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Evolution of an oxidative dearomatization enabled total synthesis of vinigrol†

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The evolution of the synthetic strategy resulting in a total synthesis of vinigrol is presented. Oxidative dearomatization/intramolecular Diels–Alder cycloaddition has served as the successful cornerstone for all of the approaches. Extensive radical cyclization efforts to form the tetracyclic core resulted in interesting and surprising reaction outcomes, none of which could be advanced to vinigrol. These cyclization obstacles were successfully overcome by using Heck instead of radical cyclizations. The total synthesis features a trifluoroethyl ether protecting group being used for the first time in organic synthesis. The logic of its selection and the group's importance beyond protecting the C8a hydroxyl group is presented along with a discussion of strategies for its removal. Because of the compact tetracyclic cage the route is built around many unusual reaction observations and solutions have emerged. For example, a first of its kind Grob fragmentation reaction featuring a trifluoroethyl leaving group has been uncovered, interesting interrupted selenium dioxide allylic oxidations have been observed as well as intriguing catalyst and counterion dependent directed hydrogenations.

Introduction

Diterpenoids are an important family of natural products,[1] which contain an incredible diversity of fused and bridged bicyclic architectures ranging from simple to complex structures such as the cancer chemotherapeutic agent paclitaxel[2] (Taxol®). Many of these diterpenoid natural products contain rare and synthetically challenging arrangement of atoms such as *anti*-Bredt olefins (paclitaxel and CP-263,114[3]), inside-out bridged bicyclic ring systems (ingenol[4] and hypoestoxide[5]) and the bis-axially bridged *cis*-decalin structure of vinigrol (**1**, Fig. 1). The structural diversity, unusual architectures and promising biological profiles of members of this family of natural products attracted our interest. We initiated a research program dedicated to their synthesis and systematic evaluation of their biological capabilities enabled by the power of diverted total synthesis.[6] To date we have synthesized an atropisomer of hypoestoxide,[7] the core of platensimycin[8] and several members of a labdane diterpenoid family.[9] In this article we present the full extent of our efforts, which resulted in a successful total synthesis of vinigrol.[10]

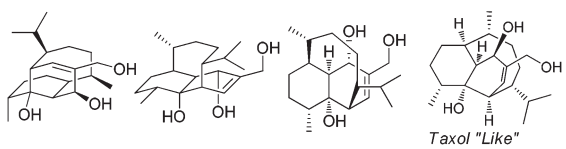

Fig. 1 Vinigrol structural perspectives.

Vinigrol's unique structure, which is displayed using four different perspectives in Fig. 1, was first reported in 1987.[11] Like Taxol®, it contains a similar [5.3.1]-bicyclic core except with an additional fused six-membered ring. Perhaps a more helpful way to describe its special architecture is as a densely decorated *cis*-decalin core with a four carbon bicyclic tether bridging the two six-membered rings. Extensive evaluation of vinigrols biological profile revealed promising activities impacting targets ranging from cancer to HIV.[12] Vinigrol's unprecedented structure immediately attracted the interest of synthetic chemists from around the globe, as reflected by the numerous publications spanning two decades presenting creative and dedicated efforts by many different research groups.[13,14] Twenty two years after its structure was disclosed, Professor Baran completed the first total synthesis of vinigrol.[15] Professor Barriault has since completed a formal synthesis of vinigrol.[16]

Our vinigrol retrosynthesis is outlined in Fig. 2. We envisioned a late stage C–C bond carbanion mediated

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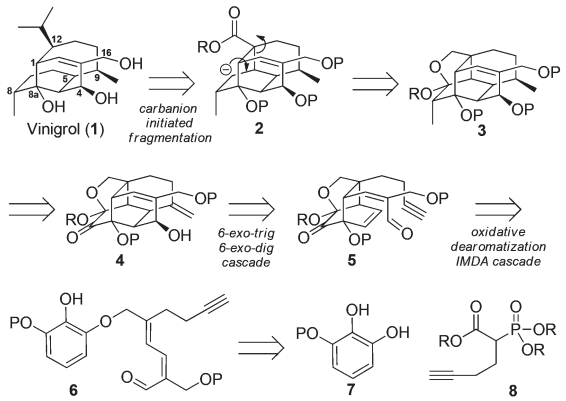


Fig. 2 Njardarson group vinigrol retrosynthesis.

fragmentation to form the unusual decalin bridged vinigrol ring system from protected tetracyclic precursor **2**. The functional groups (ester and an anion initiating group) needed for the fragmentation step would be constructed from methyl acetal **3**. We hoped that the challenging C8 and C9 methyl stereocenters could be installed in a substrate controlled manner in a single step by catalytically hydrogenating two exocyclic olefins, which we believed could be easily accessed from ketone **4**. A key retrosynthetic design feature was a 6-*exo*/6-*exo* ketyl radical cyclization cascade (**5** → **4**), which we hoped would not only create the tetracyclic cage, but also correctly install the C4-hydroxyl stereocenter. The second key design feature is a one pot oxidative dearomatization/Diels–Alder cycloaddition reaction (**6** → **5**). Resorcinol precursor **6** would be decorated with an electron withdrawing group (P) whose purpose is to guide the oxidative dearomatization reaction towards the allylic ether site. Oxidative dearomatization precursor **6** would be assembled from mono protected resorcinol derivative **7** and phosphonate **8**. We were convinced that this retrosynthetic outline was flexible enough to provide us with many options to address the synthetic goals presented.

Outlined in Fig. 3 is the most ambitious version we proposed would be possible for the radical cyclization cascade. We envisioned that this dream cascade could be made possible using several equivalents of samarium(II) diiodide in the appropriate solvent. The aldehyde would be reduced first to a ketyl radical, which would then undergo the above discussed 6-*exo*/6-*exo* radical cyclization cascade. With the tetracyclic cage constructed the ketone would then be reduced to a ketyl anion, which would eliminate the adjacent C–O carboxylate ester[17] and then undergo a second reduction, followed by elimination of methoxy and formation of a samarium enolate. The samarium enolate would then be primed for a perfect *retro*-Michael fragmentation reaction to form the vinigrol core. Thus, in this one pot samarium mediated cascade, two C–C bonds would be formed and two C–O bonds and one C–C bond would be broken.

The tetracyclic core (Fig. 4) is a key intermediate target structure, whose shape we planned to leverage to install the C4, C8, C9 and C12 stereocenters. We were confident that the

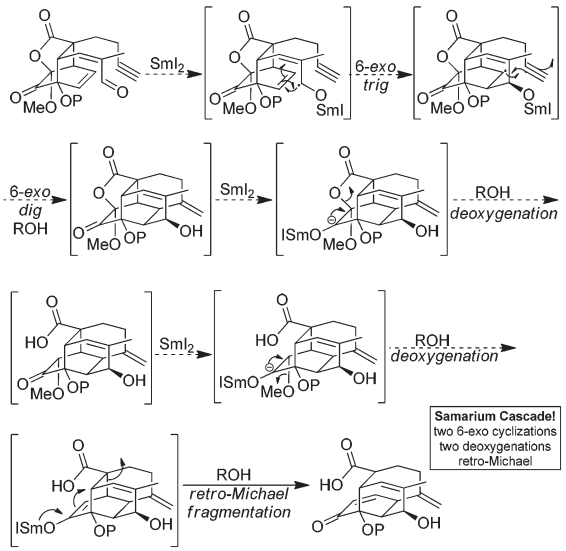


Fig. 3 Samarium(II) diiodide mediated dream cascade.

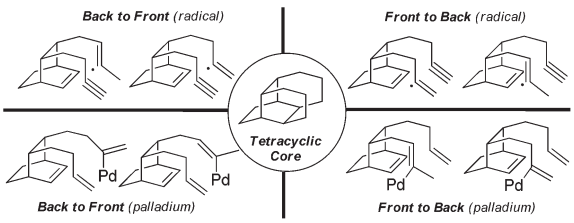


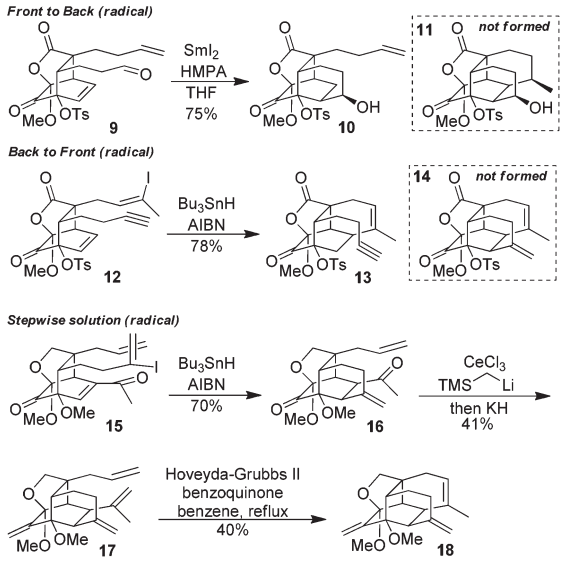
Fig. 4 Tetracyclic core – tandem cyclization choices.

cyclization cascade plans could be realized. Not only because the target rings are of optimal size (six membered), and the cyclization modes are ideal (6-*exo* only), but because the target tetracyclic core provides us with many options to assemble it. For example, a cyclization could be initiated from the front or back and the same vinyl iodide precursor could serve as either an initiating site for a radical or a palladium cyclization cascades.

The following schemes detail the evolution of our synthetic route, with discussion of the obstacles we have faced and how they were overcome to complete the total synthesis of vinigrol.

Result and discussion

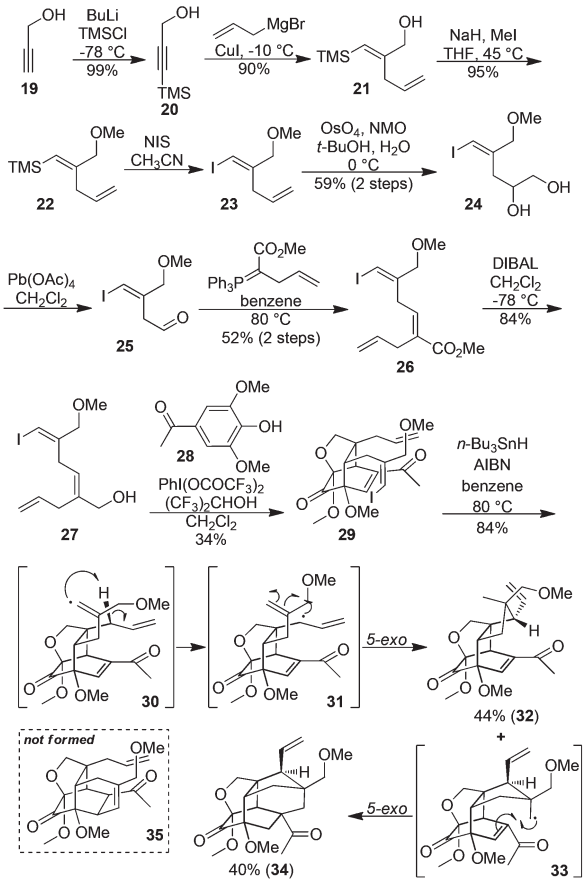
Summarized in Scheme 1 are our earlier cyclization attempts to build the tetracyclic cage.[18] In all cases, the central oxidative dearomatization/Diels–Alder cycloaddition cascade proceeded as expected to deliver the radical cyclization precursors (**9**, **12** and **15**). Attempts to convert aldehyde **9** into tetracyclic cage structure **11**, and realize key elements of the cascade dream presented in Fig. 3, failed to form **11** and only afforded cyclohexanol **10**. We were delighted to learn that as proposed the 6-*exo* ketyl radical cyclization formed the C4-hydroxyl stereocenter with the correct configuration needed for the vinigrol synthesis. Unfortunately, in this "front-to-back" cyclization



Scheme 1 Njardarsons group earlier tetracyclic core attempts.

attempt the intermediate radical reduced faster than it could undergo a second cyclization. Taking advantage of the flexibility of our synthetic route, we synthesized a second substrate (**12**), which we believed would provide the intermediate radical with a better chance of undergoing the second cyclization. We speculated that this new "back-to-front" cyclization substrate had a better shot due to the fact that the starting vinyl radical would form a tri-substituted *endo*-cyclic olefin, thus generating an initial six-membered ring containing two sp^2-hybridized carbon, compared to a ring containing only sp^3-hybridized carbons as in the case of **10**. This difference in hybridization would create more room for the second cyclization to proceed. Furthermore, we also changed the second radical acceptor from a terminal olefin to a terminal alkyne thus creating even more room for the second cyclization to succeed. Despite these significant structural changes, vinyl iodide **12** failed to form tetracyclic cage **14** and only formed mono-cyclization product **13**. We then turned to a stepwise solution wherein a radical mono-cyclization was followed by a ring closing metathesis reaction. Vinyl iodide **15** was cyclized to diketone **16**, which was then subjected to a double Petersen olefination. The resulting tetraene (**17**) was then successfully cyclized to tetracycle **18** using the Hoveyda–Grubbs second generation catalyst[19] in the presence of benzoquinone[20] to suppress unwanted olefin isomerization.

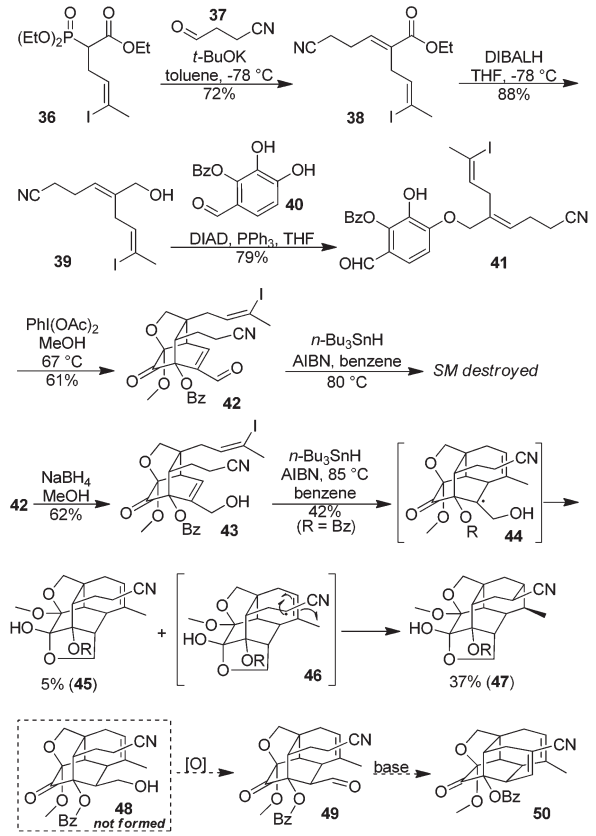
Encouraged by the rapid and successful assembly of tetracycle **18**, we set out to synthesize a more synthetically attractive substrate containing the C16-hydroxy group instead of an undesired methylene carbon at C4 (Scheme 2). Towards that end, cuprate addition to propargylic alcohol **20** afforded diene **21** as a single olefin isomer, which was then protected to afford known allyl methyl ether **22**.[21] Iododesilylation (**23**) followed by selective dihydroxylation and oxidative cleavage of the more electron rich olefin afforded aldehyde **25**. Wittig homologation and reduction of the resulting enoate (**26**)



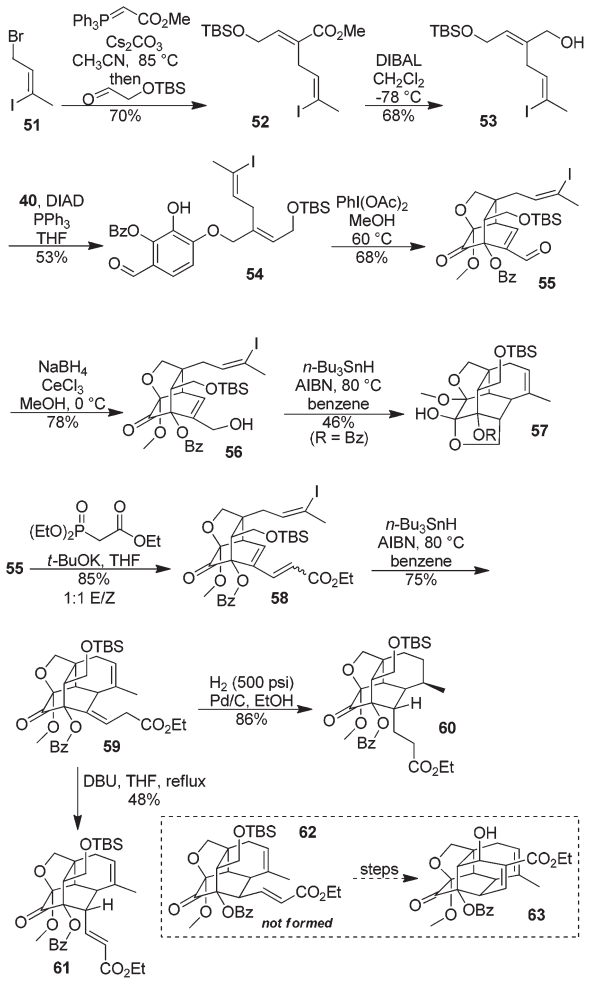
Scheme 2 Modified front to back stepwise radical approach.

yielded allylic alcohol **27**. Oxidative dearomatization of commercially available symmetrical pyrogallol derivative **28** in the presence of excess **27** produced cycloadduct **29** in modest yield. Use of hexafluoro-isopropanol (HFIP) as co-solvent in this reaction is critical for successful trapping of the intermediate cyclic pentadienyl cation with alcohol **27** followed by *in situ* intramolecular Diels–Alder cycloaddition. With **29** in hand we were ready to subject it to the sequence that was so successful in converting **15** to tetracyclic cage **18**. We were surprised and disappointed to learn that none of the desired cyclization product (**35**) was formed. The initially formed radical (**30**) took an unexpected 1,7-hydrogen abstraction pathway (**31**) followed by a 5-*exo* cyclization to form **32** and intermediate **33**, which then underwent a second cyclization to **34**.

Undaunted by this temporary setback, we decided to take advantage of the synthetic flexibility our tetracyclic cage presented us with (Fig. 4). We decided to change the cyclization mode from "front-to-back" (Scheme 2) to "back-to-front" (Scheme 3), and to employ a substrate (**43**) that would be structurally less likely to undergo any unwanted allylic abstractions, and instead, only form desired product **48**. With **48** in hand, our hope was to subject the aldehyde **49** to a simple intramolecular condensation reaction to form tetracyclic cage **50**, which we believed contained all of the necessary functionalities to be advanced to vinigrol.



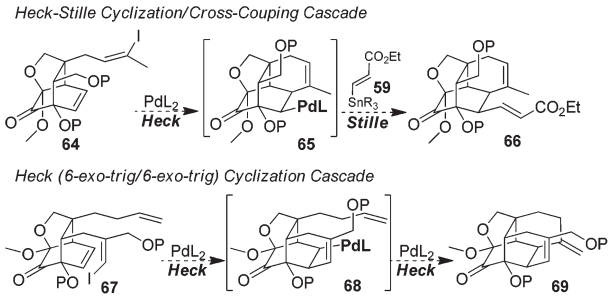
Scheme 3 Modified back to front stepwise radical route.



Scheme 4 2nd modified back to front stepwise radical route.

Our synthesis commenced by a Horner–Wadsworth–Emmons union between known phosphonate **36**[18] and known aldehyde **37**.[22] Dibal reduction of **38** afforded **39**, which was then attached to dearomatization precursor fragment **40**[23] using a Mitsunobu reaction. Our hope was that by connecting the allylic alcohol fragment **39** to the aromatic group there would be no need to use excess alcohol or worry about the efficiency of the trapping of the reactive intermediate, which had plagued formation of **29** earlier. The role of the benzoate group was not only to protect what would eventually become the C8a alcohol, but also to guide the trapping of the dearomatization intermediate with methanol towards the allylic ether site. We were gratified to learn that this design logic was indeed feasible, affording bicyclic product **42** in much higher yield than **29**. Enal **42** turned out to be a poor radical cyclization substrate. Therefore we decided to reduce the aldehyde to an alcohol (**43**). This time, the expected radical cyclization did indeed take place as planned. The only problem was that instead of getting reduced from outside the cage, as **15** had done, radical intermediate **44** was partially reduced to the other epimer (**45**). The bulk of the material underwent an unexpected 1,6-hydrogen abstraction (**46**) followed by a 6-*exo-trig* radical cyclization to form hemiacetal **47** and none of the desired ketone **48**.

Before giving up on the radicals we decided to evaluate one more substrate variation (Scheme 4). To suppress the competing intramolecular hydrogen abstraction pathway, we substituted the propionitrile fragment from Scheme 3 with a TBS-protected methylene alcohol (**56**). Towards that end, we devised a scalable one pot synthesis of enoate **52** from allylic bromide **51**.[24] Mitsunobu reaction with catechol **40** selectively functionalized the more activated phenol. Allylic ether **54** underwent the oxidative dearomatization/intramolecular Diels–Alder cycloaddition reaction to form **55**. Luche reduction then afforded radical cyclization precursor **56**. Treatment of **56** with standard radical cyclization conditions did indeed result in a successful cyclization. Unfortunately, although for this substrate an allylic abstraction pathway was not feasible, we did not get any of the desired product, but instead only **57**, resulting from reduction of the intermediate radical from inside the cage. We felt that this situation could perhaps be salvaged by creating a substrate (**58**) that would not be limited by this unfavorable reduction scenario and would instead allow us to pursue alternate reduction approaches. Olefination of aldehyde **55** proceeded smoothly, affording diene ester **58**. Our hope was that **58** would cyclize to form **62**, which could then be advanced to highly functionalized tetracyclic cage products such as **63**. Although **62** did not form, an alternate

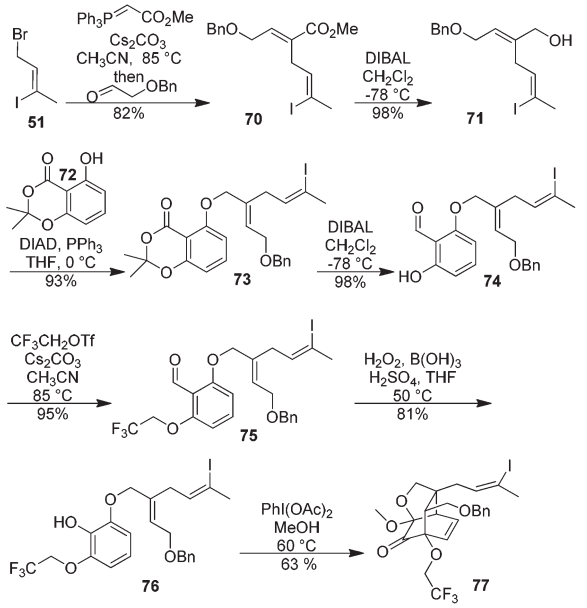


Scheme 5 Retire radicals – begin palladium chapter.

useful product (**59**) was afforded in high yield. This product, *exo*-olefin **59**, is primed for catalytic hydrogenation exploration to set the propionate ester fragment inside the cage for later condensations. Unfortunately, extensive evaluation of diverse set of hydrogenation conditions only afforded ester **60**, which has the incorrect propionate ester epimer. The only silver lining was the confirmation of our substrate controlled hydrogenation thesis to install the C9-methyl group with the correct stereochemistry. We also evaluated bases in attempt to set the correct stereochemistry for the tether, but again, only the undesired epimer (**61**) was formed and none of **62**.

Unable to get the radicals to cyclize to products that we could advance towards vinigrol we turned our focus to palladium cyclizations (Scheme 5). As discussed earlier (Fig. 4), many of our radical cyclization substrates can also serve as palladium cyclization substrates. The advantage of a palladium approach over a radical cyclization approach is that the bond forming is mechanistically controlled (initial *syn*-palladation sets the desired bond relationship) compared to the radicals, which have other pathway choices, such as unwanted reduction and hydrogen abstraction pathways. Of course, when sterics are considered, the radicals are much "smaller" than the palladium intermediates and the question we were most concerned about was whether palladium could operate in such close quarters. We decided to evaluate two complementary approaches. The first would involve an initial 6-*exo-trig* Heck cyclization (**64** → **65**) followed by an intermolecular Stille cross-coupling between hindered palladium intermediate **65** and stannane partner, such as **59**. The second scenario is reminiscent of key parts of our dream sequence (Fig. 3), wherein a tandem 6-*exo* cyclizations was envisioned to stitch up the tetracyclic cage in one swoop. In this case, we plan to evaluate the palladium catalyzed conversion of **67** to **69**.

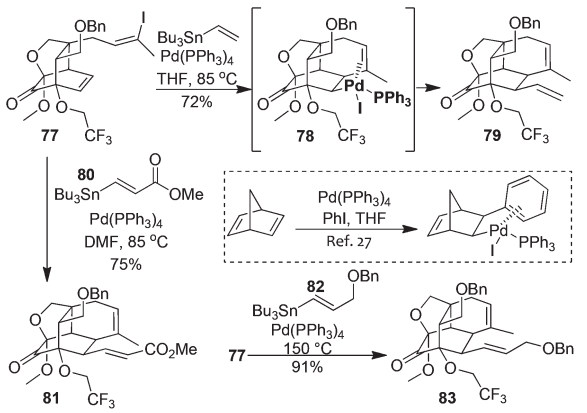
Our route towards the first palladium cyclization test substrate (**77**) is shown in Scheme 6. Enoate **70** was made in one pot from **51** and then reduced to allylic alcohol **71**. Phenol **72** was used for the Mitsunobu coupling. Selective derivatization of pyrogallol or simply pyrogallol precursors failed to provide reliable and efficient access to **76**, which is why pyrogallol surrogate **72**[25] was employed. Reduction of **73** afforded resorcinol derivative **74**. Our next task was to derivatize the phenol with an electron withdrawing group whose primary purpose would be to direct the oxidative dearomatization reaction and to tame



Scheme 6 Palladium (route 1) – oxidative dearomatization.

the resulting enol ether moiety so that the intramolecular Diels–Alder cycloaddition could proceed. Earlier (**9**, **12**, **41** and **54**) we had used either a sulfonamide or a benzoate for this purpose. Unfortunately these groups did not survive or drastically impeded the Dakin oxidation needed to form the oxidative dearomatization precursor. To solve this we needed an electron withdrawing group that was more robust, smaller and slightly less deactivating. We chose a trifluoroethyl group for this purpose (**75**). Dakin oxidation of **75** proceeded fantastically well when boronic acid[26] was used as an additive (**76**). The proposed oxidative dearomatization/Diels–Alder cycloaddition cascade proceeded favorably to form desired product **77** using trifluoroethyl ether as a deactivating group.

With vinyl iodide **77** in hand we were now in a position to test the first palladium cyclization hypothesis (Scheme 7). We were delighted to learn that upon treatment with vinyl tributylstannane and a palladium(0) catalyst, **77** was converted in high



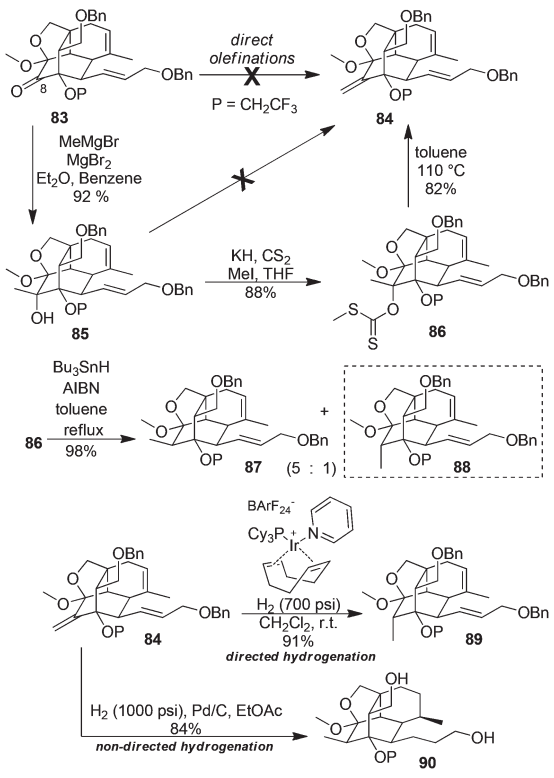
Scheme 7 Palladium (route 1) – cascade works.

yield to desired diene product **79**. Interestingly, when this reaction was done with a stoichiometric amount of palladium we could isolate and characterize rare palladium intermediate **78**,[27] which could then be treated with vinyl tributylstannane to form **79**. More functionalized stannanes **80** and **82** also participated in this palladium cascade in partnership with **77** to form **81** and **83**, respectively.

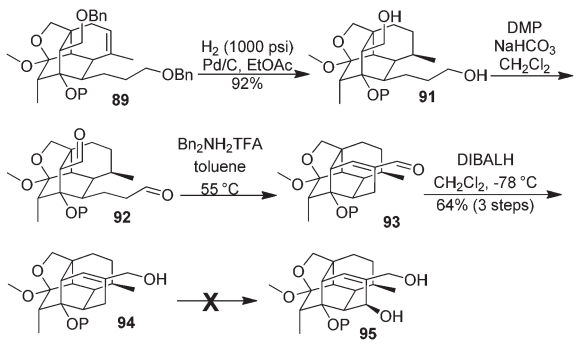
Following a successful execution of the proposed palladium cascade, we decided next to tackle olefination of the C8-ketone (**84**, Scheme 8). For this task we chose to employ ketone **83**. We were hopeful that this could be accomplished in a single step as we had done for ketone **16** (Scheme 1) using a Peterson olefination protocol. We were not surprised to learn that standard Wittig and Julia olefination type processes failed to convert **83** to **84** as this was a lesson we had also learned for **16**. We were hopeful that the Peterson approach would work. Unfortunately, the slight structural change from a methyl- (**16**) to a trifluoroethyl- (**83**) protected C8a-alcohol was enough to block this olefination approach. We reasoned that a smaller nucleophile was needed to address this challenge, and we turned our attention to addition of a methyl group with the goal of dehydrating the resulting tertiary alcohol (**85**). Addition of a methyl Grignard reagent to **83** was successful, but resulted in the formation of a poor epimeric mixture of **85**. This in theory should be inconsequential for the following step(s), but we soon learned that it was easier to further functionalize or activate *endo*-epimer **85** than the *exo*-epimer of **85**. This temporary obstacle was solved by performing the Grignard addition in the presence of magnesium bromide,[28] which resulted in the exclusive formation of **85**. Direct dehydrations to form **84** from **85** were low yielding and inconsistent. We solved this dehydration problem by derivatizing **85** as a xanthate (**86**) and then subjecting it to a thermal Chugaev elimination to form triene **84**. Xanthate **86** provided us with an opportunity to set the C8-methyl stereocenter using radical reduction protocols. We evaluated several initiators and hydride sources. Although the reduction of the xanthate proceeded in high yield, the epimeric C8-mixture was in all cases highly unfavorable, with the undesired epimer (**87**) being the major one. To further complicate things, low level calculations and epimerization studies of the ketone resulting from opening of the acetals of **87** and **88** revealed that epimer **87** was the thermodynamically favored one.

We constructed triene **84** in hopes that we could form **91**, wherein in one pot three double bonds would be reduced and two benzyl groups cleaved and in doing so installing the critical methyl stereocenters C8 and C9. Using high pressure and a palladium catalyst we could indeed reduce everything we wanted to in one pot. The only problem was that the C8 olefin reduction resulted in the formation of the incorrect methyl epimer (**90**). This presented us with a major obstacle, as clearly the tetracyclic shape was resisting functionalization as evident from our reduction and epimerization attempts. We wondered whether it would be possible to use the ethers of the adjacent acetal to direct the hydrogenation of the C8-exocyclic olefin. For this to be successful, the catalyst would need to preferentially bind to the furanyl ether over the methyl ether. It was not clear *a priori* if a catalyst directed reaction could even be accomplished in such a sterically congested setting and if any selectivity could be expected. Undeterred by these uncertainties, we set out to evaluate this approach. After extensive experimentation we found an excellent solution in the form of Pfaltz's[29] version of Crabtree's catalyst.[30] Using this catalyst and high pressure of hydrogen, we were able to convert triene **84** to **89** with complete C8-selectivity.

With **89** in hand, we set out to complete a synthesis of the tetracyclic cage and further advance towards vinigrol (Scheme 9). Exhaustive reduction of **89** in the presence of palladium on carbon and high pressure of hydrogen reduced the remaining olefin and cleaved the benzyl protecting groups



Scheme 8 Palladium (route 1) – C8-methyl installation.



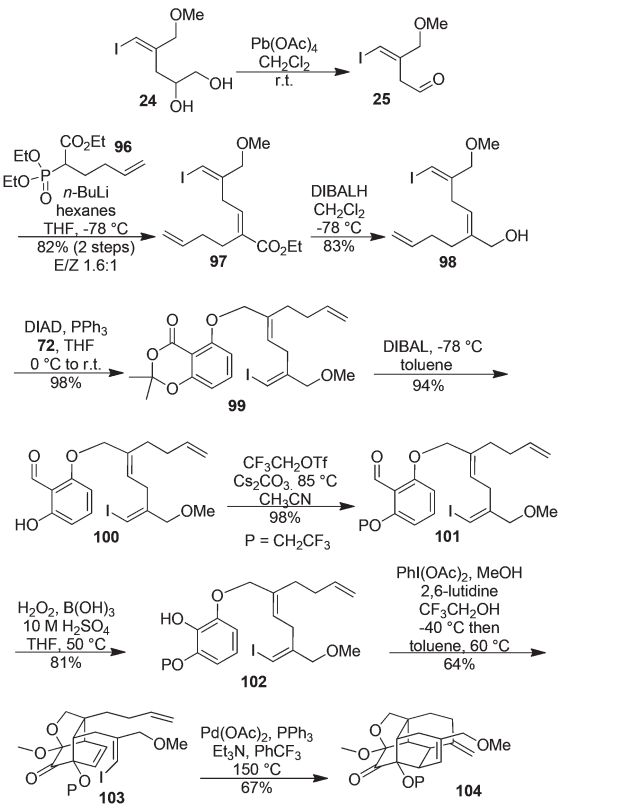
Scheme 9 Palladium (route 1) – tetracyclic cage synthesis.

(**91**). As demonstrated earlier for reduction of **59** and **84**, the C9-methyl stereocenter of **91** was predictably set using substrate control. Both alcohols were then converted to aldehydes (**92**) and then subjected to a condensation reaction mediated by dibenzyl ammonium trifluoroacetate[31] to stitch up the tetracyclic cage (**93**). With this exciting milestone behind us, we set out to install the C4-hydroxyl group (**95**), the last remaining challenge before unraveling the vinigrol core *via* a fragmentation. Unfortunately, all attempts to access **95** from **93** or **94** in one step or many using directed or non-directed strategies met with failure.

The failure of forming **95** could be contributed to a sterically congested system, wherein the six-membered ring that needs to be functionalized is permanently locked in a boat conformation with the C8a-protected hydroxyl group in axial position thus blocking approach of reagents. Our extensive explorations provided us with a key clue when we learned that a directed epoxidation of **94** (not non-directed) was possible. Although this product could not be advanced we used these insights to guide our next strategic decision, which was to target the tri-substituted olefin isomerized variant of **94**. We were confident that this isomer could also be epoxidized, thus installing the C4-hydroxyl stereocenter directly. In order to quickly put this hypothesis to the test, we first tried to catalytically isomerize the olefin of **94**. Unfortunately, all such attempts failed. We therefore set out to execute our next blueprint.

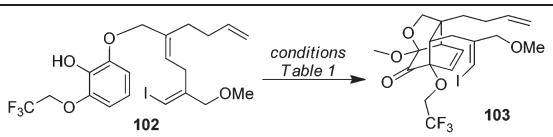
Inspired by the palladium cascade cyclization success of vinyl iodide **77**, we decided that this would be a perfect opportunity to test the double Heck cyclization cascade[32] outlined in Scheme 5. Towards that end, we set out to synthesize the requisite palladium cyclization precursor (**103**, Scheme 10). This was accomplished using the synthetic lessons from our earlier sequences. Horner–Wadsworth olefination of aldehyde **25** with known phosphonate **96**[33] afforded enoate **97** (Scheme 10). Ester reduction, Mitsunobu coupling with **72** and reduction of the lactone afforded aldehyde **100**. Trifluoroethyl ether protection and Dakin oxidation proceeded uneventfully. Oxidative dearomatization of phenol **102** then afforded palladium cyclization precursor **103**. We were delighted to learn that our proposed 6-*exo-trig*/6-*exo-trig* palladium cyclization cascade could indeed be realized (**104**) with relatively standard reaction conditions apart from the choice of solvent (trifluorotoluene). Remarkably, the complex and compact tetracyclic core was assembled from a simple achiral acyclic precursor (**102**) in only two steps using this approach.

The conditions needed to convert **102** to **103** are worth discussing as they differ significantly from the standard reaction conditions we had applied for **41**, **54** and **76**. Key insights into our extensive optimizations of this reaction are shown in Table 1. Attempts to apply the same reaction conditions used before were met with little success, producing the desired product in only 10% yield. Changing the solvent or increasing the temperature did not provide any improvements. We suspected that the oxidant (phenyliodonium diacetate, PIDA) was slowly decomposing at higher temperatures. Using this clue, we performed the oxidative dearomatization at lower temperatures (−78 °C and −40 °C), and the applied heat once we were convinced the oxidation was completed to aid the subsequent intramolecular Diels–Alder cycloaddition (60 °C). These modifications resulted in marginally improved yields (15%). It is



Scheme 10 Palladium (route 2) – tetracyclic cage synthesis.

Table 1 Oxidative dearomatization optimization studies



Solvent	Temp.[a] (°C)	Base	Time[a] (hours)	Conc.[b] (M)	Yield
MeOH	60, 60	—	2.5, 4.0	0.01	10%
DCM	60, 60	—	2.0, 1.5	0.01	10%
Toluene	60, 60	—	2.5, 4.0	0.01	6%
Toluene	110, 110	—	1.5, 2.0	0.01	0%
MeOH	−78, 60	—	1.0, 3.0	0.01	15%
MeOH	−40, 60	—	1.0, 2.0	0.01	15%
CF_3CH_2OH	−40, 60	—	1.0, 2.0	0.01	21%
CF_3CH_2OH	−40, 60	$NaHCO_3$	1.0, 2.0	0.01	30%
CF_3CH_2OH	−40, 60	2,6-Lutidine	1.0, 2.0	0.01	35%
CF_3CH_2OH	−40, 60	2,6-Lutidine	1.0, 2.0	0.005	53%
CF_3CH_2OH	−40, 60	2,6-Lutidine	1.0, 2.0	0.0025	64%

[a] First number refers to the temperature/addition time during addition of oxidant (PIDA) while the second number refers to the reaction temperature and time post addition of oxidant. [b] Final concentration. For large scale batches the reaction was diluted with toluene.

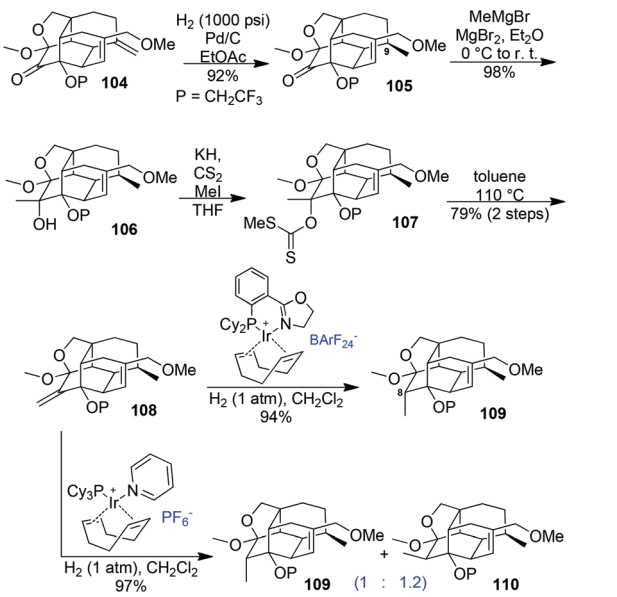
well established that trifluoroethanol can be a beneficial solvent for oxidative aromatization reactions.[34] When we employed trifluoroethanol, the reaction yield doubled as compared to the first run (21%). An inorganic base ($NaHCO_3$) was then added to the reaction in efforts to neutralize the reaction (the oxidant releases acetic acid) and suppress unwanted acid catalyzed decompositions. This modification further improved the yield to 31%. Using 2,6-lutidine instead of $NaHCO_3$ resulted in slightly better and consistent results. The final optimization modification, which resulted in a significant improvement in yield (53% and 64%), was to dilute the reaction. Our reason for dilution was that the intermediate reactive diene could perhaps more readily undergo self dimerizations instead of the desired intramolecular cycloaddition and that this competitive pathway could be blocked by controlling the concentration of the reaction. In a typical procedure, the starting material was dissolved in trifluoroethanol and cooled to −40 °C, 2,6-lutidine was then added, followed by dropwise addition of PIDA (1.05 equivalents). After stirring at −40 °C for 1.0 h, the reaction solution was diluted with trifluoroethanol to the concentration of 0.0025 M. The solution was then heated to 60 °C and stirred for 2 hours. Removal of solvent and 2,6-lutidine *in vacuo* followed by silica gel column chromatography afforded 64% yield of desired compound.

With tetracyclic structure **104** in hand we were ready to apply the cage functionalization lessons of **83** (Scheme 11). We decided to alter the sequence of events slightly, by first hydrogenating the C9-*exo*-olefin to form the C9-methyl stereocenter (**105**). Grignard addition (**106**) and the Chugaev elimination approach, which we had developed, worked and provided us with *exo*-olefin **108**.

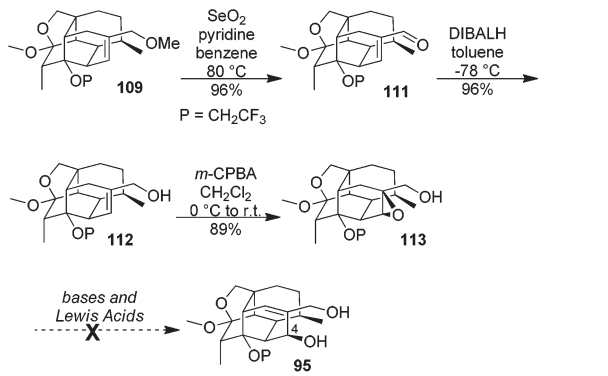
In trying to replicate the excellent directed hydrogenation results we had achieved earlier (**84**, Scheme 8) for **108** we found that using the Pfaltz ligand system[28] instead of the Crabtree ligand system, while still maintaining the same counterion, to be more reproducible and reliable in accessing **109**. Using this catalyst, the C8-methyl stereocenter was selectively and efficiently installed. When the usual Crabtree catalyst is employed, the *exo*-olefin is reduced but with no selectivity.

With the C8 and C9-methyl stereocenters successfully set, we focused our attention to installing the secondary C4-hydroxyl group. We had hypothesized, based on our earlier results, that the sterically congested tri-substituted olefin could be epoxidized using a directed approach. Allylic methyl ether **109** was selectively transformed to enal **111** using selenium dioxide.[35] Reduction afforded allylic alcohol **112**, which we were delighted to learn underwent a smooth and selective epoxidation (**113**). With the C4-oxygen correctly installed we needed to find a way to convert epoxy alcohol **113** to allylic diol **114** and thus complete the vinigrol pre-fragmentation core. However, attempts to open epoxide **115** with bases or Lewis acids[36] proved unfruitful, leading to unreacted starting material, decomposition or unproductive reductive opening of the epoxide.

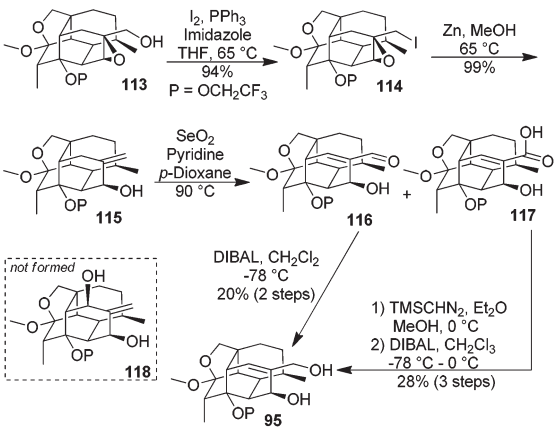
With one step conversions of **113** to **114** unsuccessful, we turned our focus to alternative solutions (Scheme 13). Towards that end, alcohol **113** was iodinated (**114**) and the iodide was treated with zinc[37] to open the epoxide and form **115**. Our plan was to use allylic oxidation approaches to convert **115** to **95**.



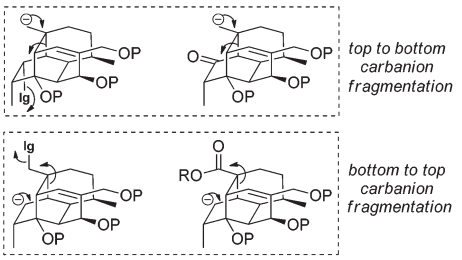
Scheme 11 Palladium (route 2) – C8 and C8-methyl groups.



Scheme 12 C4-hydroxyl installation attempts.



Scheme 13 Palladium (route 2) – installing C4-hydroxyl.

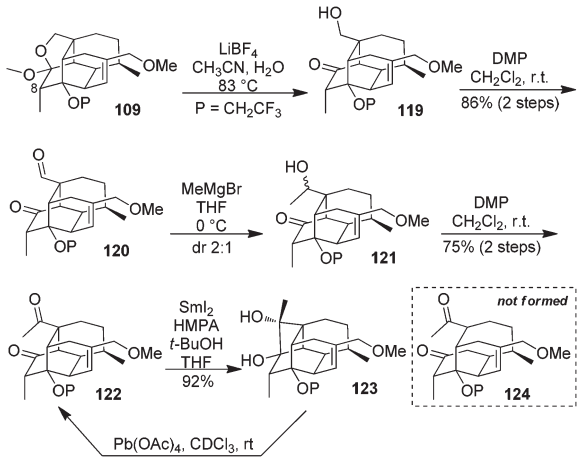


Scheme 14 Carbanion mediated fragmentation options.

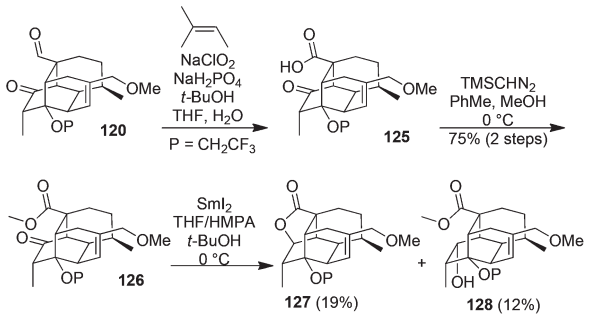
Interestingly, when *exo*-olefin **115** was treated with selenium dioxide none of the typical product (**118**) was formed, but instead a mixture of **116** and **117**. This welcomed result was one in which the steric hindrance of the cage again played a key role by interrupting the second step of the selenium oxidation resulting in a dissociation/recombination[38] instead of a sigmatropic rearrangement. The aldehyde and acid oxidation states are the result of selenium dioxide over oxidation. Aldehyde **116** was converted in a single step to **95**, while carboxylic acid **117** was esterified prior to being reduced to **95**.

Two types of fragmentation approaches were most appealing to us (Scheme 14), a Grob fragmentation[39] (two left images, lg = leaving group) and a samarium(II) iodide[40] mediated fragmentation (two right images). In both cases, we envisioned that the fragmentation could be initiated by a carbanion or a ketyl radical from either the top or the bottom of the tetracyclic cage. Although the most common form of samarium(II) iodide mediated C–C cleavages is that of strained ring systems, especially cyclopropane and cyclobutane systems, examples of larger ring or no-strain systems are rare in the literature.[41] We believed that, in the case of vinigrol such a fragmentation is feasible due to favourable release of strain energy when the tetracyclic cage is opened.

Our first fragmentation substrate (**122**, Scheme 15) was readily prepared in few steps from acetal **109**. The most critical step of this short sequence was the opening of the acetal without epimerization of the adjacent C8-methyl stereocenters. This was accomplished using lithium tetrafluoroborate.[42] Oxidation of the resulting alcohol (**119**), methyl Grignard addition and oxidation of secondary alcohol **121** afforded diketone fragmentation precursor **122**. Surprisingly, when **122** was subjected to the reaction conditions reported to be successful for samarium(II) diode mediated 1,4-diketone fragmentations, the expected C–C fragmentation (**124**) did not take place, instead pinacol coupling product **123** was the only product isolated. In addition to the convincing 2D-NMR characterization data, the structure of **123** was further confirmed when it was treated with lead(IV) acetate and was shown to clearly revert back to **122**. We wondered if the samarium intermediate was forming a chelate between the two ketyl moieties, and that this chelate was favoring formation of **123**. It has been reported that HMPA[43] is effective in preventing or slowing down such chelates in samarium reactions. Unfortunately, in our case it did not alter the outcome.



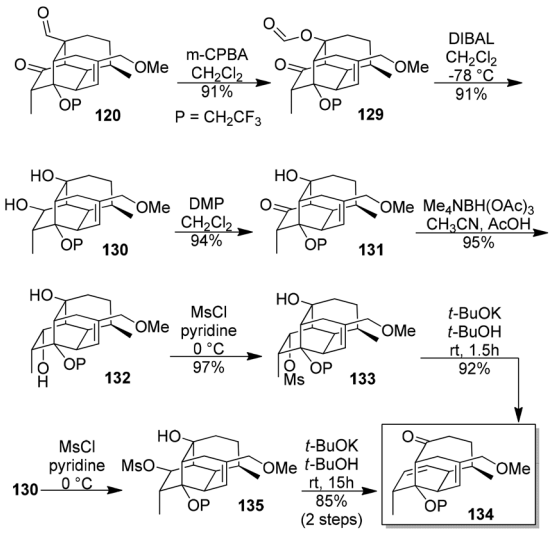
Scheme 15 Samarium diketone fragmentation attempt.



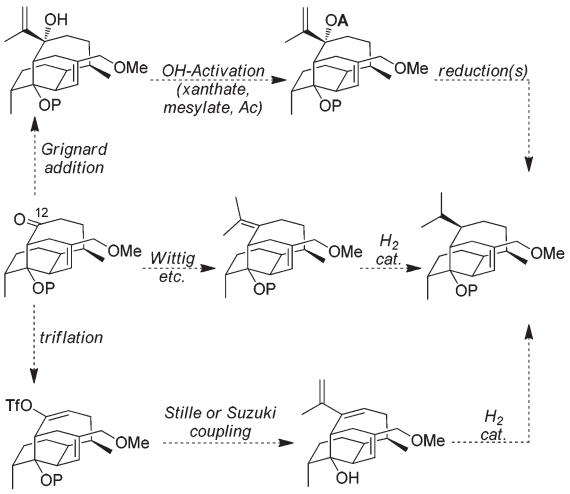
Scheme 16 Samarium keto-ester fragmentation attempt.

Dissatisfied with the failure of the samarium fragmentation of diketone **122** we decided to synthesize a different 1,4-dicarbonyl fragmentation substrate that would be less likely to undergo a pinacol coupling (**126**, Scheme 16). Synthesis of ester **126** was accomplished in two standard steps from aldehyde **120**. Again, our samarium mediated fragmentation plans failed as the only isolable products from our fragmentation attempts were lactone **127** and alcohol **128**, both resulting from protonation of the desired ketyl intermediate.

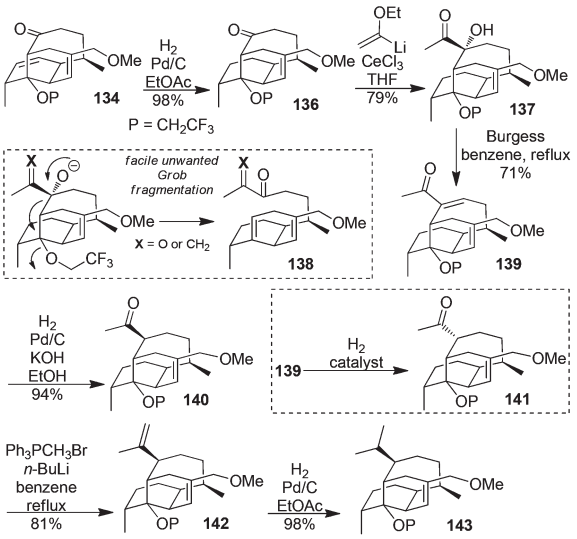
The unsuccessful attempts of samarium(II) iodide meditated fragmentation prompted investigation into a more reliable Wharton fragmentation strategy, wherein compounds **133** and **135** would be the target of synthesis (Scheme 17). From the standpoint of orbital overlap most suitable for the Wharton fragmentation, mesylate **133** was considered optimal (perfect *anti*-periplanar arrangement of relevant orbitals), while mesylate **135** offered a far less satisfactory orbital overlap. Although the stereoelectronic all-*anti* arrangement is the general prerequisite for such Wharton-type fragmentations, there are a number of examples in the literature[44] of less than ideally overlapping orbital arrangements leading to successful fragmentations. Entry into this fragmentation mode was made possible by a remarkably selective and high yielding Baeyer–Villiger oxidation of aldehyde **120**. Exhaustive reduction of **129** afforded diol **130**, which could be converted



Scheme 17 Wharton fragmentation – vinigrol core.



Scheme 18 Strategies for installing the C12-isopropyl group.



Scheme 19 Installation of C12-isopropyl group.

to Wharton-fragmentation candidate **135** by selectively mesylating the secondary alcohol. Perfectly aligned fragmentation substrate **133** needed some additional synthetic planning. Oxidation of diol **130** afforded ketone **131**, which could be converted selectively to diol **132** by employing a directed reduction strategy in the form of the Evans–Saksena[45] reduction protocol. Mesylation of the secondary alcohol then afforded **133**. We were delighted to learn that mesylates **133** and **135** both fragmented in excellent yields to vinigrol core **134**. Although mesylate **135** takes ten times longer to complete the fragmentation reaction it more importantly shortens the synthetic sequence to **134** by two steps.

With large quantities of **134** in place we set out to convert the ketone to the appropriately configured C-12 isopropyl group (Scheme 18). We considered three main approaches: (1) olefination of the ketone followed by hydrogenation, (2) conversion of the ketone to an enol triflate, which could then be converted into a 1,3-diene ready for catalytic hydrogenations and (3) isopropyl/isopropenyl addition to the ketone followed by reduction of the resulting tertiary alcohol.

Although such strategies are well documented in the literature,[46] we quickly learned that the Wittig-type and enol triflate approaches failed for ketone **134**. We therefore focused our attention to the isopropenyl addition approach. We envisioned that the olefin could be hydrogenated and that the tertiary alcohol could be deoxygenated using xanthate or sulfonate ester reduction strategies. Alternatively, the alcohol could be dehydrated and then hydrogenated. It was not clear if these reduction approaches would set the correct C-12 stereochemistry. We were reasonably confident that the alcohol reduction approaches would afford the desired stereochemical outcome as our calculations had indicated that the natural C-12 isopropyl group configuration is more stable than its epimer.

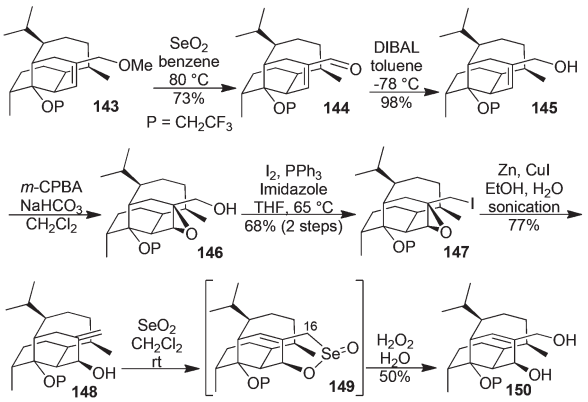
Our C-12 isopropyl installation efforts commenced with reductive removal of the newly formed olefin (**136**, Scheme 19). We chose to first use propenyl nucleophiles for additions to the ketone as it is well known that isopropyl organometallics are notoriously problematic due to a competing hydride delivery pathway. Grignard and lithium additions failed, but the corresponding cerium vinyl reagent worked excellently.[47] In our attempts to functionalize the resulting tertiary allylic alcohol as a xanthate, acetate or a mesylate is where we ran into a major unprecedented obstacle. Regardless of base or conditions we employed (large, small, strong or weak base using low or high temperatures in a range of solvents) an unwanted facile fragmentation took place. This is the first reported example of a Grob fragmentation wherein a trifluoroethyl ether serves the role of a leaving group. We decided to instead explore if direct dehydrations of the tertiary alcohol would allow us to navigate around this serious obstacle. Towards that end we changed the cerium nucleophile to the anion of ethyl vinyl ether, which following addition and *in situ*

delicately controlled hydrolysis afforded ketone **137**. After much experimentation we finally learned that Burgess reagent[48] could convert **137** to enone **139**, without falling prey to the competing fragmentation pathway.

With this major obstacle behind us, we turned our attention to the reduction of the enone double bond, with the hope of forming methyl ketone **140** preferentially over its epimer (**141**). We first explored conjugate reduction approaches using either Selectrides or copper hydrides. Both approaches were unsuccessful, affording either a 1,2-reduction or a complex mixture of products. When typical palladium catalyzed conditions (Pd/C) were employed, the enone olefin was indeed reduced but undesired ketone epimer **141** was the major product. We were gratified to learn, which was also in agreement with our calculations, that epimer **141** could be isomerized with base to desired product **140**. This approach was unsatisfactory due to the fact that these hydrogenation conditions also generated some unidentified by-products and that the reaction was found to be irreproducible. Although the reason for this was unclear, we speculated that the slightly acidic surface of the "neutral" catalyst was resulting in the partial decomposition of the vinigrol framework. To alleviate these problems, we decided to perform the hydrogenation in the presence of potassium hydroxide[49] with the hope that any unwanted acid catalyzed reactions would be suppressed and that an *in situ* epimerization would take place mediated by the base (KOH). This strategy worked wonderfully and ensured excellent and selective conversion of **139** to **140**. The isopropyl C-12 stereocenter of vinigrol was then completed using a standard olefination/reduction strategy (**143**).

With post-fragmentation allylic ether **143** in hand we set out to test if the chemistry we had developed for converting **109** to **95** (Schemes 12 and 13) could also be realized for this substrate. Selenium oxidation and DIBAL reductions proceeded uneventfully, affording allylic alcohol **145**. We were pleased to learn that the critical directed epoxidation step responsible for incorporating the C3-oxidation state with correct configuration also worked for **145**, as did the iodination step. We found the zinc mediated epoxy ring opening of **147** to be more challenging than for **114**, but by using sonication[50] the reaction proceeded smoothly to afford *exo*-olefin **148**. The outcome of the selenium oxidation for **148** also differed significantly from that of tetracyclic cage compound **115**. Gratifyingly, the second step of the mechanism of the selenium oxidation was again interrupted, thus providing us directly with the desired tri-substituted olefin (Scheme 20).

While oxidation of **115** afforded enal **116** and conjugated acid **117**, none such products were observed for **148**. Instead, the different conformation of the post-fragmentation core resulted in trapping of the selenium intermediate with the C4-hydroxyl group and formation of stable selenium heterocycle **149**. We were now confronted with oxidizing the C-16 selenium bond to a primary hydroxyl group (**150**). Based on limited literature on this subject, it was suggested that selenonic acids could be oxidized to selenonic acids by sodium periodate[51] or dimethyldioxirane (DMDO)[52] and then displaced by a

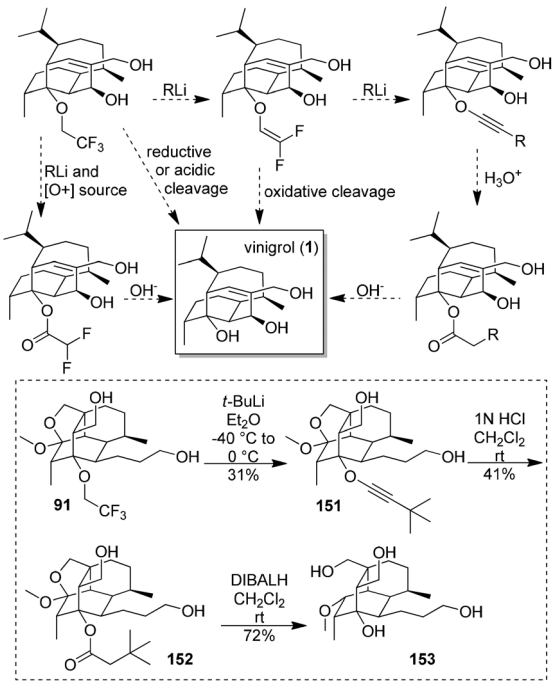


Scheme 20 Selenium adventures – installing C4-hydroxyl.

nucleophile, such as I^- or H_2O. We wondered if hydrogen peroxide could serve the role of both oxidant and nucleophile in converting **149** to **150**, which in turn would make it possible to perform the oxidation of **148** to **150** in one pot as these oxidizing agents are compatible.[53] This approach worked well, affording desired diol **150**.

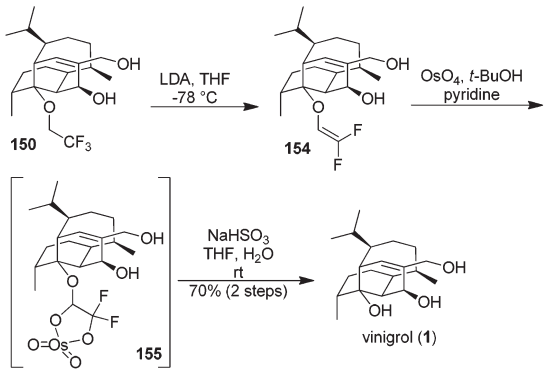
With the installation of the C4-hydroxyl group behind us, the final obstacle of the total synthesis of vinigrol we faced was the cleavage of the trifluoroethyl group. First, it is worth noting that a trifluoroethyl group has never been used as a protecting group in synthesis. With very few scattered examples of this rather stable motif being explored in the literature, deprotection conditions that were compatible with the rest of the vinigrol architecture were sought. Several strategies were investigated (Scheme 21). It is reported that trifluoroethyl ethers can be converted to base-labile esters by trifluoroacetic acid.[54] Vinigrol's susceptibility to acid obviously precluded this harsh approach. A reductive approach using sodium naphthalene[55] as a reducing agent only resulted in unreacted starting material (**150**). It is also known that trifluoroethyl ethers can be converted to acetylenic esters using alkyllithium reagents,[56] *via* a difluorovinyllithium intermediate. This is especially interesting to us because in Baran's approach to vinigrol,[15] he demonstrated in the final step that vinigrol was compatible with strong bases such as *n*-BuLi. We were curious to learn what product would result if **150** was submitted to strong bases. For example, if a difluorovinyl ether was obtained, it could potentially be cleaved under oxidative conditions. Alternatively, if the acetylenic ether shown was obtained, it could be easily hydrolyzed and cleaved. The difluorovinyl ether could be deprotonated again and trapped with an electrophilic oxygen reagent en route to vinigrol.

To evaluate the feasibility of these plans, test compound **91** was treated with large excess of *tert*-butyl lithium in diethyl ether at −40 °C (Scheme 21). To our delight, acetylenic ester **151** was obtained, albeit in poor yield (31%). Brief and careful exposure of **151** to acid then afforded ester **152**, which was reduced to free alcohol **153**. Armed with these promising, but far from ideal results we decided to test it on protected vinigrol (**150**).



Scheme 21 Strategies for removing $-CH_2CF_3$ group.

Unfortunately, when we applied the alkyl lithium conditions used for **91** to **150**, only small amounts of difluorovinyl ether **154** were formed along with extensive decomposition of starting material. All attempts to form and trap the difluorovinyl ether anion with electrophilic oxygen reagents such as molecular oxygen,[57] 2-sulfonyloxaziridine (Davis's oxaziridine),[58] molybdenum peroxide–pyridine–hexamethylphosphoramide (MoOPH),[59] and bis(trimethylsilyl)peroxide (TMSOOTMS)[60] also failed. We therefore turned our attention towards selective formation of **154** (Scheme 22). This could be accomplished by using LDA instead of alkyl lithium bases. We hypothesized that the vinyl enol ether could be oxidatively cleaved selectively over the tri-substituted olefin, which we had shown so many times to be resistant to reductions and oxidations because of its steric nature. Osmium tetraoxide[61] satisfied our criteria and was shown to selectively oxidize **154**.



Scheme 22 Successful synthesis – deprotection of CH_2CF_3.

Interestingly, the intermediate osmate ester (**155**) was surprisingly stable and needed extensive exposure to a reductive workup conditions to afford vinigrol (**1**).

Conclusion

This article describes the synthetic journey we took that eventually resulted in a successful total synthesis of vinigrol. Although our route evolved significantly over time with respect to the exact nature of reaction sequences, its fundamental retrosynthetic design principles (oxidative dearomatization/Diels–Alder cycloaddition, 6-*exo*/6-*exo* cyclization cascade, tetracyclic cage substrate control and fragmentation) have remained the same. Many useful lessons and observations can be taken from our journey, which are broadly impactful. For example, we demonstrated for the first time the usefulness of a trifluoroethyl group as both an oxygen protecting group[62] and a valuable directing group for oxidative dearomatization reactions as well as role a leaving group in a Grob fragmentation. We revealed intriguing radical as well as uncommon selenium oxidation behavior in rigid and dense architectural frameworks. Intriguing examples of substrate controlled and functional group directed hydrogenations are particularly noteworthy. Our synthetic explorations showcase the power and reliability of the oxidative dearomatization/Diels–Alder cascade in rapidly building molecular complexity, and it emphasizes the future value in developing a robust and predictable asymmetric oxidative dearomatization protocol for converting stable aromatic building blocks into reactive valuable chiral products with many available reaction modes.

Acknowledgements

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Notes and references

1 For examples of recently isolated diterpenoids, consults: (*a*) J. R. Hanson, *Nat. Prod. Rep.*, 2012, **29**, 890–898; (*b*) J. R. Hanson, *Nat. Prod. Rep.*, 2011, **28**, 1755–1772; (*c*) J. R. Hanson, *Nat. Prod. Rep.*, 2009, **26**, 1156–1171; (*d*) J. R. Hanson, *Nat. Prod. Rep.*, 2007, **24**, 1332–1341 and earlier reports in this series.

2 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325–2327.

3 (*a*) T. T. Dabrah, H. J. Harwood, L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien and P. C. Watts, *J. Antibiot.*, 1997, **50**, 1–7; (*b*) T. T. Dabrah, T. Kaneko, W. Massefski Jr. and E. B. Whipple, *J. Am. Chem. Soc.*, 1997, **119**, 1594–1598.

4 K. Zechmeister, F. Brandl, W. Hoppe, E. Hecker, H. J. Opferkuch and W. Adolf, *Tetrahedron Lett.*, 1970, **47**, 4075–4078.
5 A. A. Adesomoju, J. I. Okogun, M. P. Cava and P. J. Carroll, *Heterocycles*, 1983, **20**, 2125–2128.
6 J. T. Njardarson, C. Gaul, D. Shan, X.-Y. Huang and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 1038–1040.
7 N. A. McGrath, C. A. Lee, H. Araki, M. Brichacek and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2008, **47**, 9450–9453.
8 N. A. McGrath, E. S. Bartlett, S. Sittihan and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2009, **48**, 8543–8546.
9 D. J. Mack and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2013, **52**, 1543–1547.
10 Q. Yang, J. T. Njardarson, C. Draghici and F. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 8648–8651.
11 I. Uchida, T. Ando, N. Fukami, K. Yoshida, M. Hashimoto, T. Tada, S. Koda and Y. Morimoto, *J. Org. Chem.*, 1987, **52**, 5292–5293.
12 (*a*) T. Ando, Y. Tsurumi, N. Ohata, I. Uchida, K. Yoshida and M. Okahura, *J. Antibiot.*, 1988, **41**, 25–30; (*b*) T. Ando, K. Yoshida and M. Okahura, *J. Antibiot.*, 1998, **41**, 31–35; (*c*) D. B. Norris, P. Depledge and A. P. Jackson, *PCT Int. Appl. WO* 9107 953, 1991; (*d*) H. Nakajima, N. Yamamoto, T. Kaizu and T. Kino, *Jpn. Kokai Tokkyo Koho JP* 07206668, 1995; (*e*) J. T. Keane, *PCT Int. Appl. WO* 20011000229, 2001; (*f*) H. Onodera, M. Ichimura, K. Sakurada, A. Kawabata and T. Ota, *PCT Int. Appl. WO* 2006077954, 2006; (*g*) H. Onodera, M. Ichimura, K. Sakurada, A. Kawabata and T. Ota, *PCT Int. Appl. WO* 2006077954, 2006.
13 (*a*) J.-F. Devaux, I. Hanna and J.-Y. Lallemand, *J. Org. Chem.*, 1993, **58**, 2349–2350; (*b*) J.-F. Devaux, I. Hanna, P. Fraisse and J.-Y. Lallemand, *Tetrahedron Lett.*, 1995, **36**, 9471–9474; (*c*) J.-F. Devaux, I. Hanna, J.-Y. Lallemand and T. Prange, *J. Chem. Res. Synth.*, 1996, 32–33; (*d*) G. Mehta and K. S. Reddy, *Synlett*, 1996, 625–627; (*e*) M. Kito, T. Sakai, N. Haruta, H. Shirahama and F. Matsuda, *Synlett*, 1996, 1057–1060; (*f*) J.-F. Devaux, I. Hanna and J.-Y. Lallemand, *J. Org. Chem.*, 1997, **62**, 5062–5068; (*g*) M. Kito, T. Sakai, H. Shirahama, M. Miyashita and F. Matsuda, *Synlett*, 1997, 219–220; (*h*) F. Matsuda, T. Sakai, N. Okada and M. Miyashita, *Tetrahedron Lett.*, 1998, **39**, 863–864; (*i*) F. Matsuda, M. Kito, T. Sakai, N. Okada, M. Miyashita and H. Shirahama, *Tetrahedron*, 1999, **55**, 14369–14380; (*j*) L. Gentric, I. Hanna and L. Ricard, *Org. Lett.*, 2003, **5**, 1139–1142; (*k*) L. Gentric, I. Hanna, A. Huboux and R. Zaghdoudi, *Org. Lett.*, 2003, **5**, 3631–3634; (*l*) L. A. Paquette, R. Guevel, S. Sakamoto, I. H. Kim and J. Crawford, *J. Org. Chem.*, 2003, **68**, 6096–6107; (*m*) L. Morency and L. Barriault, *Tetrahedron Lett.*, 2004, **45**, 6105–6107; (*n*) L. A. Paquette, I. Efremov and Z. Liu, *J. Org. Chem.*, 2005, **70**, 505–509; (*o*) L. A. Paquette and I. Efremov, *J. Org. Chem.*, 2005, **70**, 510–513; (*p*) L. A. Paquette, Z. Liu and I. Efremov, *J. Org. Chem.*, 2005, **70**, 514–518; (*q*) L. Morency and L. Barriault, *J. Org. Chem.*, 2005, **70**, 8841–8853; (*r*) C. M. Grise, G. Tessier and L. Barriault, *Org. Lett.*, 2007, **9**, 1545–1548; (*s*) M. S. Souweha, G. D. Enright and A. G. Fallis, *Org. Lett.*, 2007, **9**, 5163–5166; (*t*) T. J. Maimone, A.-F. Voica and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 3054–3056.
14 The various synthetic approaches towards vinigrol have been reviewed recently: (*a*) G. Tessier and L. Barriault, *Org. Prep. Proced. Int.*, 2007, **37**, 313–353; (*b*) M. Harmata and N. L. Calkins, *Chemtracts*, 2009, **22**, 205–209; (*c*) J.-Y. Lu and D. G. Hall, *Angew. Chem., Int. Ed.*, 2010, **49**, 2286–2288; (*d*) A. D. Huters and N. K. Garg, *Chem.–Eur. J.*, 2010, **16**, 8586–8595.
15 T. J. Maimone, J. Shi, S. Ashida and P. S. Baran, *J. Am. Chem. Soc.*, 2009, **131**, 17066–17067.
16 J. Poulin, C. M. Grise-Bard and L. Barriault, *Angew. Chem., Int. Ed.*, 2012, **51**, 2111–2114.
17 D. S. Hsu and C.-C. Liao, *Org. Lett.*, 2007, **9**, 4563–4565.
18 J. G. M. Morton, C. Draghici, L. D. Kwon and J. T. Njardarson, *Org. Lett.*, 2009, **11**, 4492–4495. For our initial explorations, consult: (*a*) J. G. M. Morton, L. D. Kwon, J. Freeman and J. T. Njardarson, *Tetrahedron Lett.*, 2009, **50**, 1684–1686; (*b*) J. G. M. Morton, L. D. Kwon, J. Freeman and J. T. Njardarson, *Synlett*, 2009, 23–27.
19 J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus and A. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 791–799.
20 S. H. Hong, D. P. Sanders, C. W. Lee and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 17160–17161.
21 (*a*) L. Labaudiniere, J. Hanaizi and J.-F. Normant, *J. Org. Chem.*, 1992, **57**, 6903–6908; (*b*) J. G. Duboudin and B. J. Jousseaume, *J. Organomet. Chem.*, 1979, **168**, 1–11.
22 P. B. Shrestha-Dawadi and J. Lugtenburg, *Eur. J. Org. Chem.*, 2003, 4654–4663.
23 S. J. Mills, H. Dozol, F. Vandeput, K. Backers, T. Woodman, C. Erneux, B. Spiess and B. V. L. Potter, *ChemBioChem*, 2006, **7**, 1696–1706.
24 L. A. Paquette, S. Hormuth and C. J. Lovely, *J. Org. Chem.*, 1995, **60**, 4813–4821.
25 A. Hadfield, H. Schweitzer, M. P. Trova and K. Green, *Synth. Commun.*, 1994, **24**, 1025–1028.
26 A. Roy, K. R. Reddy, P. K. Mohanta, H. Ila and H. Junjappa, *Synth. Commun.*, 1999, **29**, 3781–3791.
27 C.-S. Li, D.-C. Jou and C.-H. Cheng, *Organometallics*, 1993, **12**, 3945–3954.
28 W.-J. Juo, T.-H. Lee, W.-C. Liu, S. Ko, S. K. Chittimalla, C. P. Rao and C.-C. Liao, *J. Org. Chem.*, 2007, **72**, 7992–8004.
29 B. Wustenberg and A. Pfaltz, *Adv. Synth. Catal.*, 2008, **350**, 174–178.
30 R. Crabtree, *Acc. Chem. Res.*, 1979, **12**, 331–337.
31 (*a*) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck and J.-L. Gras, *J. Am. Chem. Soc.*, 1978, **100**, 8031–8034; (*b*) S. A. Snyder and E. J. Corey, *Tetrahedron Lett.*, 2006, **47**, 2083–2086.

32 For a review of intramolecular tandem Heck reactions, see: J. T. Link and L. E. Overman, in *Metal-catalyzed Cross-coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, New York, 1998, pp. 231–169.
33 R. C. Petter, S. Banerjee and S. Englard, *J. Org. Chem.*, 1990, **55**, 3088–3097.
34 Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk and J. Eichhorn, *J. Org. Chem.*, 1996, **61**, 5857–5864.
35 P. C. Bulman and T. J. McCarthy, *Compr. Org. Synth.*, 1991, **7**, 83.
36 (*a*) N. K. Brennan, X. Guo and L. A. Paquette, *J. Org. Chem.*, 2005, **70**, 732–734; (*b*) S. Murata, M. Suzuki and R. Noyori, *J. Am. Chem. Soc.*, 1979, **101**, 2738–2739; (*c*) S. Terao, M. Shiraishiand and K. Kato, *Synthesis*, 1979, 467–468; (*d*) A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 6513–6514; (*e*) J. S. Yadav, T. Shekharam and V. R. Gadgil, *J. Chem. Soc., Chem. Commun.*, 1990, 843–844.
37 K. C. Nicolaou, M. E. Duggan and T. Ladduwahetty, *Tetrahedron Lett.*, 1984, **25**, 2069–2072.
38 M. A. Warpehoski, B. Chabaud and K. B. Sharpless, *J. Org. Chem.*, 1982, **47**, 2897–2900.
39 For an excellent review of Grob fragmentations, see: K. Prantz and J. Mulzer, *Chem. Rev.*, 2010, **110**, 3741–3766.
40 For a recent review of SmI_2 mediated fragmentations, see: D. Bradley, G. Williams, K. Blann and J. Caddy, *Org. Prep. Proced. Int.*, 2001, **33**, 565–602.
41 (*a*) A. Haque and S. Ghosh, *J. Chem. Soc., Chem. Commun.*, 1997, 2039–2040; (*b*) D. B. G. Williams, K. Blann and C. W. Holzapfel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 219–220; (*c*) T. Honda, K. Naito, S. Yamane and Y. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1992, 1218–1220.
42 B. H. Lipshutz and D. F. Harvey, *Synth. Commun.*, 1982, **12**, 267–277.
43 Z. Hou, Y. Zhang and Y. Wakatsuki, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 149–153.
44 (*a*) E. J. Corey, R. B. Mitra and H. Uda, *J. Am. Chem. Soc.*, 1963, **85**, 362–363; (*b*) D. Renneberg, H. Pfander and C. J. Leumann, *J. Org. Chem.*, 2000, **65**, 9069–9079; (*c*) V. A. Khripach, V. N. Zhabinskii, G. P. Fando, A. I. Kuchto, A. S. Lyakhov, A. A. Govorova, M. B. Groen, J. van der Louw and A. de Groot, *Steroids*, 2004, **69**, 495–499.
45 (*a*) A. K. Saksena and P. Mangiaracina, *Tetrahedron Lett.*, 1983, **24**, 273–276; (*b*) D. A. Evans and K. T. Chapman, *Tetrahedron Lett.*, 1986, **27**, 5939–5942.
46 For hydrogenation approach, see: (*a*) W. Oppolzer and R. D. Wylie, *Helv. Chim. Acta*, 1980, **63**, 1198–1203; (*b*) S. W. Baldwin and R. E. Gawley, *Tetrahedron Lett.*, 1975, **46**, 3969–3972; (*c*) H.-J. Gutke, K. Oesterreich, D. Spitzner and N. A. Braun, *Tetrahedron*, 2001, **57**, 997–1003; (*d*) A. Srikrishna and G. Satyanarayana, *Tetrahedron Lett.*, 2006, **47**, 367–370; (*e*) S. Karimi, *J. Nat. Prod.*, 2001, **64**, 406–410; (*f*) K. C. Nicolaou, D. L. F. Gray and J. Tae, *J. Am. Chem. Soc.*, 2004, **126**, 613–627. For radical deoxygenation approach, see: (*g*) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, **16**, 1574–1585; (*h*) D. J. Wardrop, R. E. Forslund, C. L. Landrie, A. I. Velter, D. Wink and S. Bushan, *Tetrahedron: Asymmetry*, 2003, **14**, 929–940; (*i*) S. C. Dolan and J. MacMillan, *J. Chem. Soc., Chem. Commun.*, 1985, 1588–1589; (*j*) V. Lecomte, E. Stephan, M.-N. Rager and G. Jaouen, *J. Org. Chem.*, 2004, **69**, 3216–3219. For reductive deoxygenation approach, see: (*k*) E. N. Alesso, D. E. Bianchi, L. M. Finkielsztein, B. Lantano, G. Y. Moltrasio and J. M. Aguirre, *Tetrahedron Lett.*, 1995, **36**, 3299–3302; (*l*) R. Tedesco, R. Fiaschi and E. Napolitano, *J. Org. Chem.*, 1995, **60**, 5316–5318. For palladium-mediated deoxygenation approach, see: (*m*) T. Manddai, S. Suzuki, T. Murakami, M. Fujita, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, 1992, **33**, 2987–2990; (*n*) Q. Zhang and J. A. Porco, *Org. Lett.*, 2012, **14**, 1796–1799. For triflate approach, see: (*o*) D. Comins and A. Dehghani, *Tetrahedron Lett.*, 1992, **33**, 6299–6302; (*p*) T. Ibuka, T. Aoyagi and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 1985, 1452–1454; (*q*) E. Shirakawa, Y. Imazaki and T. Hayashi, *Chem. Lett.*, 2008, **37**, 654–655; (*r*) X. J. Han, B. M. Stoltz and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 7600–7605.
47 (*a*) M. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, 1984, **25**, 4233–4236; (*b*) T. F. Braish, J. C. Saddler and P. L. Fuchs, *J. Org. Chem.*, 1988, **53**, 3647–3658.
48 G. M. Atkins and E. M. Burgess, *J. Am. Chem. Soc.*, 1968, **90**, 4744–4745.
49 A. L. Wilds, J. A. Johnson and R. E. Sutton, *J. Am. Chem. Soc.*, 1950, **72**, 5524–5529.
50 L. A. Sarandeses, A. Mourino and J.-L. Luche, *J. Chem. Soc., Chem. Commun.*, 1991, 818–820.
51 W. J. Tenn, B. L. Conley, C. H. Hövelmann, M. Ahlquist, R. J. Nielsen, D. H. Ess, J. Oxgaard, S. M. Bischof, W. A. Goddard and R. A. Periana, *J. Am. Chem. Soc.*, 2009, **131**, 2466–2468.
52 M. Abdo and S. Knapp, *J. Am. Chem. Soc.*, 2008, **130**, 9234–9235.
53 (*a*) M. J. Francis, P. K. Grant, K. S. Low and R. T. Weavers, *Tetrahedron*, 1976, **32**, 95–101; (*b*) C. W. Wilson and P. E. Shaw, *J. Org. Chem.*, 1973, **38**, 1684–1687.
54 H. Schwertfeger, C. Würtele, M. Serafin, H. Hausmann, R. M. K. Carlson, J. E. P. Dahl and P. R. Schreiner, *J. Org. Chem.*, 2008, **73**, 7789–7792.
55 (*a*) G. D. Sargent, *J. Am. Chem. Soc.*, 1971, **93**, 5268–5269; (*b*) S. W. Baldwin and J. C. Tomesch, *J. Org. Chem.*, 1980, **45**, 1455–1462.
56 (*a*) T. Nakai, K. Tanaka and N. Ishikawa, *Chem. Lett.*, 1976, 1263–1266; (*b*) K. Tanaka, S. Shiraishi, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 1978, **19**, 3103–3106; (*c*) P. J. Kocienski and T. N. Snaddon, *Org. Synth.*, 2008, **85**, 45–52.
57 (*a*) H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 1975, **16**, 1731–1734; (*b*) L. A. Paquette, D. T. DeRussy, N. A. Pegg, R. T. Taylor and T. M. Zydowsky, *J. Org. Chem.*, 1989, **54**, 4576–4581; (*c*) M. Moller, M. Husemann and G. Boche, *J. Organomet. Chem.*, 2001, **624**, 47–52;

(*d*) H. Lubin, A. Tessier, G. Chaume, J. Pytkowicz and T. Brigaud, *Org. Lett.*, 2010, **12**, 1496–1499.

58 (*a*) F. A. Davis, J. Wei, A. C. Sheppard and S. Gubernick, *Tetrahedron Lett.*, 1987, **28**, 5115–5118; (*b*) F. A. Davis and A. C. Sheppard, *Tetrahedron*, 1989, **45**, 5703–5742.

59 (*a*) E. Vedejs, *J. Am. Chem. Soc.*, 1974, **98**, 5944–5945; (*b*) B. C. Milgram, B. B. Liau and M. D. Shair, *Org. Lett.*, 2011, **13**, 6436–6439.

60 (*a*) M. Taddei and A. Ricci, *Synthesis*, 1986, 633–635; (*b*) M. Pohmakotr and C. Winotai, *Synth. Commun.*, 1988, **18**, 2141–2146; (*c*) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10596–10612.

61 W. A. Herrmann, S. J. Eder and W. Scherer, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1345–1347.

62 Q. Yang and J. T. Njardarson, *Tetrahedron Lett.*, 2013, **54**, 7080–7082.

