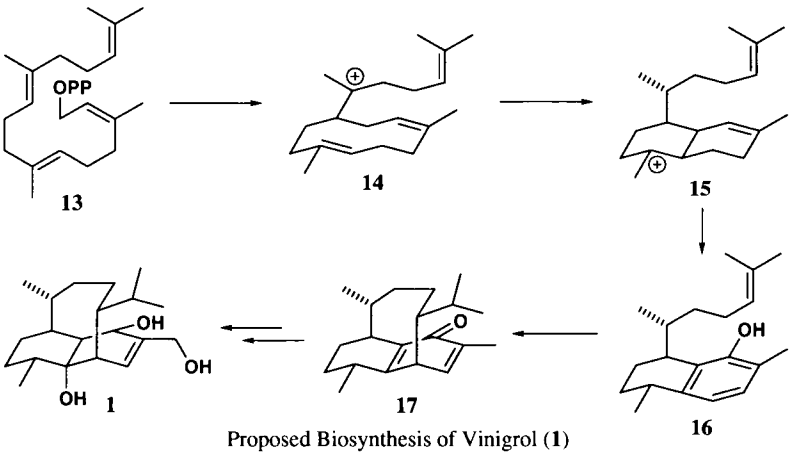
nuin framework **10** is created from an enzymatically-assisted cyclization of farnesyl pyrophosphate (FPP) **7**,[10,11] followed by a series of hydride shifts (**8**→**9**) to give intermediate **9**. It seems that the installation of the tertiary alcohol on **10** occur late in the synthesis.



Proposed Biogenesis of Artennuin B (**11**) and Artemisinin (**12**)

Scheme 2

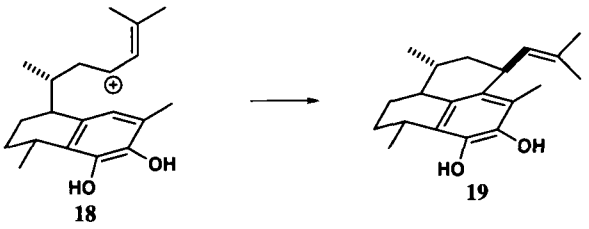
From this study, Corey and Goodman suggested that the decalin unit embedded in vinigrol could be obtained from an enzyme-assisted cyclization of geranyl geranyl pyrophosphate (GGPP) **13** (*Scheme 3*).[9,12] Similarly to the arteannuin biosynthesis, intermediate **14** is converted to tetahydronaphtalene **16** *via* a series of hydride shifts, elimination and oxidation processes. The latter oxidation product **16** represents an ideal candidate for an oxidative phenolic coupling to



Proposed Biosynthesis of Vinigrol (**1**)

Scheme 3

create the eight-membered ring present in **17**. From this intermediate, one can imagine a series of enzyme-assisted oxidation on the framework to obtain vinigrol (**1**). Their proposed biogenesis of **1** is supported by the biosynthesis of the related diterpene, pseudopterosin (**19**) (*Scheme 4*).[13] In fact, *seco*-pseudopterosin intermediates similar to **18** were isolated from the same broths thereby



Proposed Biosynthesis of Pseudopterosin (**19**)

Scheme 4

illustrating the involvement of a possible common intermediate in both biosyntheses.[14] Moreover, the similar relative stereochemistry of pseudopterosin **19** and vinigrol (**1**) increase the probability of a common intermediate.

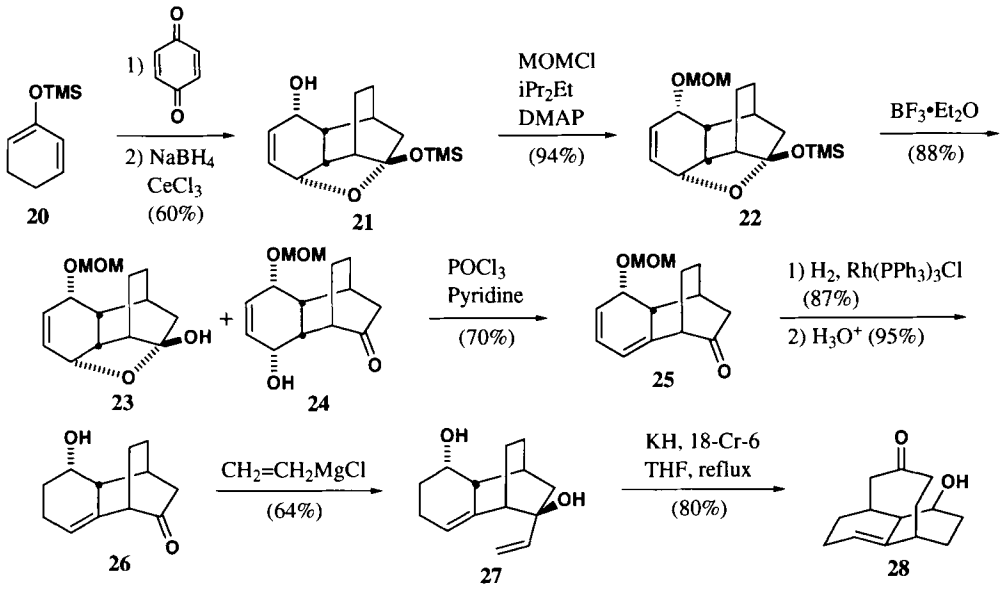
IV. SYNTHETIC APPROACHES

Over the years, many major research groups have reported progress toward the synthesis of vinigrol (**1**). The schemes below illustrate diverse strategies ranging from ring-closing metathesis to tandem oxy-Cope/Claisen/ene rearrangement that have been utilized for the construction of the unusual architecture of vinigrol (**1**). These approaches will now be discussed in more details focusing on the advantages and drawbacks of each.

1. via the Oxy-Cope Rearrangement

a) Hanna's Approach

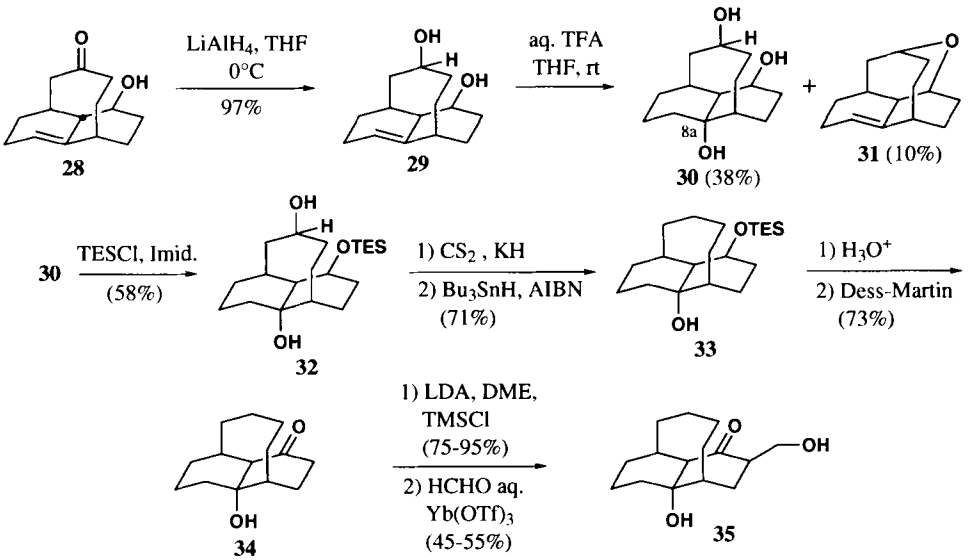
The first reported attempts at the synthesis of vinigrol (**1**) used the well-proven anionic oxy-Cope rearrangement as the key step for the formation of its tricyclic skeleton. Hanna's group was the first to report the construction of the tricyclic ring system of vinigrol in 1993.[15] Their strategy relied on the anionic oxy-Cope reaction of **27** to generate the *ansa* bridge system **28** (*Scheme 5*). The synthesis began with the Diels-Alder reaction between known 2-[(trimethylsilyl) oxy]-1,3-cyclohexadiene (**20**)[16] and 1,4-benzoquinone. The resulting crude product was reduced under Luche's conditions[17] to afford **21** as a sole diastereomer. The hydroxy group was protected as its methoxymethyl ether **22**; treatment of **22** with trifluoroborane etherate followed by hydrolysis afforded the hydroxyketone **24** and its hemiketal **23**. Dehydration of **24** with phosphorus oxychloride in pyridine gave **25**. Selective hydrogenation over Wilkinson's catalyst followed by acid hydrolysis generated alcohol **26**. The free hydroxy group was necessary to ensure facial selectivity for the addition of vinylmagnesium chloride; the *endo* vinyl product **27** was obtained as the sole isomer.[18] The influence of hydroxy group on π-facial selectivity in the nucleophilic addition of various Grignard reagents (MeMgBr, CH_2=CHMgBr, (E)-*i*PrCH_2=CHMgBr, and others) to bicyclo[2.2.2]octan-2-ones was further investigated by Hanna's group.[19] The vinigrol skeleton **28** was then obtained by anionic oxy-Cope rearrangement of **27** in refluxing THF with an excess of potassium hydride in the presence of 18-crown-6 ether. To date, it is the shortest route to the vinigrol carbon core.



Construction of the Tricyclic Core

Scheme 5

Hanna's group later reported the functionalization of **28** (*Scheme 6*).[20] Their goal was threefold: (1) reductive removal of the carbonyl group at C-10, (2) introduction of a tertiary alcohol at C-8a, and (3) functionalization of ring A. Attempts to remove the carbonyl group using known methodologies such as Huang-Minlon reduction, conversion to the tosylhydrazone, to the diethyl phosphate or the dithioacetal, and subsequent reduction[21] did not lead in the desired



Functionalization of the Core

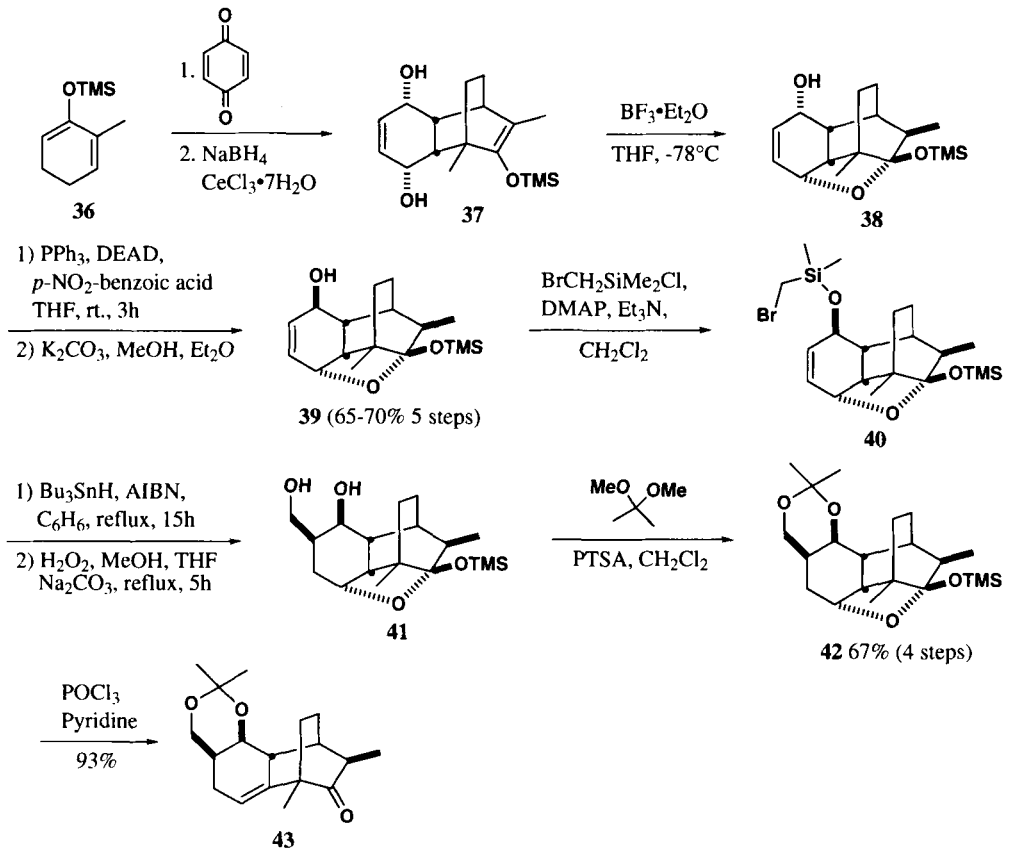
Scheme 6

compound. Removal of the carbonyl by reduction with lithium aluminum hydride, followed by the Barton deoxygenation procedure[22] or Ireland protocol[23] was not successful either. The solution came from the observation that upon treatment of **29** with 25% aqueous trifluoroacetic acid in THF at room temperature, triol **30** was obtained along with ether **31**. Thus, the hydroxy group at C-8a was set up with the correct stereochemistry. After selective protection of the secondary alcohol at C4 on **30**, deoxygenation of the secondary alcohol on **32** was achieved using the Barton deoxygenation procedure to give **33**. Desilylation, followed by Dess-Martin oxidation[24] provided with hydroxy ketone **34**. Introduction of the hydroxymethyl unit at C3 was accomplished *via* the silyl enol ether according to Kobayashi's procedure.[25]

Treatment of **35** with LDA, followed by addition of chlorotrimethylsilane afforded a mixture of mono- and disilylated enol ether. Exposure of the corresponding enol ether to 37% aqueous formaldehyde in the presence of a catalytic amount of ytterbium triflate in THF led to a separable mixture of starting ketone **33** and the desired hydroxymethyl ketone **35**. However, attempts to generate the α,β-unsaturated ketone by selenylation of **35** and subsequent selenoxide oxidation using various conditions were fruitless.

At this point, the challenges to complete the synthesis of vinigrol (**1**) were the stereoselective introduction of the two methyl substituents at C-8 and C-9, of the isopropyl group at C-12, with the correct stereochemistry and introduction of the double bond at C-2. In order to overcome the stereoselectivity issue, Hanna reported the installation of the methyl groups at C-8 and C-9 as well as the isopropyl unit at C-12 prior to the anionic oxy-Cope rearrangement. To this end, they generated the functionalized ketone **43** (*Scheme 7*).[26] The synthesis began with a Diels-Alder reaction between readily available trimethylsilyl enol ether **36**[27,28] and 1,4-benzoquinone, followed by reduction under Luche's condition to afford **37**. The ketal **38** was obtained by exposure of **37** with trifluoroborane etherate. Inversion of the hydroxyl at C-4 was achieved by Mitsunobu inversion,[29,30] using 4-nitrobenzoic acid,[31] followed by cleavage of the ester under mild conditions to afford **39**. Stereoselective introduction of the hydroxymethyl group at C-3 was accomplished using Stork's procedure.[32] To this end, bromomethyldimethylsilyl ether **40**, prepared by silylation of **39** ($BrCH_2SiMeCl$, DMAP, Et_3N), was subjected to AIBN and $HSnBu_3$ in high dilution standard high-dilution, radical-generating conditions followed by Tamao oxidation (H_2O_2, Na_2CO_3, THF-MeOH) to provide diol **41**.[33,34]

Protection of the 1,3-diol moiety in **41** as an acetonide with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid, followed by dehydration using phophorus oxychloride afforded tricyclic ketone **43**. The installation of the isopropyl unit was achieved by a Grignard reaction between ketone **43** and 3-methylbutynylmagnesium bromide[35,36] (*Scheme 8*) to give a 4.2:1 mixture of *endo*- and *exo*-propargyl alcohols **44** and **45**. Preferential addition of the nucleophile mainly on the *endo* face is explained by the presence of the *exo*-methyl group at C-9. Partial hydrogenation of **44** gave olefin **46** possessing the Z-geometry. However, all attemps of oxy-Cope rearrangement on **46** under anionic (KH or KHMDS in refluxing THF or toluene, with

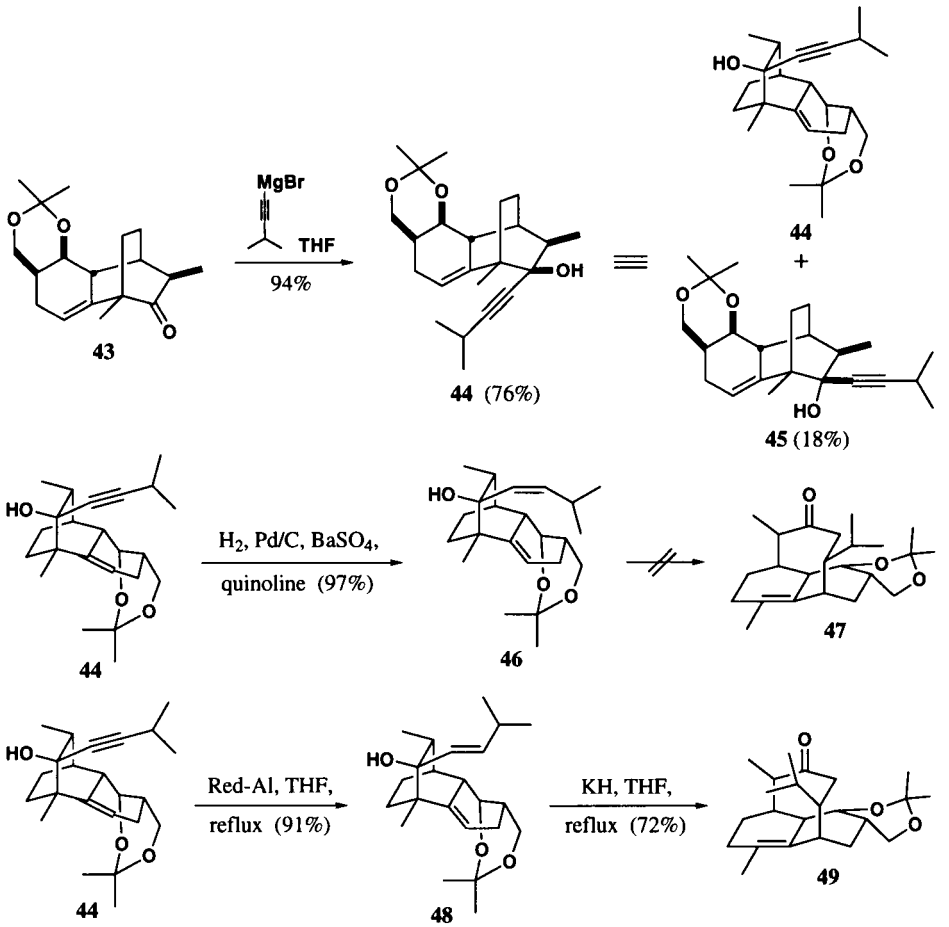


Synthesis of a Ketone **43**

Scheme 7

18-cr-6) or thermolytic (refluxing in decalin) conditions failed. Hanna explains this lack of reactivity by steric congestion between the double bond and the isopropyl group when the side chain of **46** is forced to reach the transition state. On the other hand, when the E-isomer **48** was treated with potassium hydride in refluxing THF, compound **49** was obtained, but both alkyl groups at C-9 and C-12 in **49** had the opposite stereochemistry to that of vinigrol (**1**). Even though epimerization of the methyl group at C-9 could be achieved under basic conditions, epimerization of the isopropyl was a posing a problem.

The solution to the isopropyl stereochemistry problem came from the fact that when the isopropyl group is replaced by an isopropenyl (*Scheme 9*), the vinigrol carbon framework **54**, with the proper relative configuration at C-12, is obtained by the oxy-Cope rearrangement of **53**. Its preparation was initiated by treatment of **43** with an excess of Grignard reagent **50**, prepared from 2-methyl-1-en-3-yne[37] and ethylmagnesium bromide, to provide a mixture of *endo* and *exo* alcohols **51** and **52**. Diene **53**, obtained by partial reduction of the triple bond in **51** using Rieke zinc,[38,39] was treated with sodium hydride in THF to furnish tricyclic compound **54**. The additional

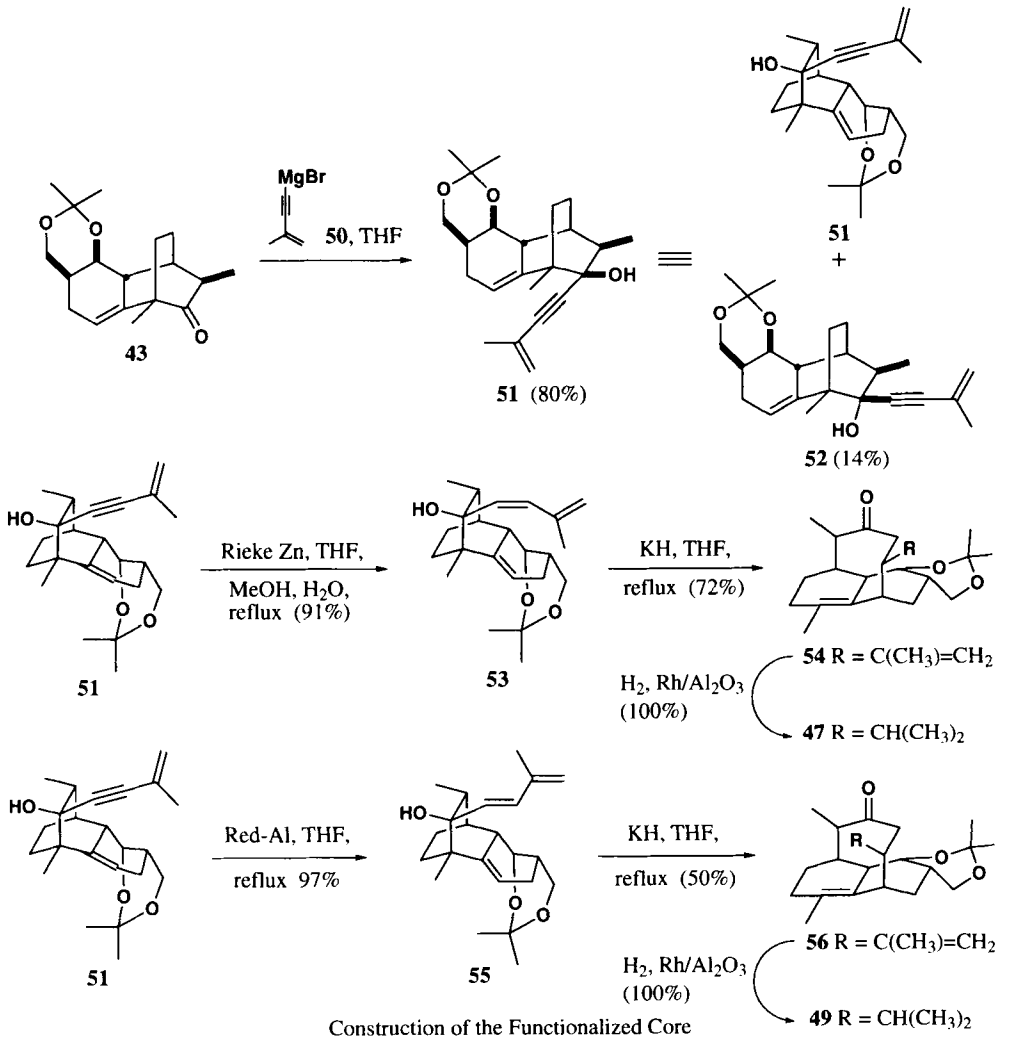


Construction of an Advanced Core of Vinigrol

Scheme 8

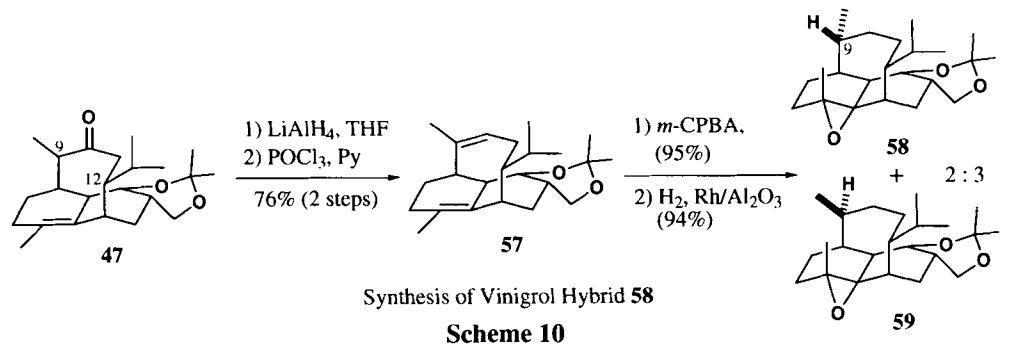
unsaturation on the terminal position in **53** provides a rate acceleration effect on the anionic oxy-Cope rearrangement, presumably resulting in a enhanced stabilization of the transition state.[40,41] Catalytic hydrogenation of **54** in the presence of rhodium on alumina selectively reduced the terminal olefin to afford ketone **47** quantitatively. *E*-isomer **55**, under the same conditions (NaH, THF, reflux, then catalytic hydrogenation), provided compound **49**, previously obtained from **48**.

The next stage in the synthesis was then to invert the stereochemistry of the methyl group at C9 and removal of the carbonyl group at C10. Ketone **47** was thus reduced with lithium aluminum hydride, then dehydrated using phophorus oxychloride to afford diene **57** (*Scheme 10*). Selective epoxidation of the tetrasubstituted double bond was accomplished by using one equivalent of *m*-CPBA at 0°C and hydrogenation of the remaining double bond gave a 2:3 mixture of **58** and **59**. The relative configuration of the methyl group at C9 in **58** was found to have the same stereochemistry as that of vinigrol (**1**). Besides the fact that the last step of the



Construction of the Functionalized Core

Scheme 9



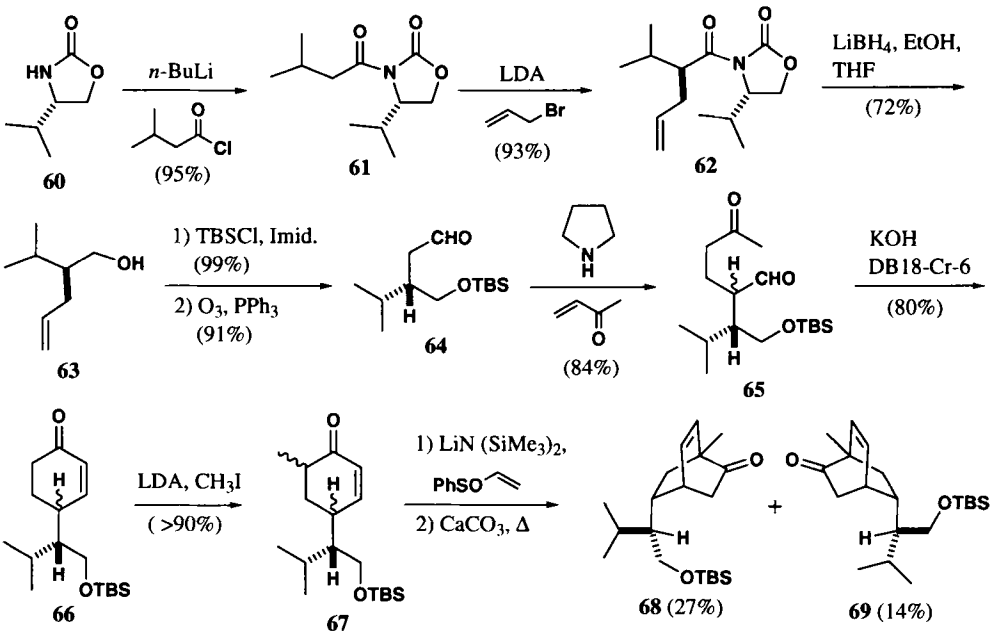
Synthesis of Vinigrol Hybrid **58**

Scheme 10

synthesis shows poor selectivity and that the reported route is racemic, compound **58** is the closest intermediate to vinigrol (**1**). The authors installed the isopropyl unit at C12 and the two methyl groups at C8 and C9 in the correct stereochemistry and properly functionalized the tricyclic core for the end game. Although, Hanna and coworkers have not yet reported the completion of the synthesis, to date, this constitutes the only synthesis of the complete tricyclic core of vinigrol.

b) Paquette's Approach

Paquette and his group showed an early interest in the synthesis of vinigrol (**1**).[42] Their strategy also took advantage of the anionic oxy-Cope reaction[43] to construct the *cis*-decalin portion of the molecule from the corresponding bicyclo[2.2.2.]octenol. The synthesis commenced with the acylation of the lithiated form of (S)-oxazolidinone **60**[44,45] with isovaleryl chloride to give **61** (*Scheme 11*).[46,47,48] C-Alkylation of **61** with allyl bromide provided **62** in high enantiomeric excess.[49,50,51] Removal of the chiral auxiliary to afford alcohol **63** was achieved

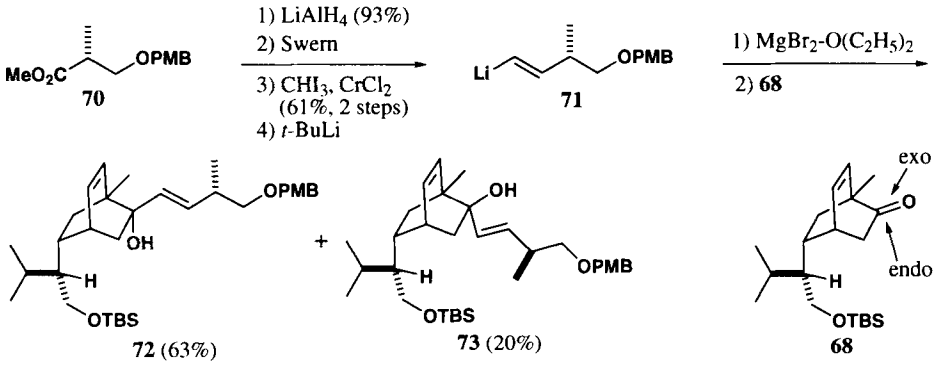


Synthesis of Bicyclo[2.2.2.]octenone **68**

Scheme 11

using lithium borohydride in THF containing 1 equivalent of ethanol.[52,53] Protection of the primary alcohol, followed by ozonolysis yielded aldehyde **64**. Alkylation of the aldehyde with methyl vinyl ketone was achieved through the pyrrolidine enamine to afford **65**.[54] Treatment of the resulting keto aldehyde with potassium hydroxide and dibenzo-18-crown-6 afforded cyclohexenone **66**.[55] Bicyclo [2.2.2]octenone **68** and its diastereoisomer **69** was obtained by a double-Michael reaction of methylated compound **67** with phenyl vinyl sulfoxide followed by thermal extrusion of benzenesulfenic acid.

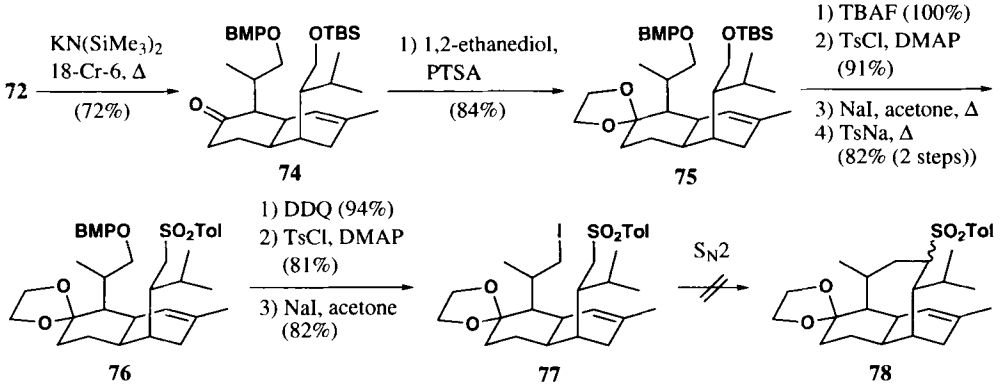
Vinyllithium **71** was easily prepared in four steps from (R)-(-)-methyl-3-hydroxy-2-methylpropionate (*Scheme 12*). Reduction of the ester **70** with a $LiAlH_4$, followed by oxidation of the resulting alcohol under Swern conditions provided the corresponding aldehyde. The latter was submitted to the Takai reaction[56] to furnish the corresponding *E*-iodovinylic intermediate without loss of enantiomeric purity. The lithiated alkene **71** was obtained by metal-halogen exchange involving *t*-butyllithium.[57] Addition of **71** to a cold solution of ketone **68** in ether and in the presence of magnesium bromide gave the *exo* product **72** along with the minor *endo* addition product **73** in a ratio of 5.7:1. In order to suppress the formation of **73**, various conditions such as solvent, reaction temperature and the presence of additives were screened to improve facial selectivity. However, no effect on the product distribution was observed.



Synthesis of a Bicyclo[2.2.2.]octenol**72**

Scheme 12

With compound **72** in hand, the authors continued the study and generated the *cis*-decalin core of vinigrol (**1**) (*Scheme 13*). Rapid heating of **72** in the presence of potassium hexamethyldisilazide and 18-cr-6 in a sealed tube for 1h, followed by rapid cooling, afforded the *cis*-decalin **74**. The initial strategy for the formation of the octalin belt was based on the intramolecular S_N2

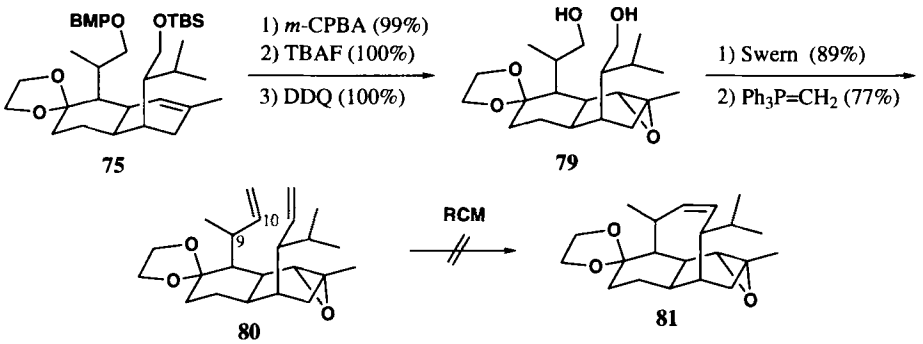


Attempt to Construct Vinigrol Tricyclic Core *via* S_N2

Scheme 13

displacement. To this end, the ketone moiety was first protected as its corresponding acetal to give **75**, then the silyl ether was cleaved. The resulting alcohol was transformed to sulfone **76**. After cleavage of the *p*-methoxybenzyl group, the primary alcohol was converted into crystalline primary iodide **77**. Single crystal X-ray confirmed that the stereochemistry of all the stereogenic centers present on the octalin belt corresponded to those in vinigrol (**1**). It also showed both side-chains to be directed to the equatorial plane, thus positioning the nucleophilic center far from the electrophilic carbon. As a result, all attempts to close the eight-membered ring in **78** proved to be unsuccessful. They attribute this failure to the inability of the reaction centers to orient themselves properly along the necessary trajectory. To overcome this restriction, other medium-sized ring construction reactions have been studied, such as ring-closing olefin metathesis, radical cyclizations, ring contraction, and Dieckman reaction.

In a first attempt, the authors attempted to exploit the ring closing metathesis (RCM) to create the octalin belt. The p-bond in **75** was protected as an epoxide and both hydroxyl functionalities were deprotected to give **79** (*Scheme 14*).[58] Swern oxidation followed by Wittig reaction afforded diene **80**. When submitted to RCM conditions using Grubbs' first[59] and second-generation catalyst,[60] the cyclization product **81** was not observed. Instead, isomerization of the double bond at C-10 at higher temperature was observed, suggesting that internal coupling is kinetically disfavored.

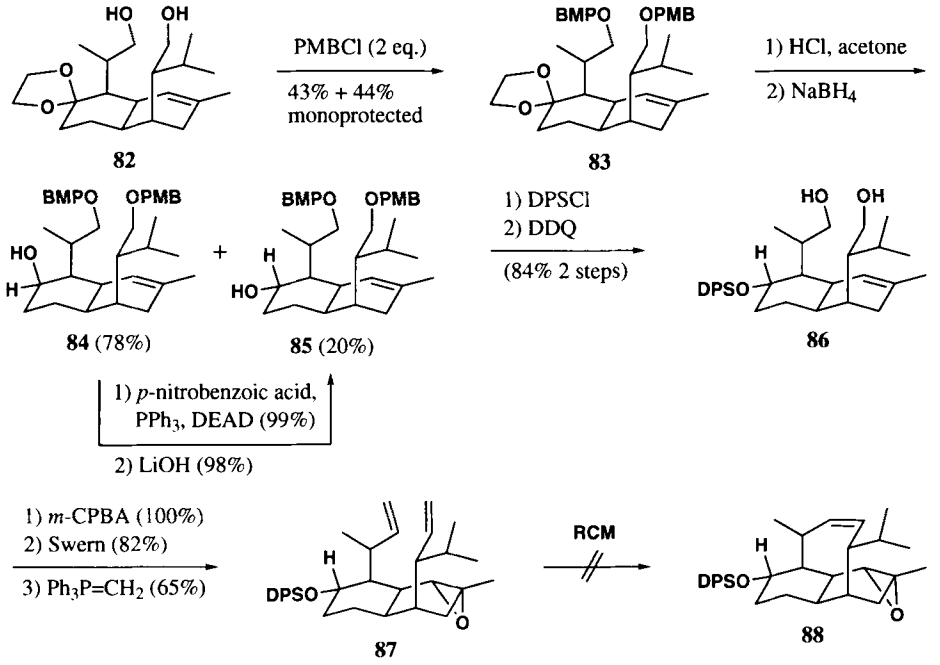


First Attempt to Construct Vinigrol Tricyclic Core *via* RCM

Scheme 14

An attempt to perform RCM with a bulky substituent at C-7 was made (*Scheme 15*). It was expected that such substituent at C8 would facilitate conformational change thus favoring to the linkage between the two terminal olefins. Diol **82**, easily prepared from **75**, was transformed into ether **83**. Acid hydrolysis of the 1,3-dioxane moiety followed by reduction of the resulting ketone with sodium borohydride gave a mixture of alcohols **84** and **85**. The major diastereomer **84** was converted to **85** by an improved version of the Mitsunobu reaction.[61] The free hydroxy group in **85** was protected as the *tert*-butyldiphenylsilyl ether (DPS) and deprotection of the primary alcohols provided diol **86**. Epoxidation of the double bond, Swern oxidation

followed by a Wittig reaction afforded diene **87**. At this point, diene **87** was subjected to a ring closing metathesis. Unfortunately, all attempts to generate **88** under various conditions were unsuccessful.

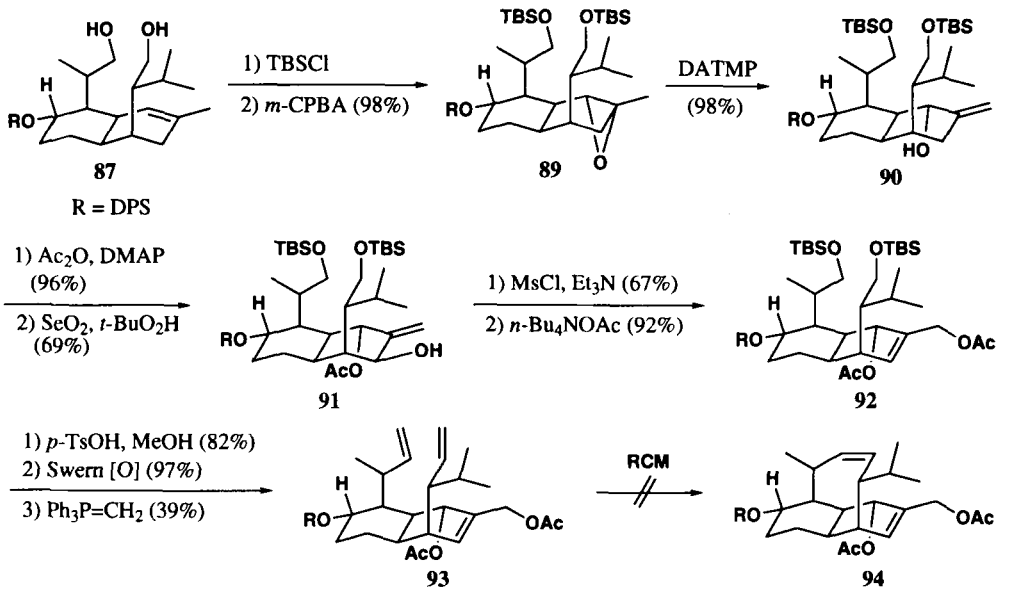


Second Attempt to Construct Vinigrol Tricyclic Core *via* RCM

Scheme 15

In light of these results, a strategy with migration of the double bond from $\Delta^{3,4}$ to $\Delta^{2,3}$ was elaborated aimed at increasing conformational flexibility (*Scheme 16*). The study began by treatment of diol **87** with TBSCl followed by epoxidation afforded **89**. Exposure of this epoxide with diethylaluminum 2,2,6,6-tetramethylpiperidine (DATMP)[62] gave alkene **90**. After acetylation, the resulting acetate was converted to alcohol **91** by exposure to selenium dioxide and *t*-butyl hydroperoxide. Reaction of **91** with methanesulfonyl chloride gave the desired mesylate which was spontaneously attacked by the chloride ion *via* a S_N2' to give the corresponding allyl chloride possessing the double bond in the intraannular location.[63] S_N2 displacement of the chlorine with tetrabutylammonium acetate[64] afforded diacetate **92**. Selective desilylation with *p*-toluenesulfonic acid allowed for the conversion to diene **93**. Unfortunately, all attempts to attach the two terminal olefins *via* RCM failed (**93**→**94**).

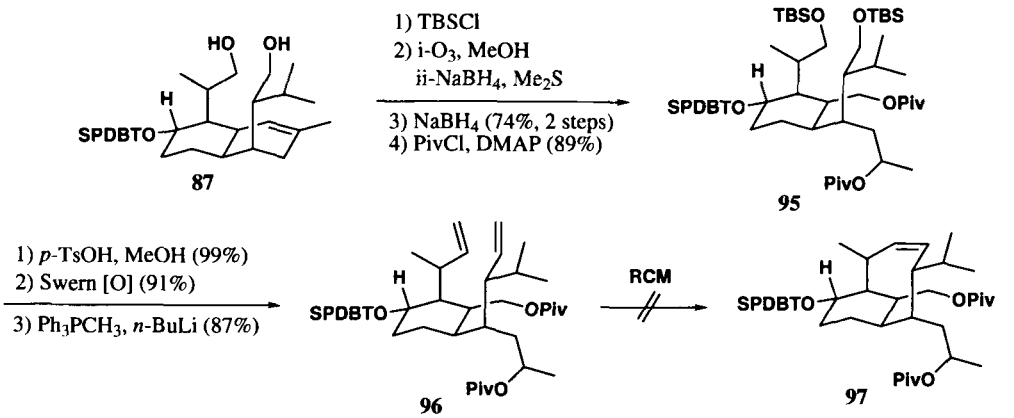
In order to further increase the conformational flexibility, Paquette and coworkers tried to install the cyclooctene belt before the *cis*-decalin unit. They assumed that cleavage of the $\Delta^{3,4}$ double bond in **87** could favor the formation of the bicyclo[5.3.1]undecane unit **97** embedded in vinigrol (**1**) *via* a RCM (*Scheme 17*). If successful, this would then make it possible to generate the cyclohexene ring at a later stage. To this end, olefin **96** was prepared from diol **87** using the



Third Attempt to Construct Vinigrol Tricyclic Core *via* RCM

Scheme 16

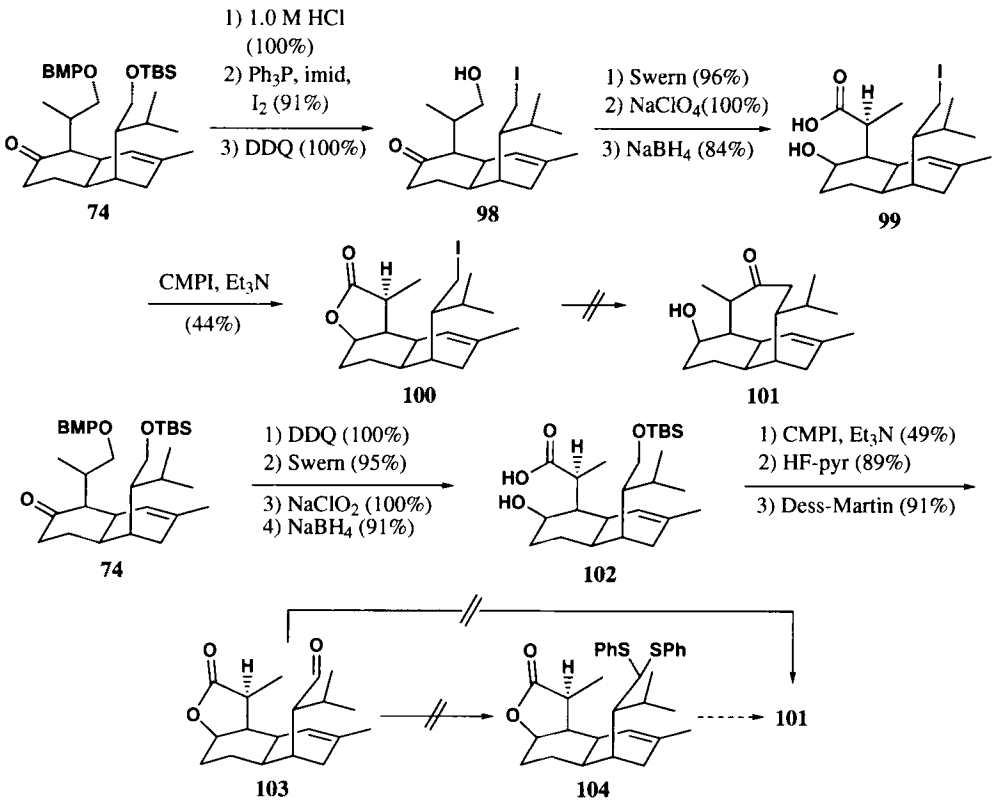
chemical transformations depicted in *Scheme 17*. Again, all attempts to generate the octalin belt in **97** were met with failures. The steric congestion by the side-chains was used to explain the failure of RCM to generate the *ansa* bridge of vinigrol.



Fourth Attempt to Construct Vinigrol Tricyclic Core *via* RCM

Scheme 17

In view of the inability to generate the vinigrol skeleton *via* S_N2 displacement or RCM, Paquette and co-workers proposed that imposing a conformational constraint to the system with a lactone ring would overcome the steric issues (*Scheme 18*).[65] In other words, the transformation from **100** to **101** could be driven by the migration of a negative charge from carbon to oxygen,



Attempts to Construct the Vinigrol Tricyclic Core Using a Lactone Bridge

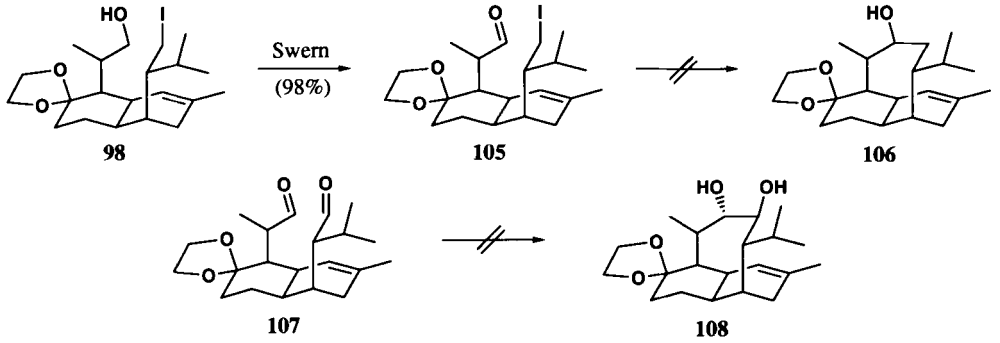
Scheme 18

thus providing a thermodynamic driving force. Lactone **100** was thus prepared from **74** as depicted in *Scheme 18*. To induce intramolecular opening of the lactone ring, several routes were explored. An initial experiment consisting of the treatment of iodolactone **100** with *t*-butyllithium to provide the corresponding alkyllithium intermediate followed by nucleophilic attack at the lactone carbonyl failed to give the desired tricyclic compound.[66,67,68] Upon treatment of **76** with zinc powder in DME containing sodium iodide and water,[69] only deiodinated material was recovered. Barbier-type reaction involving magnesium or modifications of Molander's protocol[70,71] were also examined, but without success.

A final attempt involving the lactone lock was tried. It was based on the preparation of dithioacetal **104** and takes advantage of titanium promoted reaction[72] to access the vinigrol core **101**. Carboxylic acid **102** was obtained after oxidation and reduction of **74**. Lactone aldehyde **103** was obtained using Mukaiyama conditions for lactonisation of **102**, followed by oxidation of the free alcohol. Cyclization of lactone aldehyde **103** using McMurry reaction with $TiCl_3/Zn$[73] was attempted but led only to extensive decomposition. It was also found that **103** could not be converted into dithioacetal **104** in the presence of Lewis acid.[74,75] In light of the pitfalls encountered in the previous approaches, Paquette and co-workers attempted a direct connection of the

functionalized side-chains to access the vinigrol framework. Their strategies used three different routes such as a reductive transannular cyclization, an adaptation of the Ramberg-Bäcklund rearrangement, and a lactam-sulfoxide ring contraction protocol.[76]

An initial synthetic scheme involved the intramolecular alkylation of an aldehyde with a nucleophilic center generated by halogen-metal exchange (*Scheme 19*). Treatment of **105** with Mg, Zn or Li in high dilution conditions failed to give the desired cyclization product. More active metals such as Na or K only led to partial degradation. Pinacol coupling of dialdehyde **107**[77] was also envisioned, even though it was established from **77** (*Scheme 13*) that the side-chains are in a distal relationship one to another. It was considered that heating could have provided with a better well-suited conformer, despite the fact that pinacol coupling is usually conducted at low temperature.[78] Nevertheless, coupling was attempted with SmI_2[79] and $TiCl_4/Zn$[80], but the tricyclic intermediate **108** was not isolated.

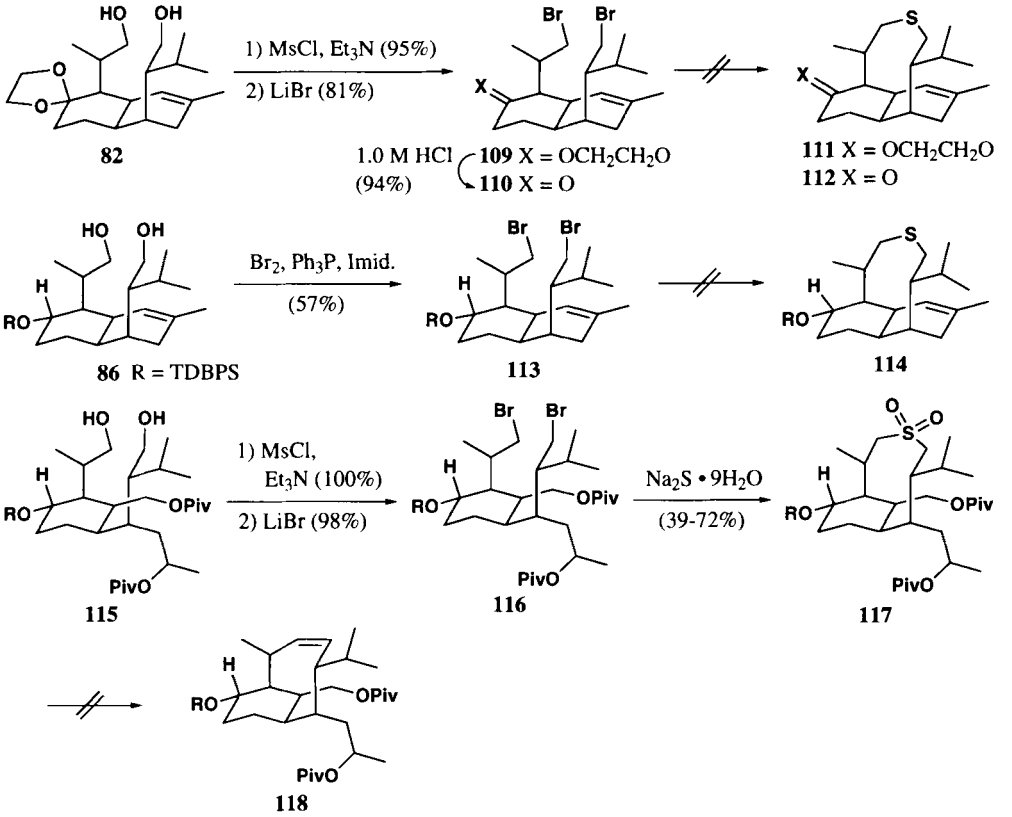


Attempts to Construct Vinigrol Tricyclic Core

Scheme 19

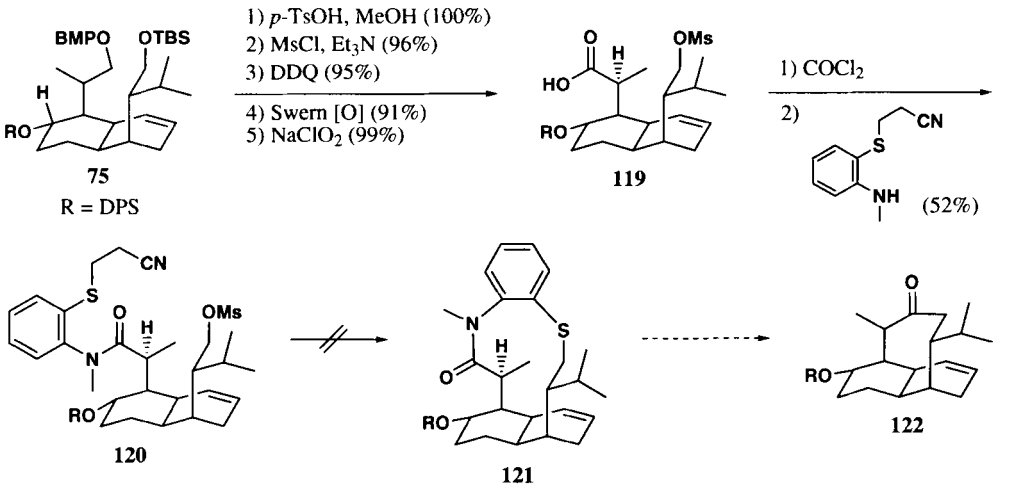
The second approach utilized an adaptation of the Ramberg-Bäcklund rearrangement.[81,82] In order to investigate its usefulness, thiacyclononane such as **111** or **112** needed to be synthesized (*Scheme 20*). Dibromo intermediate **109** was thus prepared from diol **82**; however, thiacyclononane **111** could not be obtained, nor **112** from ketone **110**. In the hypothesis of a bulky substituent in b-orientation at C-7 would facilitate the cyclization, compound **113** was prepared and heated in ethanol or hexamethylphosphoramide (HMPA) at high dilution with sodium sulfide. Unfortunately, no tricyclic intermediate **114** was formed. Finally, an encouraging result was obtained when the less strained dibromo compound **116** was treated with sodium sulfide in dimethylformamide (DMF). Surprisingly, sulfone **117** was obtained instead of the expected sulfide. However, sulfone **117** proved unreactive under Ramberg-Bäcklund conditions[83] and no alkene **118** was obtained.

The final strategy relied on lactam-sulfoxide ring contraction utilizing a procedure reported by Ohtsuka and Oishi[84] as a way to access the problematic eight-membered ring. In this procedure, a base-promoted cyclization with extrusion of four atoms could allow the transformation of **121** into **122** (*Scheme 21*). Compound **120** was prepared from **75** and submitted to various



Attempt to Construct Vinigrol Tricyclic Core by Ramberg-Bäcklund Rearrangement

Scheme 20

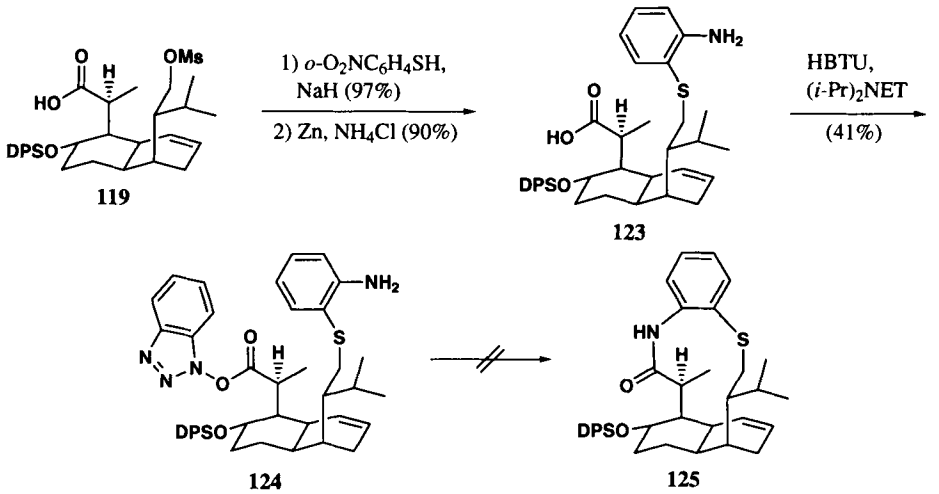


First Attempt to Construct Vinigrol Tricyclic Core Using a Ring Contraction

Scheme 21

conditions (K_2CO_3/$NaBH_4$/DMF/130°C[85], K_2CO_3/$NaBH_4$/ DMA/$HOCH_2CH_2OH$/130°C[86], *t*-BuOK/*t*-BuOH/dioxane/60°C[87]). Based on the mechanism of this reaction, it was expected that **120** would cyclize after a base-promoted elimination to unmask the thiophenoxide anion that would displace the mesylate group to give macrocycle **121**. Despite considerable experimental efforts, the formation of macrocycle **121** was not detected.

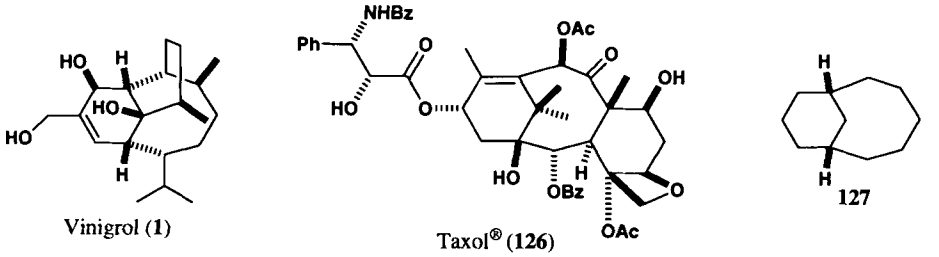
Based on these results, the authors tried to install the C-S bond at C11 in order to perform the cyclization. To this end, amino acid **123** was prepared from carboxylic acid **119** (*Scheme 22*). Reaction with *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate (HBTU) (4 equiv) and diisopropylethylamine (10 equiv)[88] resulted in the formation of benzotriazole-activated ester **124** instead of the macrocycle **125**. Moreover, heating a



Second Attempt to Construct Vinigrol Tricyclic Core Using a Ring Contraction

Scheme 22

solution of **124** in toluene with diisopropylethylamine[89] did not give the macrocycle **125**. In view of their inability to construct the macrocycle, Paquette's group could not study the feasibility of ring contraction for the purpose of their synthesis.



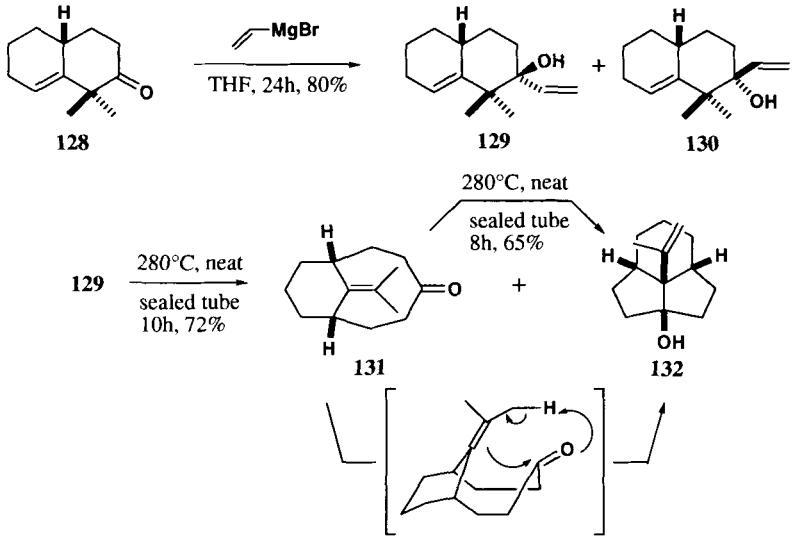
Bicyclo[5.3.1]undecane Rings in Natural Products

Fig. 2

Despite considerable research efforts spread over a decade to cyclize the two functionalized side-chains on different *cis*-decalin derivatives aimed at obtaining the tricyclic core of vinigrol (**1**), Paquette *et al.* were not able to access the octalin bridge. Information collected from the crystal structure of **77** clearly established that the two of functionalized arms are in the equatorial position thus hampering the formation of the eight-membered ring. This was also observed with the cleavage of one of the constituent rings, thus indicating that the eight membered ring should be synthesized prior the two other rings when alkylation and related methods are being envisioned in a retrosynthetic analysis of vinigrol (**1**).

c) Mehta's Approach

Another application of the oxy-Cope towards the synthesis of vinigrol (**1**) was reported by Mehta and co-workers.[90] Mehta demonstrated that bicyclo[5.3.1]undecane ring system **127** incorporated in taxol® (**126**) and vinigrol (**1**) (*Fig. 2*) could be obtained by a thermal [3,3] sigmatropic rearrangement (*Scheme 23*). Starting from readily available 1,1-dimethyl-8-octal-2-one[91] (**128**), a 7:3 mixture of diastereomeric carbinol **129** and **130** were produced after treatment with

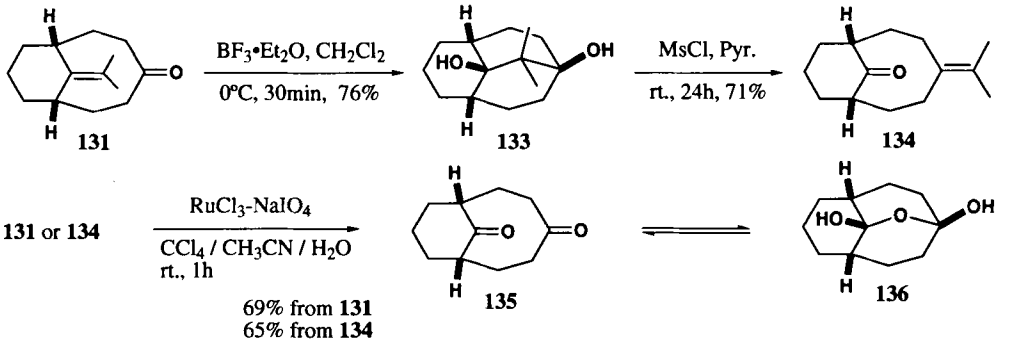


Mehta's Approach to Bicyclo[5.3.1]undecane

Scheme 23

vinylmagnesium bromide. The thermal oxy-Cope rearrangement of **129** gave a 2:1 mixture of the bicyclo[5.3.1]undecane **131** and tricyclic compound **132**. As shown in *Scheme 23*, the formation of **132** is the result of a [3,3] sigmatropic rearrangement (**129→131**) followed by an intramolecular carbonyl-ene reaction (**131→132**). Interestingly, when compound **129** was submitted to anionic oxy-Cope conditions (KH in THF with 18-crown-6) no rearranged product was obtained. Bicyclo[5.3.1]undecane **131** was converted into ketone **134** *via* a transannular carbonyl-olefin

cyclization with trifluoroborane etherate (**131→133**) followed by a dehydration in the presence of mesyl chloride and pyridine (*Scheme 24*). Finally, exposure of **131** and **134** to catalytic ruthenium oxidation[92] gave bicyclo[5.3.1]undecane-4,11-dione **135**, which readily hydrated to **136**. This procedure is a very simple route to bicyclo[5.3.1]undecane. However, there is not much handle to introduce the required functionalities for the synthesis of vinigrol (**1**) and no further progress by Mehta has been reported.

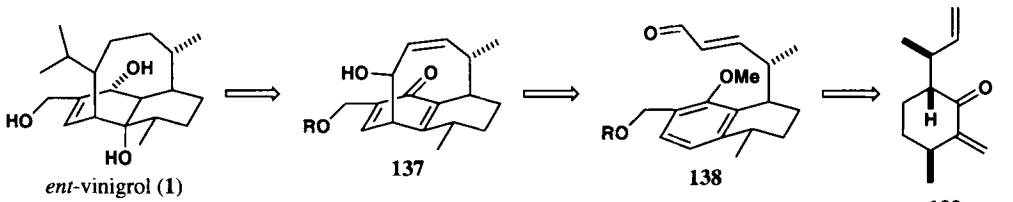


Mehta's Approach to Bicyclo[5.3.1]undecane

Scheme 24

2. Electrophilic Aromatic Condensation

An initial approach toward the synthesis of the enantiomer of vinigrol (**1**) was proposed by Corey and Palani (*Scheme 25*).[93] Their strategy relied on intramolecular Friedel-Crafts alkylation to generate the octalin belt in **137** from aldehyde **138**. Substituted tetrahydronaphtalene **138**

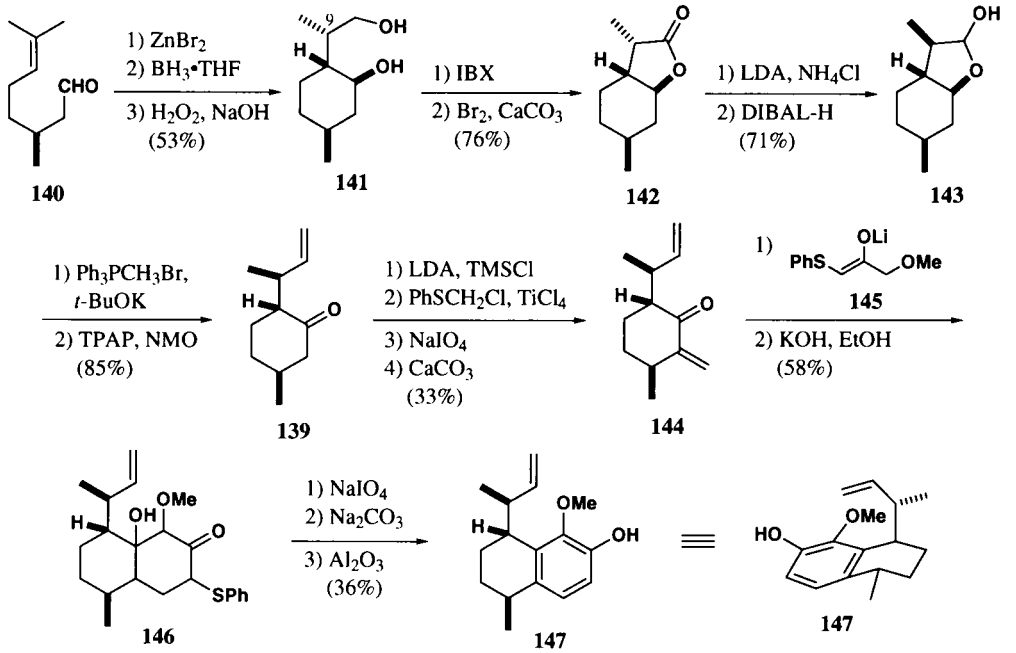


Corey's Approach to *ent*-Vinigrol (**1**)

Scheme 25

was prepared from exocyclic enone **139**. Their synthesis began with commercially available (1S)-citronellal **140** which upon treatment with $ZnBr_2$ gave the corresponding homoallylic alcohol (*Scheme 26*). The latter underwent hydroboration followed by an oxidative workup to give diol **141**.

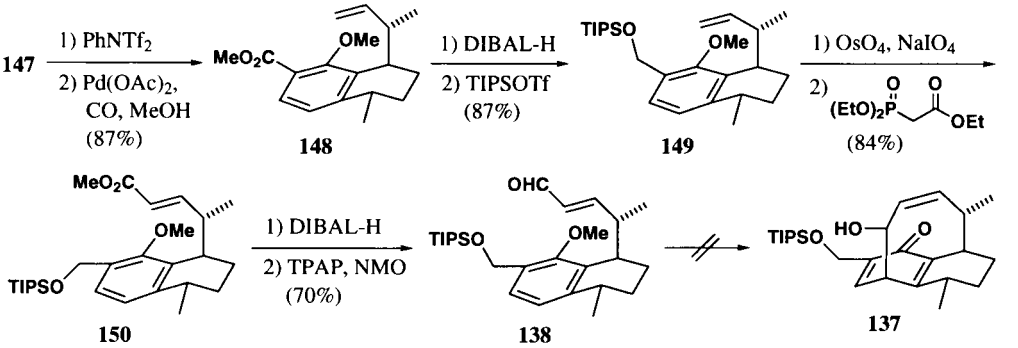
In order to obtain the proper stereochemistry at C-9, inversion of the methyl group was required. To this end, oxidation of the primary alcohol gave lactone **142** which upon exposure to LDA at low temperature followed by a quench with ammonium chloride, produced the corresponding lactone having the correct stereochemistry at C-9. Reduction of the lactone moiety with



Electrophilic Aromatic Condensation Approach

Scheme 26

Dibal-H afforded lactol **143**. A Wittig reaction to generate the terminal olefin and oxidation of the resulting secondary alcohol gave ketone **139**, which was converted to exocyclic enone **144**. 1,4-Addition of the enolate of 1-methoxy-3-phenylsulfanyl-propan-2-one **145** to exocyclic enone **144**, followed by an aldol condensation afforded decalin **146**. Oxidative elimination of the sulfide and alumina-assisted dehydration gave phenol **147**. The latter was converted to the triflate and exposed to CO and $Pd(OAc)_2$ in MeOH to form methyl ester **148** which was transformed into silyloxyether **149** *via* reduction with Dibal-H and protection the primary alcohol with triisopropylsilyl triflate (TIPSOTf) (*Scheme 27*). Lemieux-Johnson oxidation of the terminal double



Electrophilic Aromatic Condensation Approach

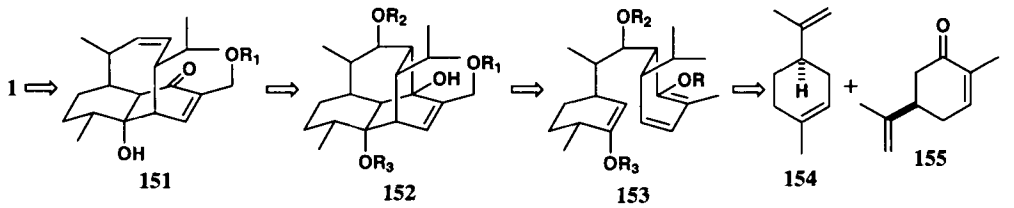
Scheme 27

bond in **149** followed by an olefination reaction on the resulting aldehyde gave the methyl ester **150** easily converted into the corresponding aldehyde **138** *via* a reduction/oxidation sequence.

At this point, the electrophilic aromatic condensation to form the octalin belt was investigated. To this end, aldehyde **138** was treated with various Lewis acids, including trifluoroborane etherate, tribromoborane and trichloroborane. Unfortunately, the desired tricycle **137** was not obtained. A close inspection of **137** reveals that the *ansa* bridge bears a tetrasubstituted *E* olefin (in respect to the eight membered ring) which causes strain in the molecule. One might propose that this could destabilize the transition state thus preventing the reaction from occurring. The use of more a more electrophilic carbonyl such as an acid chloride was also unsuccessful and this route was abandoned.

3. Intramolecular Diels-Alder Reaction

In 1997, a second approach was designed by Corey and Goodman.[9] Their retrosynthesis analysis reveal that the tricycle core of vinigrol could be generated *via* intramolecular Diels-Alder reaction of **153** followed by a Grob fragmentation of the cycloadduct **152** to afford **151** as an advanced precursor to vinigrol (*Scheme 28*). The Diels-Alder precursor **153** could be prepared from an aldol reaction between derivatives of limonene **154** and carvone **155**. It was proposed that the close proximity of the reacting diene and dienophile would overcome the disfavorable electronic properties.

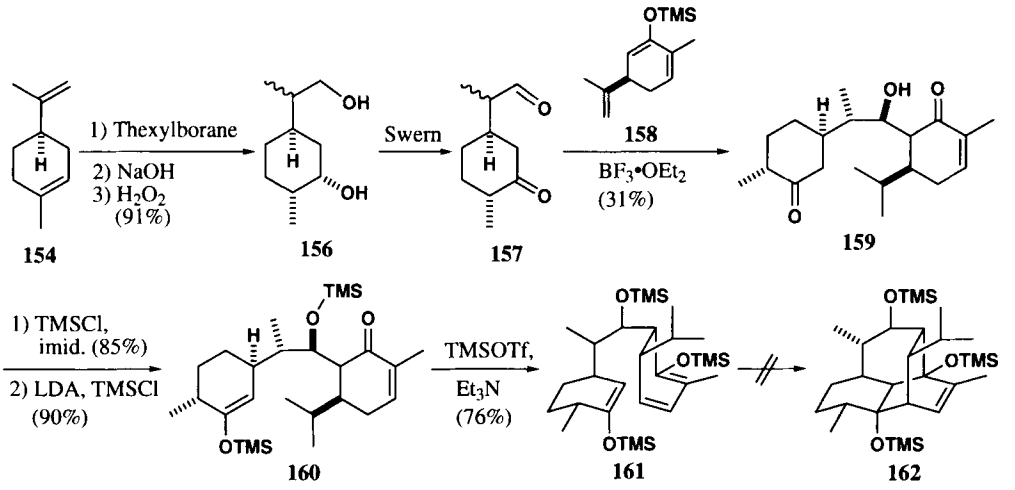


Corey's Intramolecular Diels-Alder Approach

Scheme 28

This synthesis began by a reduction of the exocyclic olefin in **154** with thexylborane[94] (*Scheme 29*). Although the reduction of the cyclic olefin is chemoselective, it gave an inseparable mixture of diastereomers. Several efforts to separate the two diastereoisomers, including enzymatic resolution, were unsuccessful. Swern oxidation of **156** afforded a mixture of isomers **157**. Aldol coupling of **157** with TMS enol ether **158**[95] was carried out under Mukaiyama conditions[96] and afforded a mixture of diastereomers from which **159** was isolated after column chromatography. At this point, the preparation of the Diels-Alder precursor **161** was achieved by two successive enolization/trapping sequences. The first one utilized LDA and TMSCl to generate the kinetic enol ethers (**159→160**). The latter was treated with TMSOTf in the presence of triethylamine to provide **161**. Unfortunately, all attempts for the thermal Diels-Alder reaction were unsuccessful and resulted only in isomerization of the double bond. The electron-rich

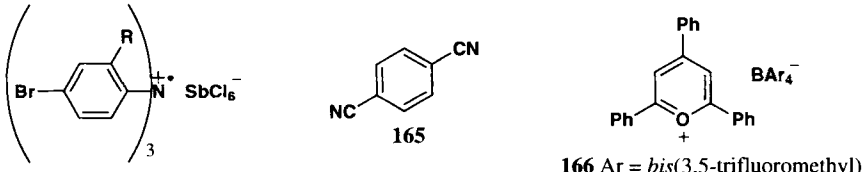
nature of both the diene and the dienophile, as well as the steric congestion in the transition state are accountable for the failure of triene **161** to undergo an intramolecular [4+2]cycloaddition.



Intramolecular Diels-Alder Approach

Scheme 29

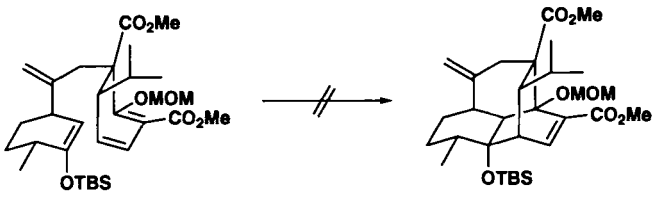
A solution to this problem would be to remove electron density from one of the olefins. Cation radical cycloadditions became an option since it has been reported that it provides access to Diels-Alder products which are difficult to access by thermal or Lewis acid catalyzed Diels-Alder reaction.[97] Catalysts **163**[98], **164**[99], **165**[100] and **166**[101] are known to induce cation radical cycloadditions (*Fig. 3*). They were scanned for their ability to catalyze the Diels-Alder reaction of triene **161**; however, only decomposition of the substrate was observed.



Catalysts for Cation Radical Cycloadditions

Fig. 3

Another approach to solve about the electronic impediment was to install an electron-withdrawing group on the diene in order to modify the electronic nature of the cycloaddition step. For this purpose, triene **167** was synthesized with the added advantage of minimizing the steric congestion attributed to the protecting groups and including a handle from which the primary alcohol in vinigrol could be accessed (*Scheme 30*). However, all attempts to obtain cycloadduct **168** failed. Diverse protecting groups were scanned and attempts were made to deoxygenate the diene moiety but none resulted in the desired tetracycle **168**. Consequently, this approach was abandoned.

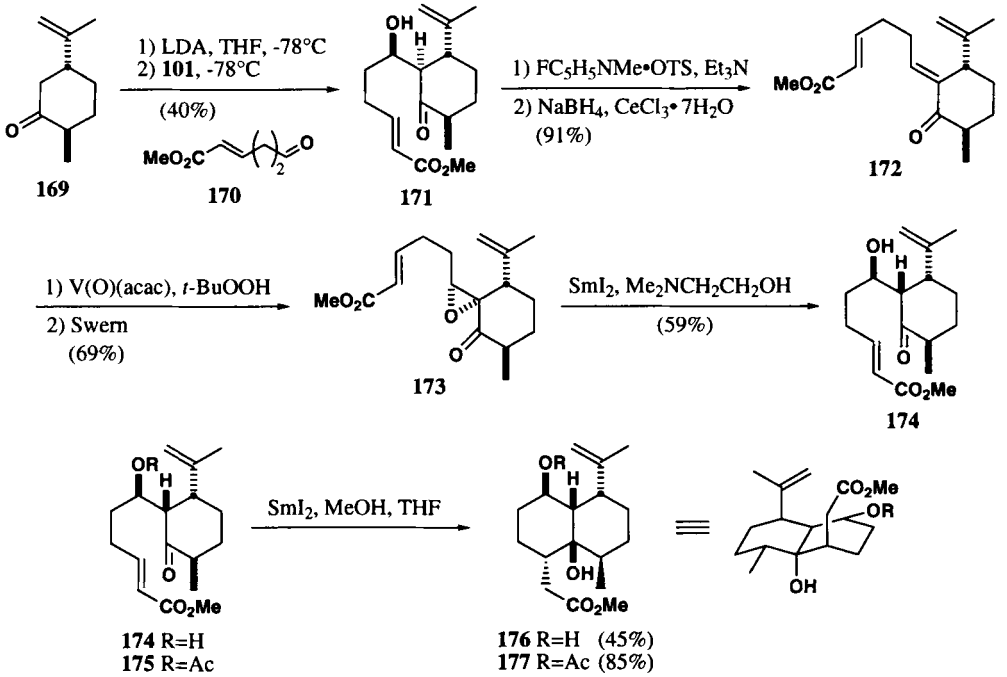


Inverse Electron-Demand Diels-Alder Reaction

Scheme 30

4. Barbier SmI_2-Mediated Cyclization

In 1996, Matsuda reported the formation of the *cis*-decalin skeleton of vinigrol (**1**) *via* samarium(II) iodide promoted ketyl-olefin coupling.[102] Samarium(II) iodide is known to promote reductive coupling reactions[103] and the presence of a hydroxy group in the starting material is also known for facilitating the coupling and controlling the stereochemistry.[104] The hydroxy ketone **174**, required for the coupling, was prepared by a short synthetic sequence (*Scheme 31*). The stereoselective cross-aldol reaction of (*E*)-methyl 5-formylpent-2-enoate (**170**) with the lithium enolate of (+)-dihydrocarvone (**169**) gave *anti*-β-hydroxy ketone **171**. Dehydration, followed by 1,2-reduction of the enone under conditions developed by Luche afforded alcohol **172**. Catalyzed hydroxy-directed epoxidation with VO(acac) and t-BuOOH followed by a Swern



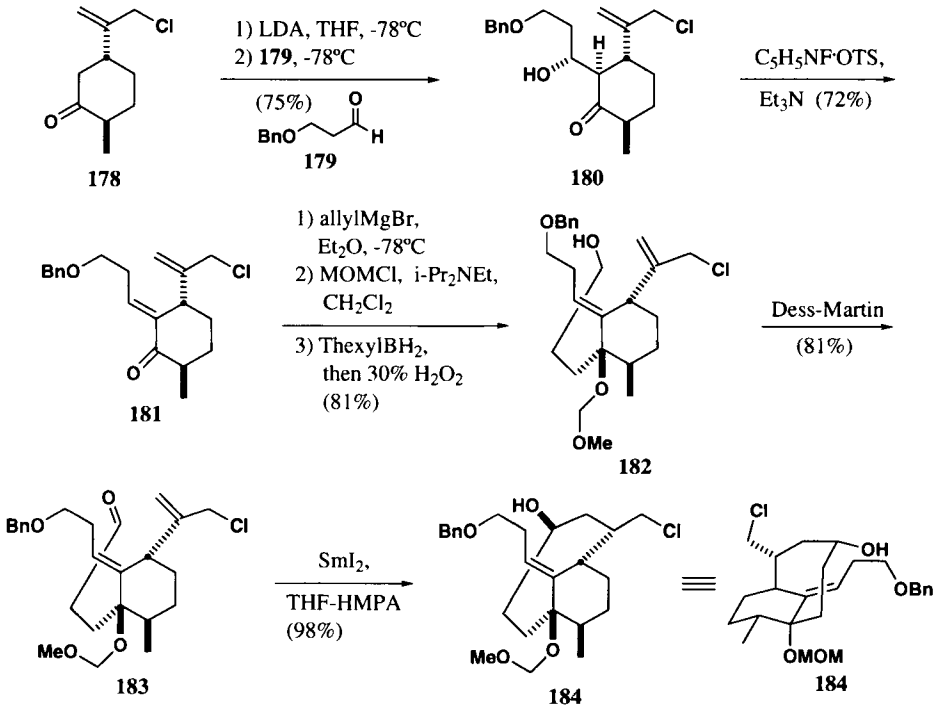
Matsuda's Construction of the *cis*-Decalin

Scheme 31

oxidation gave a 4:1 diastereomeric mixture of the α,β-epoxy ketone **173**. Reductive cleavage of the epoxide with samarium(II) iodide provided the hydroxy ketone **174**. The *cis*-decalin **176** was obtained after a reductive Barbier cyclization promoted by samarium (II) iodide in THF/MeOH. Interestingly, when the reaction was carried out at -78°C, only reduction of the ketone and of the unsaturated ester was observed.

Gratifyingly, the desired cyclization product was produced when the reaction was performed at room temperature. It was noticed that better yields were obtained (**175→177**) if alcohol **174** was converted to the corresponding acetate **175** prior to the cyclization. The lower yield of the Barbier cyclization of **174** is due to the chelation between the Sm(III) cation and the b-hydroxy group.

Using a similar approach, Matsuda and co-workers reported the construction of the bicyclo[5.3.1]undecene portion of vinigrol (**184**) (*Scheme 32*).[105,106] Stereoselective aldol reaction of (+)-chlorodihydrocarvone (**178**)[107] with 3-benzyloxypropionaldehyde (**179**)[108] gave **180** which, upon the subsequent dehydration using 2-fluoropyridium tosylate salt, provided with the



Matsuda's Construction of the Octalin Belt

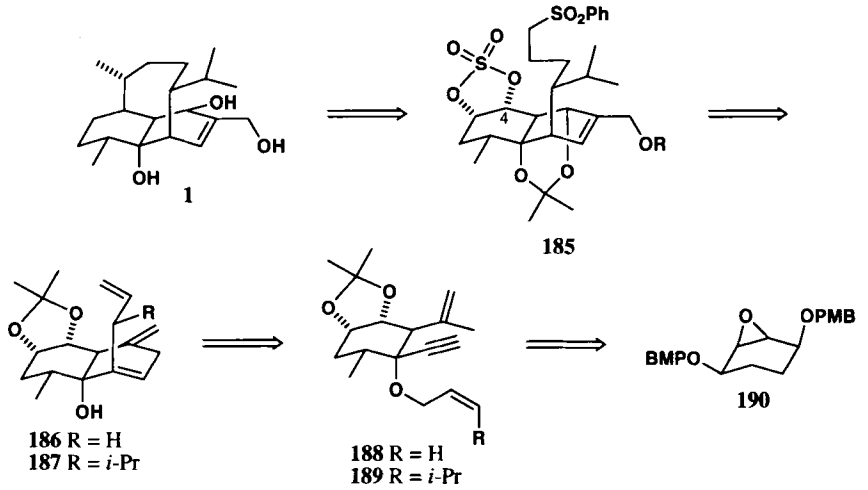
Scheme 32

enone **181**. Grignard alkylation, protection of the alcohol as its methoxymethyl ether and regioselective hydroboration of the terminal olefin afforded alcohol **182**. Oxidation with Dess-Martin periodinane gave aldehyde **183**. The synthesis of the bicyclo[5.3.1]undecene **184** was achieved

by treatment of **183** with samarium(II) iodide in the presence of HMPA. Many SmI_2-induced reactions benefit from the presence of HMPA to accelerate the electron-transfer process[109,110] and in this case, the presence of HMPA was necessary for the cyclization to occur in near quantitative yield. Despite the elegant syntheses of the decalin unit **177** and bicyclo[5.3.1]undecene portion **184** of vinigrol using the SmI_2 mediated-Barbier cyclization, the completion of the tricyclic core of vinigrol of the remaining six-membered ring nor the stereoselective introduction of the *iso*-propyl unit at C-12 have not been reported yet.

5. Tandem Oxy-Cope/Claisen/Ene Rearrangement

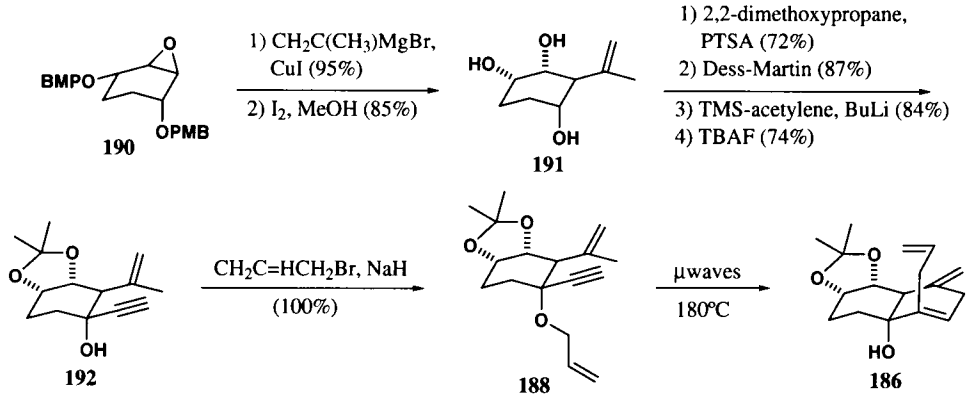
The architectural complexity and the impressive biological activity of vinigrol (**1**) have also caught our attention. Our first retrosynthetic analysis illustrated in *Scheme 33* reveals that the octalin belt surmounting the *cis*-decalin in **1** could be created *via* an intramolecular S_N2 displacement of the cyclic sulfate at C4 by a sulfone anion.[111] Since *cis*-decalins can exist in two conformations, the acetonide moiety in **185** is essential to maintain the *cis*-decalin unit in the conformer prone to cyclization. The latter could be obtained from *cis*-decalin **186** or **187** which could be realized in one step from a tandem oxy-Cope/Claisen/ene reaction of allyl ether **188** or **189**.[112]



Proposed Retrosynthesis of Vinigrol

Scheme 33

The synthesis began with the opening of readily available *meso*-**190**[113] with an organocuprate, followed by cleavage of the benzyl protecting groups to give triol **191** (*Scheme 34*). The *cis*-1,2 diol was protected as its acetonide and the resulting alcohol was oxidized with Dess-Martin's periodinane. Addition of lithium trimethylsilylacetylide to the ketone, followed by treatment with fluoride ion provided alcohol **192** as a sole isomer. Allylation of the tertiary alcohol with allyl bromide afforded allyl ether **188**. Compound **188** was dissolved in degassed



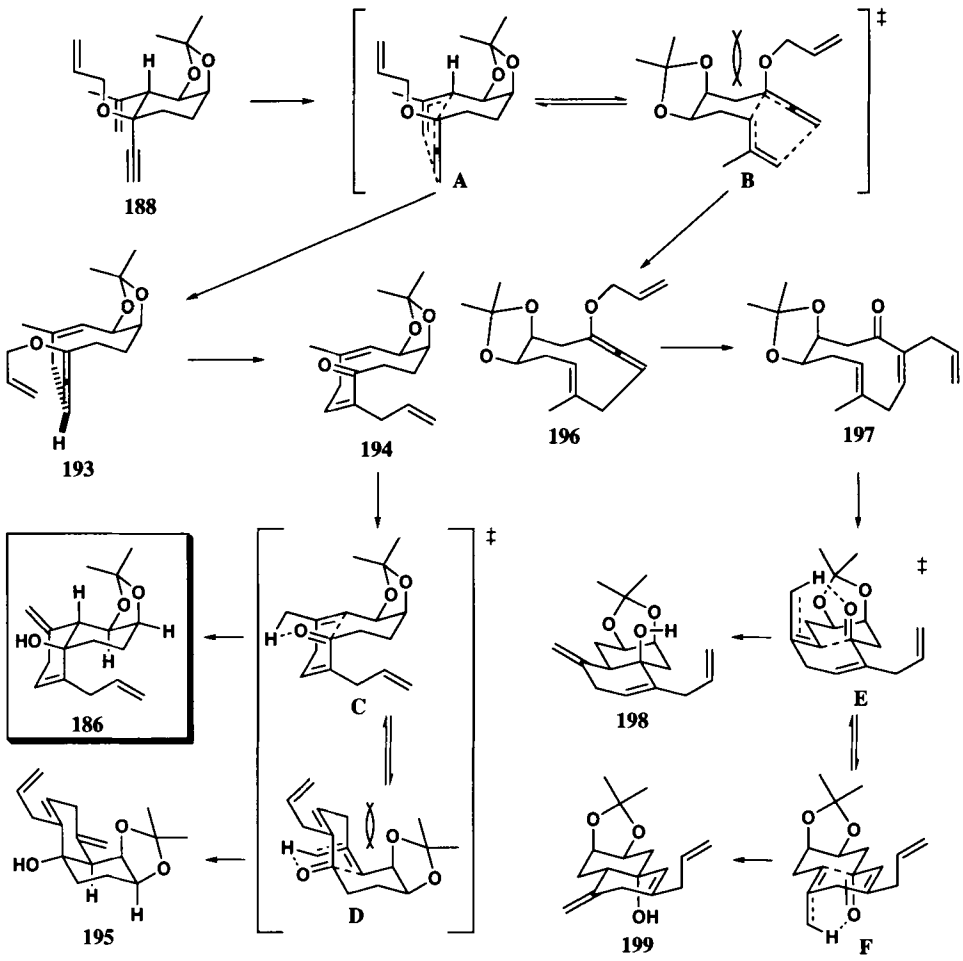
Construction of the *cis*-Decalin

Scheme 34

toluene and subjected to microwave irradiation[114] (180°C) for 1 hr to provide the desired *cis*-decalin **186**. High diastereoselectivity of the tandem process can be rationalized by the reaction mechanism depicted in *Scheme 35*. Allyl ether **188** can undergo an oxy-Cope rearrangement *via* two possible transition states, **A** and **B**. Assuming a rapid equilibrium exists between the two conformers, only the energy difference between the transition states will account for the diastereomeric ratio. A close examination of transition state **B** shows the existence of 1,3-diaxial interactions between the allyl ether side-chain and the acetonide moiety whereas in **A** the allyl ether chain is oriented in an equatorial position. This favors the formation of **193** over **196** and is supported by the fact that no *trans*-decalins **198** or **199** were isolated from the crude mixture resulting from the transannular ene reaction of **188**. The highly strained allene **193** undergoes a Claisen rearrangement which creates the macrocyclic enone **194** *in situ*. The latter is poised to cyclize *via* a transannular carbonyl-ene reaction through two possible reactive macrocyclic conformations, **C** and **D**. An inspection of transition state **D** reveals strong 1,3-diaxial methylene *O*-acetonide interactions which favor the transition state **C** over **D** thereby affording decalin **186** as the sole isomer.

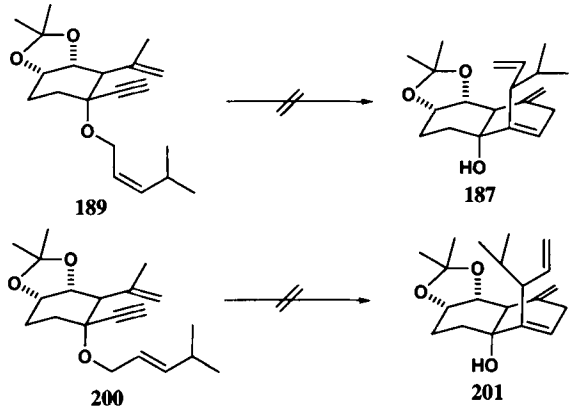
The insertion of the isopropyl unit at C-12 of **187** was then investigated (*Scheme 36*). To this end, precursor **189** was prepared from alcohol **192**, sodium hydride and *cis*-1-mesylate-4-methyl-2-pentene in quantitative yield.[115] However, microwave irradiation of **189** at various temperature did not afford *cis*-decalin **187**. This result is similar to those reported by Hanna and co-workers (*vide supra*).[26] *trans*-Allyl ether **200** was thus prepared[116] and irradiated, but no product **201** resulting from tandem oxy-Cope/Claisen/ene reaction was observed.

These results led us to conclude that large substituents at the terminal position are detrimental to the tandem rearrangement sequence. At this point, we postulated that the installation of the *iso*-propyl group on **186** at a later stage might be problematic and challenging. Therefore, this approach was abandoned.



Proposed Mechanism for the Tandem Oxy-Cope/Claisen/Ene Reaction

Scheme 35



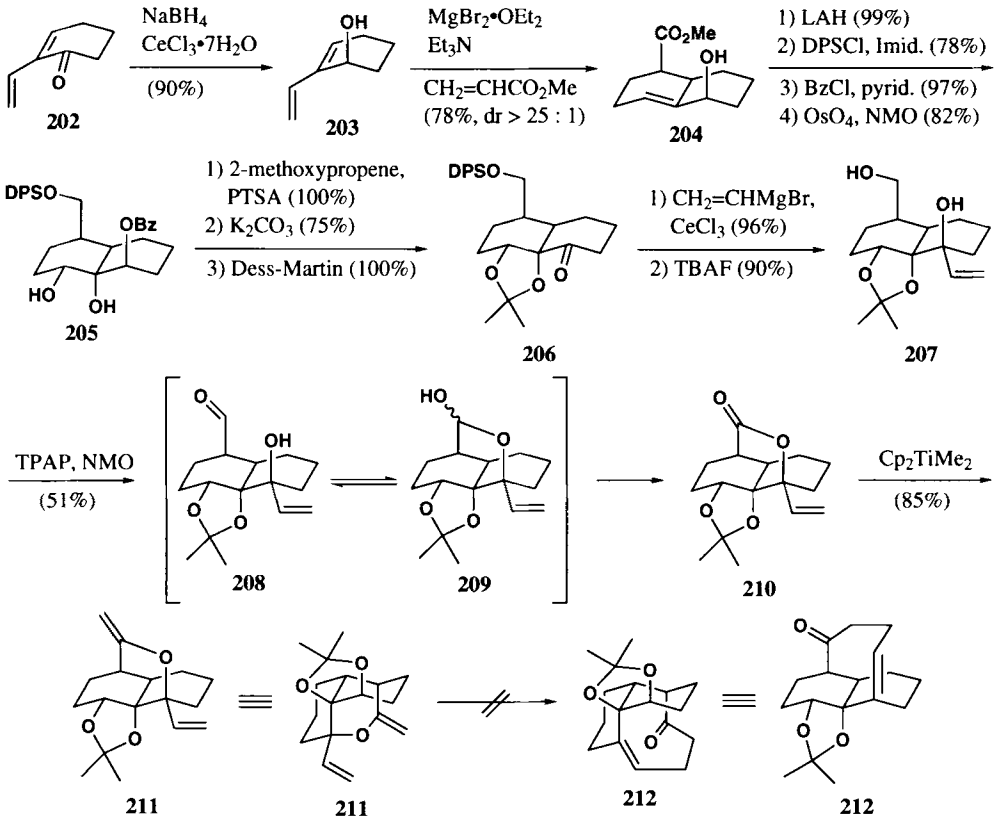
Construction of the Funtionalized *cis*-Decalin

Scheme 36

6. Hydroxy-Diels-Alder/Claisen Reaction

In the light of the previous results reported above, it was decided to explore new avenues to construct the tricyclic core of vinigrol (**1**). Three different synthetic pathways for the formation of the eight-membered ring were investigated. In 2005, we reported the synthesis of the octalin ring of vinigrol (**1**) *via* sequential hydroxy-directed Diels-Alder (HDDA)/Claisen rearrangement.[117]

A ring expansion triggered by a Claisen rearrangement[118] of **211** to obtain tricycle **212** (*Scheme 37*) was attempted initially. This synthesis began with the 1,2-reduction of enone **202** to give hydroxy-diene **203**. Treatment of **203** with $MgBr_2{\cdot}OEt_2/Et_3N$[119] generated *in situ* the corresponding magnesium alkoxide which was poised to undergo an HDDA reaction with methyl



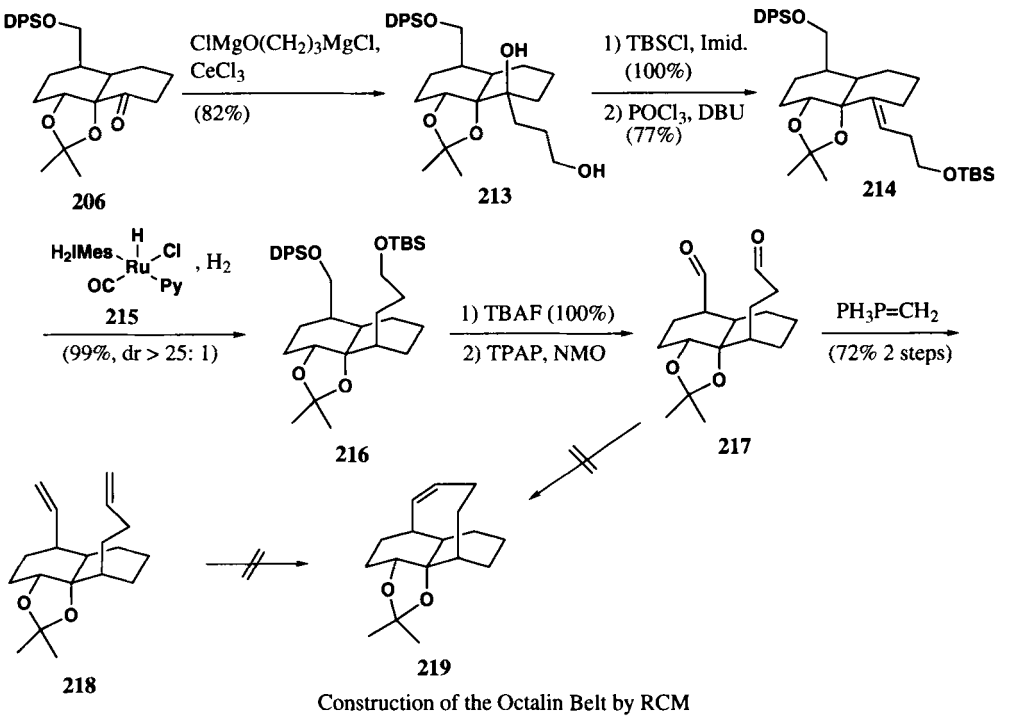
Construction of the Octalin Belt by Ring Expansion

Scheme 37

acrylate to provide the *cis*-decalin precursor of vinigrol **204** as the sole isomer.[120] Reduction of the ester, followed by selective protection of the primary alcohol as its silyl ether and of the secondary alcohol as a benzoate, allowed for the formation of diol **205** by dihydroxylation of the double bond. The diol **205** was then protected as an acetonide and the benzoate removed with

potassium carbonate. The resulting alcohol was oxidized into ketone **206**. The addition of vinylmagnesium bromide to ketone **206** in the presence of cerium chloride followed by treatment with TBAF afforded diol **207**. Ruthenium-mediated oxidation[121] of diol **207** led to the formation *in situ* of aldehyde **208**, which can exist in equilibrium with lactol **209**. The latter mixture was further oxidized to give lactone **210**, then treated with Petasis' reagent[122,123] to give the desired enol ether **211**. All the requisite carbons having been installed, attempts were made to generate the octalin belt by the Claisen rearrangement of **211**. Initial attempts to obtain **212** under thermal conditions or using microwaves proved unsuccessful. Hard and soft Lewis acids were then screened as catalysts for the rearrangement.[124] However, all runs using $Pd(0)L_4$, $Pd(II)L_2$[125,126], $AgBF_4$, $AlMe_3$, $AlMe_2Cl$, Dibal-H, i-Bu_3Al[127], methylaluminum *bis*(4-bromo-di-*tert*-butylphenoxyde (MABr)[128], and $Mg(OTf)_2$ in various solvents and under different conditions resulted in the degradation of **211** or its partial recovery.

A second approach relied on RCM of diene **218** to form the eight-membered ring in **219** (*Scheme 38*). On the basis of semi-empirical calculation and the ease of formation of lactone **210**, it was anticipated that the reactive conformer **218** could be trapped in the RCM conditions



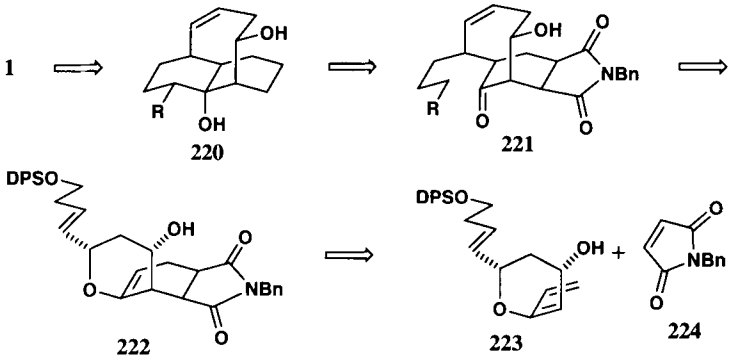
Construction of the Octalin Belt by RCM

Scheme 38

to give tricycle **219**. Treatment of ketone **206** with $ClMg(CH_2)_3OMgCl$[129] and $CeCl_3$ gave alcohol **213**, that was selectively protected and dehydrated to afford trisubstituted alkene **214**. A large number of metal-catalyzed hydrogenation protocols were scanned for the reduction of the

trisubstituted exocyclic double bond and it was found that hydrogenation in the presence of ruthenium-based catalyst **215** afforded stereoselectively decalin **216**.[130,131] Removal of both silicon protective groups on **216** with TBAF followed by TPAP oxidation of the resulting diol gave dialdehyde **217**. The latter was immediately treated with $Ph_3P{=}CH_2$ to provide diene **218**. Unfortunately, all attemps to cyclize **218** *via* RCM using Grubbs' first- and second-generation catalyst were not successful as was an attempt to obtain tricycle **219** by $TiCl_3$-mediated coupling reaction of dialdehyde **217** in conditions described by McMurry. In agreement with these results, Paquette reported at the same time unsuccessful approaches to generate the cyclooctane ring using various ring-closing protocols, as discussed earlier.

In a third approach, the *ansa* belt in **220** (*Scheme 39*) was generated before the *cis*-decalin portion of the framework. Intramolecular alkylation of **221** should close the last ring and give tricycle **220**. The bicyclo[5.3.1]undecanone subunit **221** could be prepared from a sequential HDDA/Claisen rearrangement between diene **223** and dienophile **224**.[132]

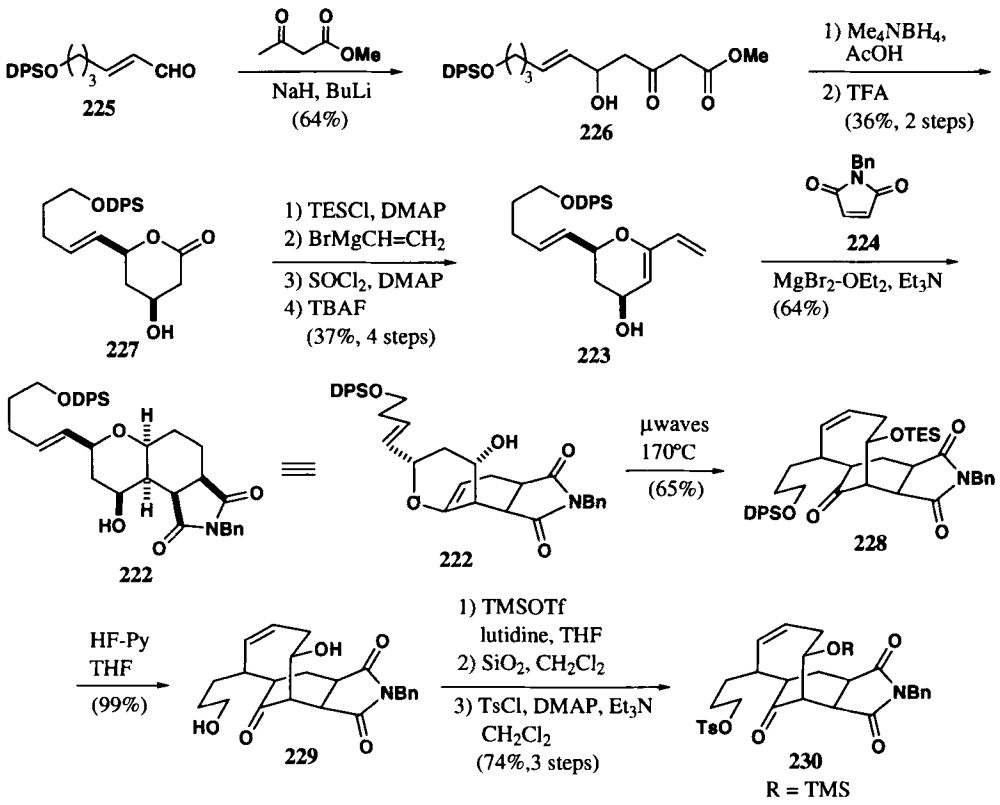


Synthesis of the Octalin Belt by a Sequential HDDA/Claisen Reaction

Scheme 39

This synthesis started by the addition of Weiler's dianion[133] on aldehyde **225** to afford b-ketoester **226** (*Scheme 40*). Diastereoselective reduction of **226** with Me_4NBH_4[134] afforded the corresponding 1,3-anti diol, that upon treatment with TFA afforded lactone **227**. Protection of the secondary alcohol, followed by addition of vinylmagnesium bromide provided the corresponding lactol. Dehydration in the presence of $SOCl_2$ and DMAP and selective removal of the TES protecting group gave semicyclic diene **223**. HDDA reaction of **223** and N-benzylmaleimide furnished cycloadduct **222** as a sole diastereoisomer. Exposure of the bicyclo[4.4.0]decene **222** to microwave radiation afforded the desired Claisen product **228**. Treatment with HF-pyridine provided with the monoprotected alcohol **229**. The latter was converted to the corresponding sulfone **231**and nitrile **233** (*Scheme 41*). Both compounds were submitted to various deprotonation conditions and, unfortunately, no cyclization products were observed.[135]

It appears that the severe steric congestion at the bridgehead ketone inhibits any cyclizations or nucleophilic additions. Recently, it was found that only small nucleophiles such as



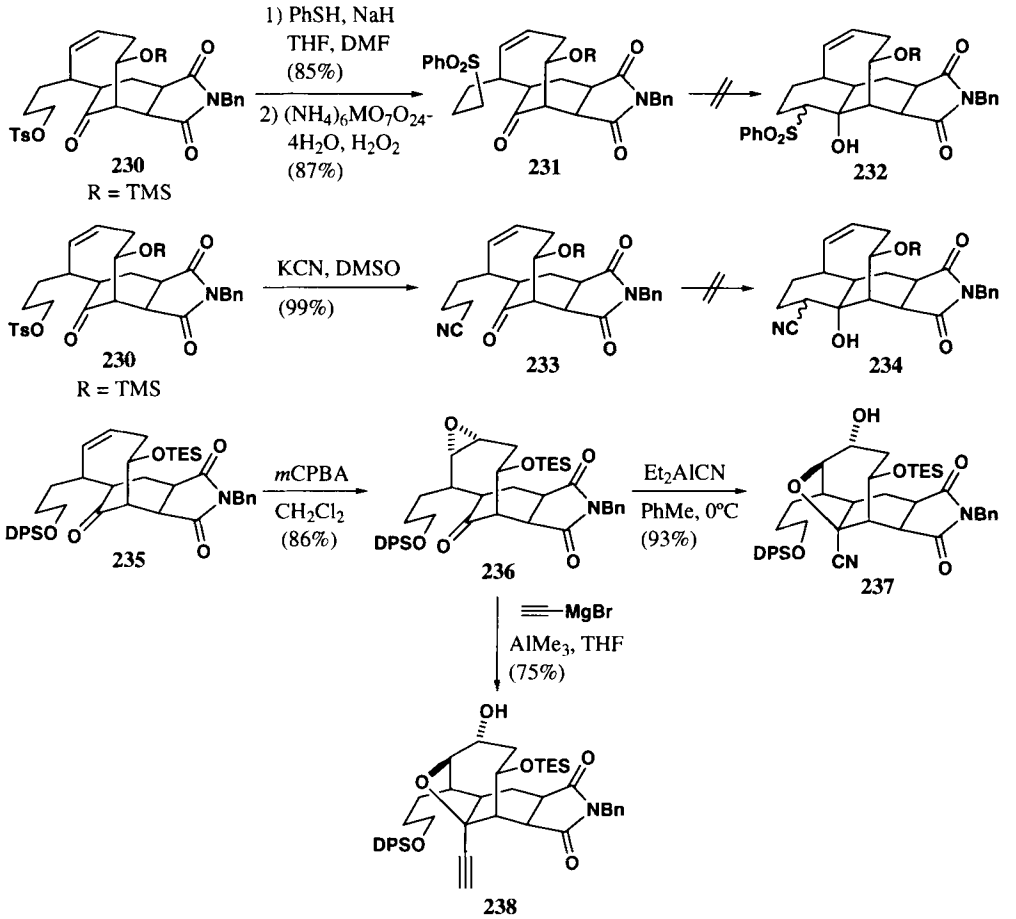
Construction of Bicyclo[5.3.1]Undecanone Subunit

Scheme 40

acetylinic anion and cyano group can be added onto the carbonyl group when an epoxide at C9-C10 is present in the eight membered ring (in lieu of the double bond).[135] Treatment of epoxide **236** with Et_2AlCN in toluene or with ethynylmagnesium bromide in the presence of $AlMe_3$ gave ethers **237** and **238** respectively. Attempts to invert the stereochemistry at C-8a proved to be fruitless.

Conclusion and Future Work

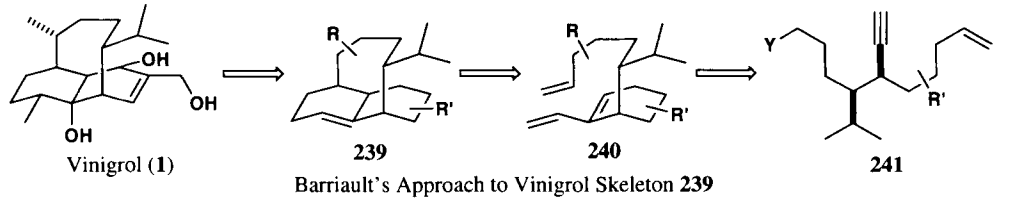
Vinigrol synthesis offers a fantastic playground for synthetic organic chemists. The unusual architecture of vinigrol (**1**) stimulates researchers to design new tactics and strategies to construct vinigrol tricyclic framework. As a result, considerable efforts have been devoted toward the total synthesis of vinigrol. From these approaches, it was learned that the formation of two of the three rings of vinigrol can be achieved without posing serious problems. However, the formation of the third ring, especially the eight-membered ring, *via* alkylation type reactions or ring closure metathesis is problematic and not possible if the decalin unit adopt a lower energy conformation where the side-arms are in the opposite direction to each other. On the other hand, research by Hanna and coworkers demonstrated that the vinigrol tricyclic framework can be



Attempts to Close the Last Ring

Scheme 41

generated *via* anionic oxy-Cope from a 1,5-hexadiene where a locked decalin subunit is embedded (**27**→**28**, *Scheme 5*). In the light of these results, we are currently investigating a shorter route for the enantioselective construction of vinigrol tricyclic system **239** (*Scheme 42*). Our new approach took cognizance of the fact that the six and eight-membered rings could be generated from a regioselective intramolecular Diels-Alder reaction of triene **240**. The latter could be obtained from an ene-yne metathesis of **241**. Completion of **239** is underway and will be reported in due course.



Barriault's Approach to Vinigrol Skeleton **239**

Scheme 42

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