Rapid Assembly of Vinigrol's Unique Carbocyclic Skeleton

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Detailed in this account are our efforts toward 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 Co. reported the isolation of a novel diterpenoid they had named vinigrol (Figure 1, 1), with an unprecedented 1,5butane-tethered *cis*-decalin core.¹ Vinigrol has since been shown to be potent as an antihypertensive and plateletinhibiting agent, as well as have an inhibitory effect on Ca^{2+} movement.² Subsequently, vinigrol was shown to be a tumor necrosis factor (TNF) antagonist³ 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 toward vinigrol.

In our quest toward 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. Toward 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 weakness in either one of the key transformations. This paper details our current route, which overcomes the limitations encountered in the previous routes in addition to being more efficient and easily processable.

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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 prefragmentation 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-dimethoxypyrogallol. Unfortunately, it was quickly realized that the resulting monoquinone ketal was very unstable and rearomatized before the desired Diels—Alder cycloaddition could occur. Electronic deactiva-

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tion with 4-halopyrogallols was not sufficient, thus leading us to investigate the reactivity profile of monotosylated derivative 9 (Scheme 2). This strategy was shown to be very



effective, as first demonstrated by the hypervalent iodidemediated oxidation of **9** in the presence of allyl alcohol, which afforded cycloadduct **10**. Unfortunately, more relevant trisubstituted 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 *o*-quinones, these ketals are more stable as a result of the acyl group's 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 side chain (17) was accessed in three steps. This was accomplished by alkylation of triethyl phosphonoacete (13) with bromide 14, followed by a



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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 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.

Scheme 4. Back to Front Radical Cyclization Attempt



Known bromide 22¹⁰ 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 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 monocyclized 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). Toward 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 analogue (**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

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⁽⁹⁾ Similar monocyclization 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 Bu₃P/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 the Supporting Information.

Scheme 6. Front to Back Vinyl Radical Cyclizations



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 *o*-quinone monoketal 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 benzoquinone¹⁴ to the desired vinigrol prefragmentation cage structure **43**. Scheme 7. Efficient Synthesis of the Tetracyclic Cage



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 toward the completion of the total synthesis of vinigrol (1) will be reported in due course.

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Note Added after ASAP Publication. There were errors in the bottom structures of Figure 1 and in the toc/abstract graphic in the version published ASAP September 3, 2009; the corrected version published ASAP September 11, 2009.

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.

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