Published in final edited form as:
Org Lett. 2009 October 15; 11(20): 4492–4495. doi:10.1021/ol901519k.

Rapid Assembly of Vinigrol's Unique Carbocyclic Skeleton

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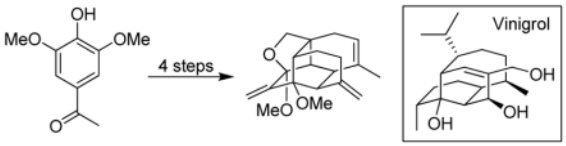
Abstract



Detailed in this account are our efforts towards the total synthesis of vinigrol. A highly expedient and convergent synthetic approach made possible by the use of a strategic oxidative dearomatization reaction coupled with a series of ensuing substrate controlled transformations is discussed.

In 1987 researchers at Fujisawa Pharmaceutical company reported the isolation of a novel diterpenoid, they had named vinigrol (Figure 1, 1), with an unprecedented 1,5-butane tethered *cis*-decalin core.[1] Vinigrol has since been shown to be potent as an antihypertensive and platelet-inhibiting agent, as well as having an inhibitory effect on Ca^{2+} movement.[2] Subsequently vinigrol was shown to be a tumour necrosis factor (TNF) antagonist[3] with the ability to inhibit the progression of AIDS-related complex to AIDS.[4] Giving this promising biological profile and structure, it is not surprising that a number of synthetic research groups took notice.[5] Twenty years since its isolation, vinigrol has yet to succumb to total synthesis. Interestingly, the first published route by Hanna remains one of the most advanced progresses towards vinigrol.

In our quest towards completing an expedient total synthesis of vinigrol we have focused our efforts on synthetic strategies utilizing an oxidative dearomatization coupled with an intramolecular Diels-Alder reaction as the key steps. Towards that end we have disclosed our efforts employing the Wessely and Adler-Becker oxidative dearomatization reactions.[6] Although these disconnections were shown to be conceptually sound they both suffered from weakeness in either one of the key transformations. This communication details our current route, which overcomes the limitations encountered in the previous routes in addition to being more efficient and easily processable.

Retrosynthetic analysis for our proposed total synthesis of vinigrol (**1**) is detailed in Scheme 1. Late stage substrate controlled hydrogenation of both olefins followed by formation of an enol triflate, cross coupling of the triflate to form the allylic alcohol and deprotection will advance intermediate **2** to vinigrol. The natural product core will be revealed using a *retro*-Michael fragmentation of caged structure **3**, which in turn can be rapidly accessed *via* **4** following substrate controlled hydrogenation of the *exo* olefin and samarium mediated deoxygenation of the mixed ketal moiety. Tandem 6-*exo* radical cyclizations will deliver the

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Supporting Information Available: Experimental Details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

pre-fragmentation polycyclic core (**4**) from cycloadduct **5**. This intermediate will be assembled from the oxidative dearomatization/Diels-Alder union of pyrogallol derivative **6** and acrylic acid **7**. In the ideal synthetic scenario a one pot samarium cascade can be envisioned starting from **5** directly to ring expanded **3** via consecutive 6-*exo* ketyl mediated radical cyclizations followed by double α-keto deoxygenation and a retro Michael fragmentation of the resulting enolate.

Our studies first focused on dearomatizing commercially available symmetrical 1,3-dimethoxy pyrogallol. Unfortunately it was quickly realized that the resulting *mono*-quinone ketal was very unstable and rearomatized before the desired Diels-Alder cycloaddition could occur. Electronic deactivation with 4-halopyrogallols was not sufficient, thus leading us to investigate the reactivity profile of *mono*-tosylated derivative **9** (Scheme 2). This strategy was shown to be very effective, as first demonstrated by the hypervalent iodide mediated oxidation of **9** in the presence of allyl alcohol, which afforded cycloadduct **10**. Unfortunately more relevant *tri*-substituted allylic alcohols were not trapped very efficiently in our early attempts. We therefore turned our attention to lead(IV) acetate oxidations. Gratifyingly, these oxidations proceeded smoothly forming mixed quinone ketal **11** and more importantly allowing incorporation of tiglic acid (**12**). Unlike the dialkyl ketal *ortho*-quinones these ketals are more stable as a result of the acyl groups inductive effects and need to be heated to access the [2.2.2] cycloadducts.[7]

Our initial efforts have focused on establishing the viability of the proposed oxidative dearomatization strategy (Scheme 3). A suitable carboxylate sidechain (**17**) was accessed in three steps. This was accomplished by alkylation of triethyl phosphonoacete (**13**) with bromide **14**, followed by a Horner-Wadsworth-Emmons condensation with aldehyde **16**[8] and hydrolysis to form trisubstituted acrylic acid **17**. We were delighted to learn that when phenol **9** was oxidized in the presence of **17** a union of the two took place to form a stable adduct, which upon heating provided desired bicyclic cycloadduct **18** in good yield. Deprotection of the silyl ether and Swern oxidation of the primary alcohol then afforded aldehyde **19**. This substrate provided us with several 6-*exo*/6-*exo* cyclization strategies by initiating cyclization either at the aldehyde or alkyne terminus. We decided to first explore samarium mediated cyclizations. Upon treatment of **19** with samarium diiodide in the presence of HMPA a rapid cyclization took place forming **20** as a single diastereomer, with the desired correct stereochemistry of the newly formed secondary hydroxyl group. For this substrate (**19**), the expected second 6-*exo* radical cyclization did not take place to form the tetracyclic core (**21**) of vinigrol.[9]

We had predicted that there might be both steric and conformational challenges with the second radical cyclization. One way to improve the cyclization chances would be to use cyclization partners that were mostly sp^2 and sp^3 hybridized in order to create more space for the the more challenging second cyclization to occur. We decided to evaluate such a less encumbered system in combination with a more reactive starting vinyl radical. The rapid synthesis and evaluation of this substrate (**26**) is shown in Scheme 4. Known bromide **22**[10] was utilized to afford phosphonate **23**. Condensation of aldehyde **24** and ester hydrolysis furnished acrylic acid **25**, which again was reliably and selectively coupled to pyrogallol derivative **9** using the the same lead(IV) oxidative dearomatization protocol. Upon heating, cycloadduct **26** was obtained in only seven steps from propargylic alcohol **22**. Unfortunately all attempted radical cyclizations of this vinyl iodide substrate only afforded *mono*-cyclized product **27**, with no sign of any products arising from the desired 6-*exo*/6-*exo* radical cascade.

Having not succeeded in forming the vinigrol core using a radical cyclization cascade we decided to evaluate a stepwise approach, that would build upon our existing route and the lessons learned but employ instead a substituted pyrogallol precursor. We postulated that commercially available pyrogallol **30** would offer us an excellent entry point (Scheme 5). All

eight of its core carbon atoms and an oxygen atom would end up in the final structure. Moreover, it is symmetrical and has a deactivating group (acyl group instead of a phenolic tosylate). Towards that end, acrylic acid **29** was accessed using classic chemical transformations from phosphonoacetate **28**. The oxidative dearomatization union of acid **29** and phenol **30** afforded bicyclic ketal **31** in very good yield. X-ray crystallography of the vinyl bromide analog (**32**) confirmed chemical connectivity.[11]

Radical cyclization of **31** yielded a single diastereomer (Scheme 6), which was shown to be the desired ketone **33** having trapped the radical from the bottom face. Olefination attempts to access RCM precursor **34** proved extremely challenging and were met with no success. We were able to olefinate the less hindered radical cyclization precursor (**32**). When the resulting tetraene (**36**) was used for the radical cyclization *en route* to metathesis precursor **34**, triene **37** was instead isolated as the only product. Following cyclization the intermediate allylic radical had migrated to form a tetrasubstituted alkene.

Inspired by the convergent and rapid union of pyrogallol ketone **30** and carboxylate moiety **29** we decided to make two critical modifications. We felt that the oxidative dearomatization union could be further improved and we were eager to suppress the acyl migration often observed during the intramolecular Diels-Alder reaction. Additionally, although the lactone was clearly attractive for eventual oxidation economy in the short term it was complicating our search for the optimal cyclization sequence. By using an alcohol instead of a carboxylate in the oxidative dearomatization step we would access a more stable ketal, which would be helpful for later steps. We also expected that the intermediate ketal would more likely undergo the intramolecular Diels-Alder reaction *in situ* while not suffering from any competing acyl migrations. The main question we faced was whether we could use the allylic alcohol as a nucleophile, which challenged us earlier (Scheme 2), or alternatively to *pre*-tether it to the aromatic core. Our efforts are detailed in Scheme 7.

We used the sequence detailed in Scheme 5 to obtain allylic alcohol **38**. This was done by reducing the ester obtained from the Horner-Wadsworth-Emmons reaction with Dibal-H. We were delighted to learn that when alcohol **38** was coupled with phenol **30** in the presence of iodobenzene *bis*(trifluoroacetate) the mixed *ortho*-quinone *mono*-ketal was formed, and as predicted underwent an *in situ* Diels-Alder reaction to cycloadduct **39**. As for the previous substrates the radical cyclization proceeded smoothly, exclusively forming *exo*-ketone **40**.[12] This hindered ketone was successfully *bis*-olefinated (**41**) using the Peterson olefination protocol. Gratifyingly, and despite significant steric hindrance, tetraene **41** could be cyclized using the Grubbs-Hoveyda catalyst (**42**)[13] in the presence of benzoquinone[14] to the desired vinigrol pre-fragmentation cage structure **43**. This seemingly simple core contains all except three of the carbon atoms needed for the total synthesis.

In summary, we have detailed a new and efficient synthetic strategy for vinigrol. It relies on a strategic oxidative dearomatization/Diels Alder reaction followed by a short sequence of critical substrate controlled transformations. This latest approach constructs vinigrol's tetracyclic core (**43**) in only four steps from commercially available ketone **30**. Our efforts towards the completion of the total synthesis of vinigrol (**1**) will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank NIH-NIGMS (RO1 GM086584) and Cornell University for support of this synthetic program. This material is also based upon work supported under a National Science Foundation Graduate Research Fellowship (JGMM). We would like to gratefully thank Emil Lobkovsky (Cornell University) for X-ray structure analysis.

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9. Similar *mono*-cyclization results were also obtained when an acyl selenide was used. This substrate could be accessed in two steps from aldehyde 19 via a Pinnick oxidation followed by treatment of the resulting carboxylic acid with Bu_3P/PhSeCl.
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11. Bromide 32 was obtained from a route identical the one shown in Scheme 5, the only difference being the use of Br-BBN. For further information, see Supporting Information.
12. When *tris*-trimethylsilane (TTMS) was used as reducing agent instead of tributylstannane, the radical cyclization proceeded smoothly but analysis of the product revealed that both the *exo*-methylene and methyl ketone groups had isomerized during the reaction to a tri-substituted *endo*-olefin and an *endo*-ketone respectively.
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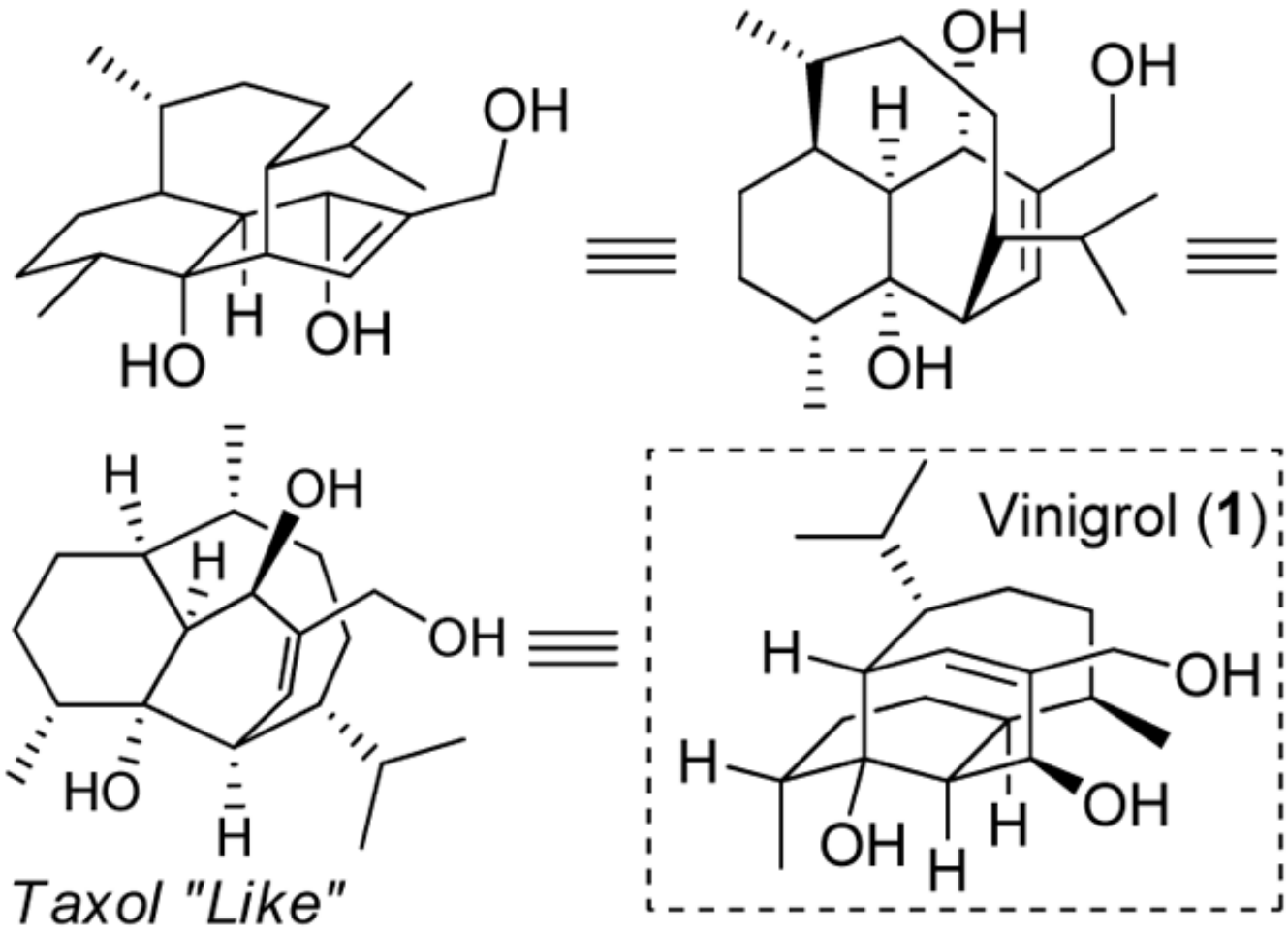
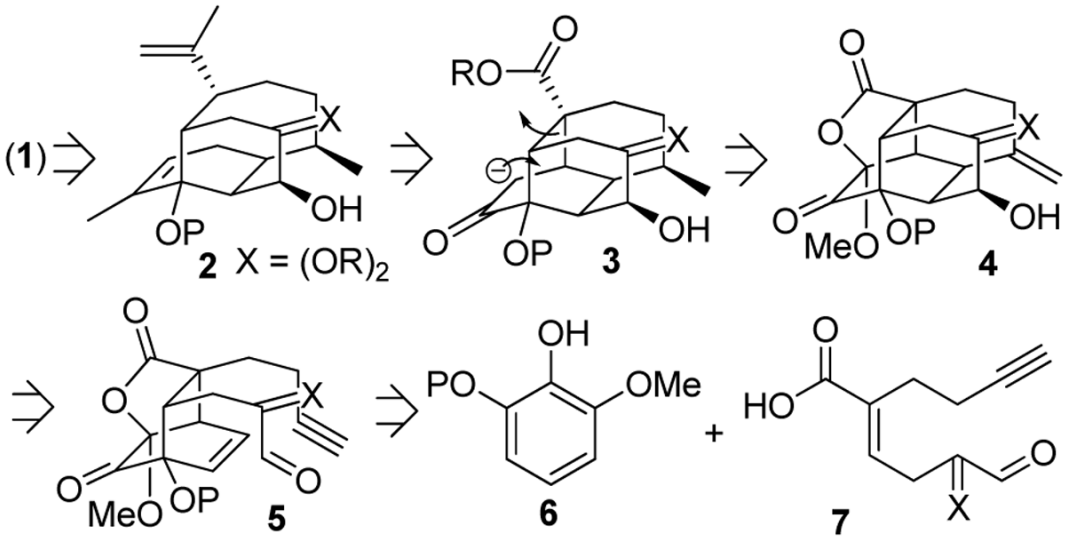
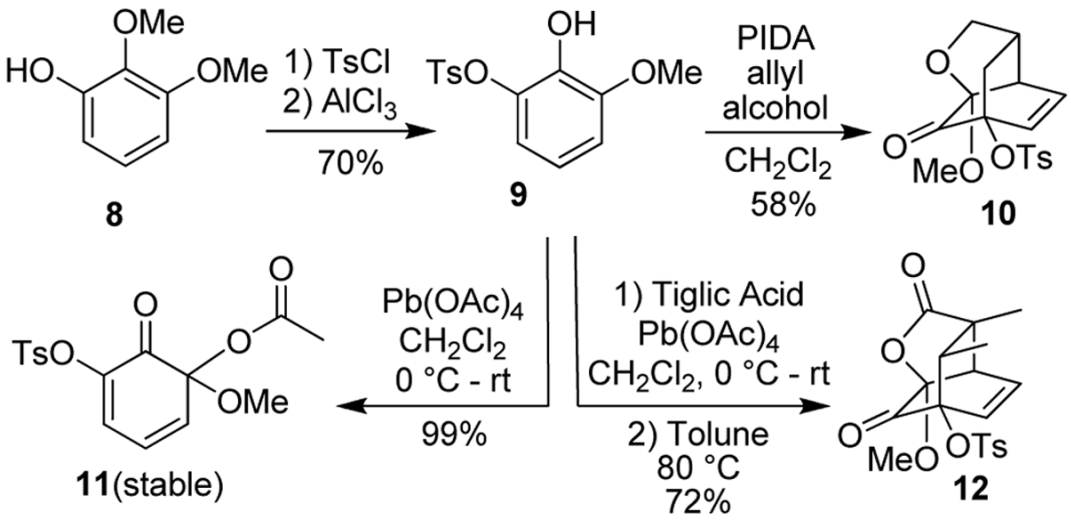


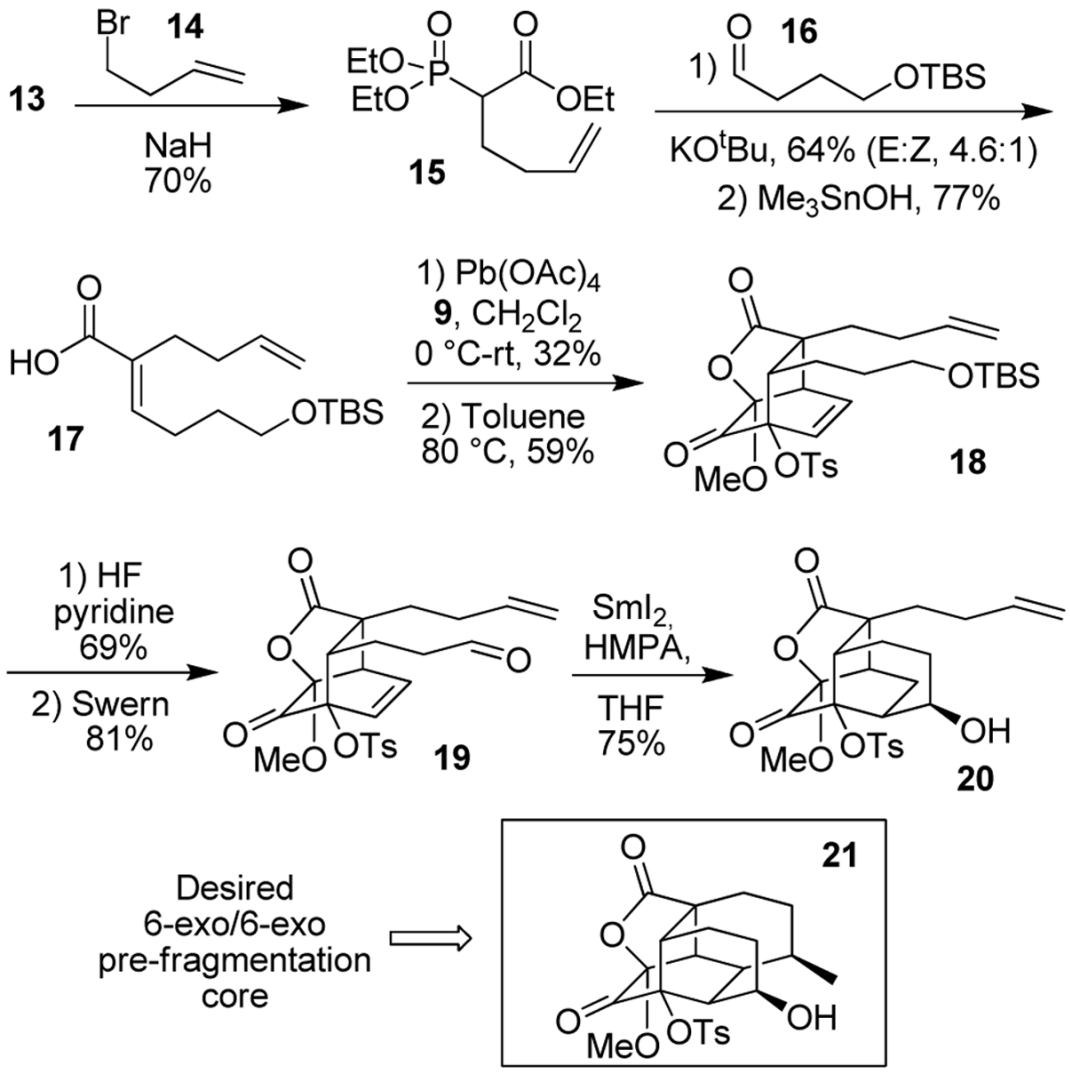
Figure 1.
The Structure of Vinigrol



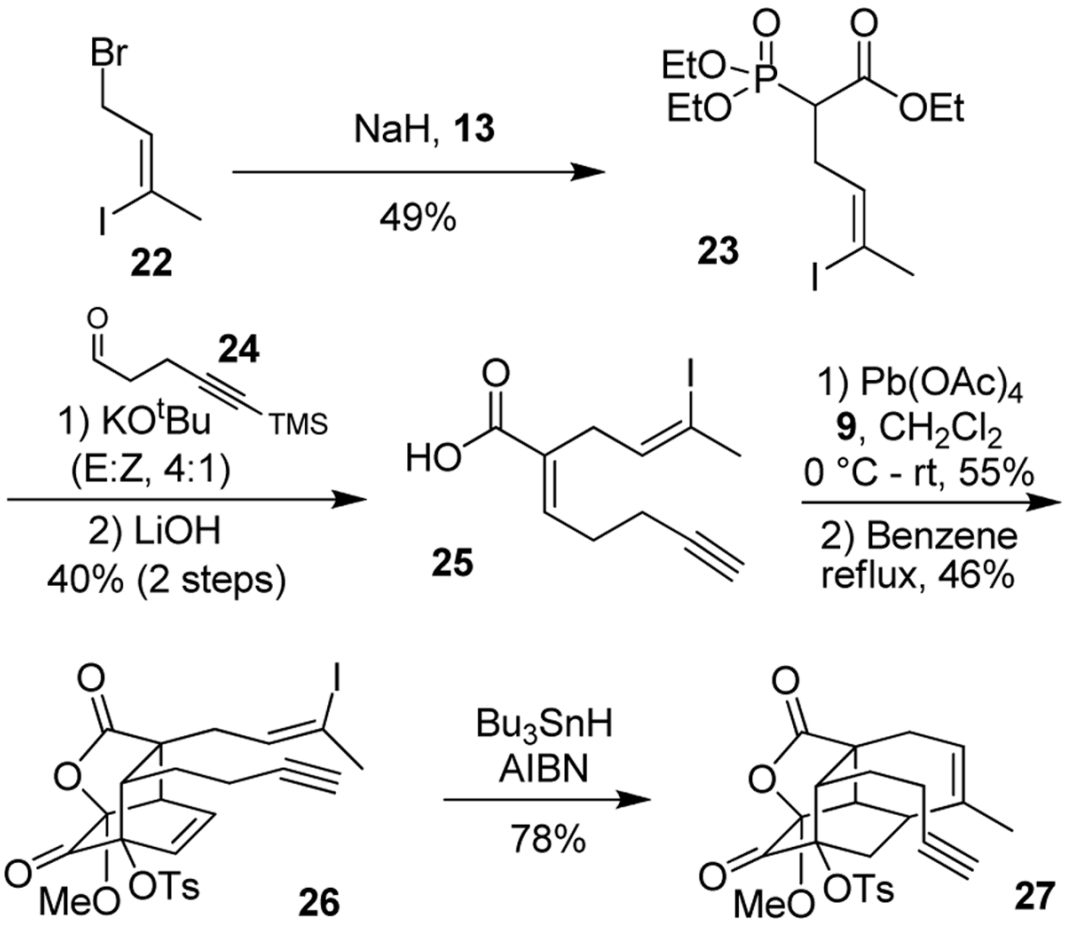
Scheme 1.
Vinigrol Retrosynthesis



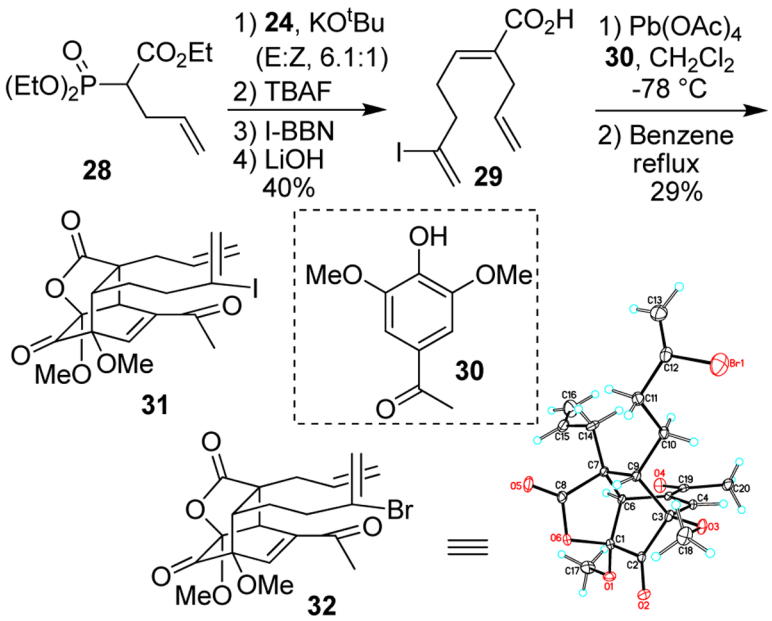
Scheme 2.
Identifying Optimal Pyrogallol Substrate



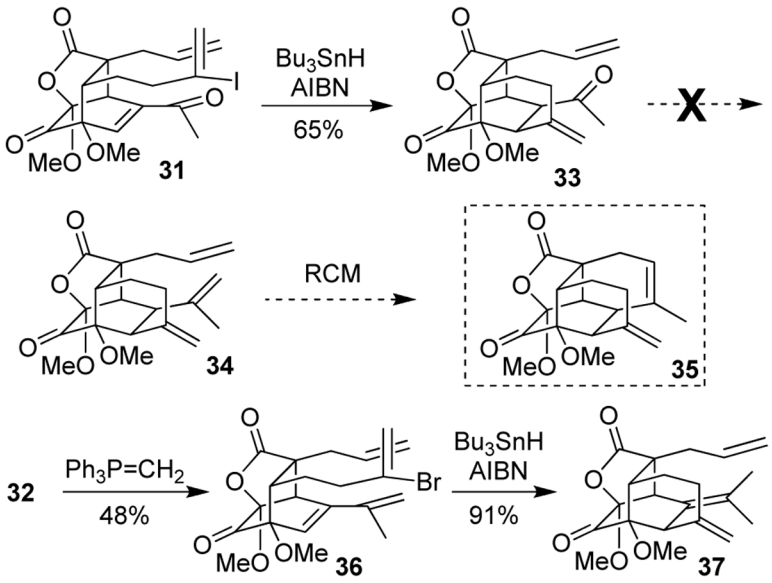
Scheme 3.
Synthesis of Radical Cascade Precursors



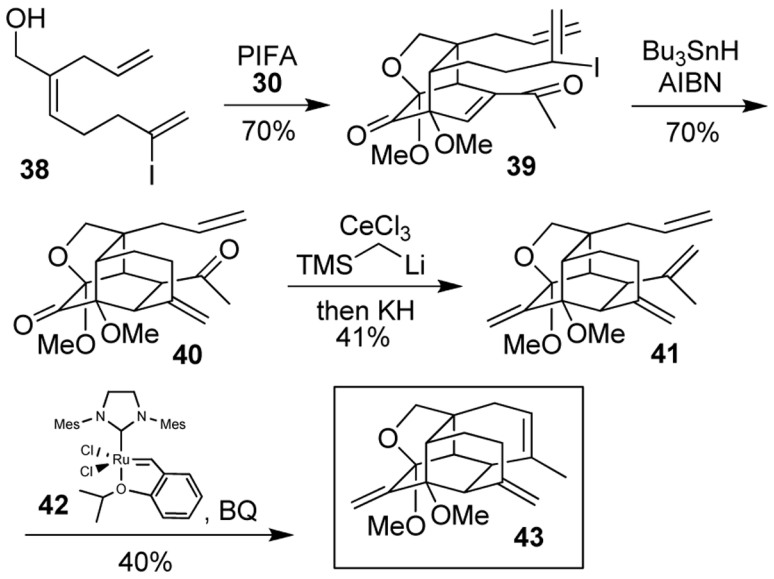
Scheme 4.
Back to Front Radical Cyclization Attempt



Scheme 5.
New Front to Back Cyclization Substrate



Scheme 6.
Front to Back Vinyl Radical Cyclizations



Scheme 7.
Efficient Synthesis of the Tetracyclic Cage