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An Adler–Becker oxidation approach to vinigrol

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ABSTRACT

Detailed in this Letter is an Adler–Becker oxidation strategy towards vinigrol. The effects of substitution were shown to greatly impact successes of both the oxidative dearomatization and Diels–Alder reactions.

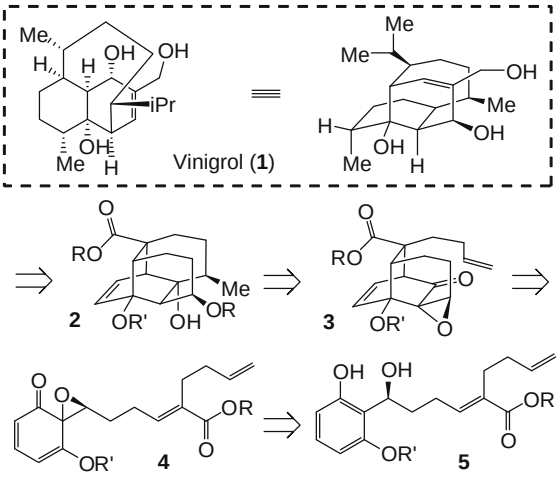
Vinigrol (**1**, Scheme 1) is a structurally novel diterpenoid, first isolated from the fungus *Virgaria nigra*.[1] From a medicinal point of view, vinigrol is of interest due to demonstrated antihypertensive and platelet-inhibiting properties and tumour necrosis factor antagonist activity.[2] Given the combination of a structurally unique, synthetically challenging carbon framework and potential pharmaceutical applications, it is of no surprise that several research groups have published reports towards the synthesis of vinigrol.[3] Yet despite an elapsed sixteen years of work by the synthetic community, a total synthesis of vinigrol has yet to be seen.

Our retrosynthetic approach relies on three key synthetic operations: An oxidative dearomatization of a resorcinol core (**5**), intramolecular Diels–Alder reaction of the resulting dienone (**4**) and a fragmentation of a tetracyclic precursor (**2**). The *spiro*-epoxide moiety in **4** would rigidify the tether, bring the dienophile closer to the diene and following a successful intramolecular Diels–Alder reaction be reductively opened[4] to the desired secondary alcohol. Following this general blueprint, we recently reported our initial vinigrol synthetic efforts employing the underutilized Wessely oxidation reaction for the critical dearomatization step.[5] Concurrent with these efforts, which have suffered from poor Wessely oxidation yields, we have pursued a similar approach using instead an Adler–Becker oxidative dearomatization protocol (Scheme 2) in hopes of addressing this limitation.

First reported in 1971, the Adler–Becker reaction is the periodate-mediated oxidative dearomatization of salicyl alcohols (**6**) to *spiro*-epoxydienones (**7**).[6] The majority of examples utilizing this reaction do so with primary benzylic alcohols (R = H).[7] Only a handful of reports in the literature[8] utilize secondary alcohols (R = C), indicating that oxidation of such substrates is far more challenging. A notable exception is the oxidation of reduced tetralone derivatives, which have been most famously utilized for the total synthesis of the natural product triptolide.[9] This handful of secondary alcohol examples suggests that fused alcohol substrates would fair better than acyclic ones in a synthetic strategy.

Our initial explorations utilized the common synthetic intermediates **8** and **10** (Scheme 3) from our Wessely oxidation efforts.[5] In agreement with precedence, acyclic resorcinol substrates such as **8** failed to form *spiro*-epoxy dienones (**9**) using either classical or modified Adler–Becker reaction conditions. On the other hand, Stetter cyclization substrate **10** proceeded smoothly in methanol-water to form the bright yellow, fused *spiro*-dienone pyran **11**.

Turning our attention towards advancing a more functionalized variant (Scheme 4), our keto ester **12** was selectively reduced in the presence of DIBAL-H to aldehyde **13**. Horner–Wadsworth–Emmons homologation using phosphonate **14** afforded enoate **15**. Ketone reduction provided an Adler–Becker oxidation substrate that dearomatized readily to **16** upon treatment with sodium periodate. Disappointingly, this tetraene did not undergo the desired intramolecular Diels–Alder reaction to cycloadduct **17**. Mild heating returned only starting material, with higher temperature (>150 °C) leading to decomposition. At-



Scheme 1. Vinigrol retrosynthetic analysis.

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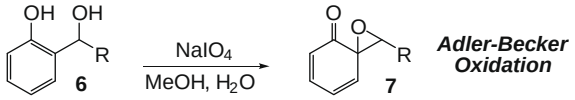
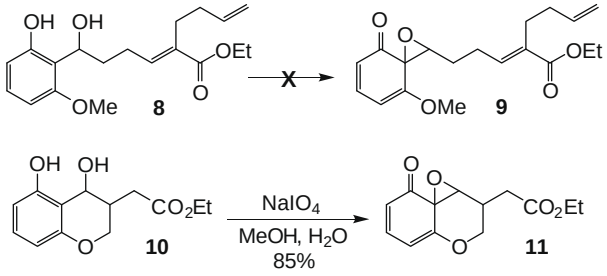
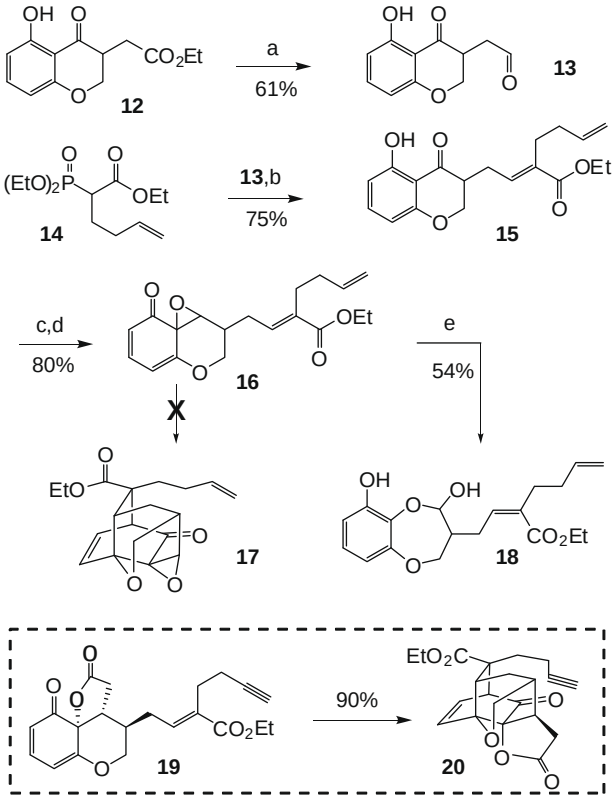


Scheme 2. The Adler–Becker dearomatization reaction.



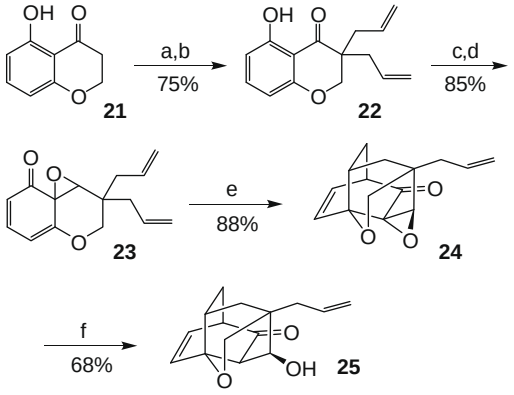
Scheme 3. Acyclic versus rigid secondary alcohol Adler–Becker substrates.



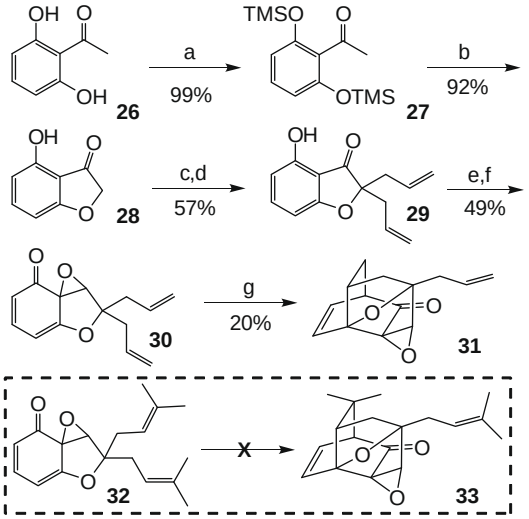
Scheme 4. Acyclic versus rigid secondary alcohol Adler–Becker substrates. Reagents and conditions: (a) 2.2 equiv DIBAL-H, PhMe, −78 °C; (b) *t*-BuOK, PhMe, −78 °C; (c) $NaBH_4$, Et_2O, 0 °C; (d) $NaIO_4$, MeOH, H_2O; e) $EtAlCl_2$, 0 °C.

tempts at low temperature, Lewis-acid-mediated Diels–Alder cycloadditions also failed in generating the desired bicycle. Rather, reaction with $EtAlC_2$ at 0 °C led to the rearrangement product **18**. This is in stark contrast with our Wessely oxidation results, wherein the oxidation reaction to **19** proved very challenging while the cycloaddition to **20** proceeded smoothly.

Unsatisfied with this result, we regrouped to a simpler substrate to explore this approach further. Beginning from known chromanone **21**[10] (Scheme 5), exhaustive allylation was followed by deprotection to afford ketone **22**. Reduction and Adler–Becker



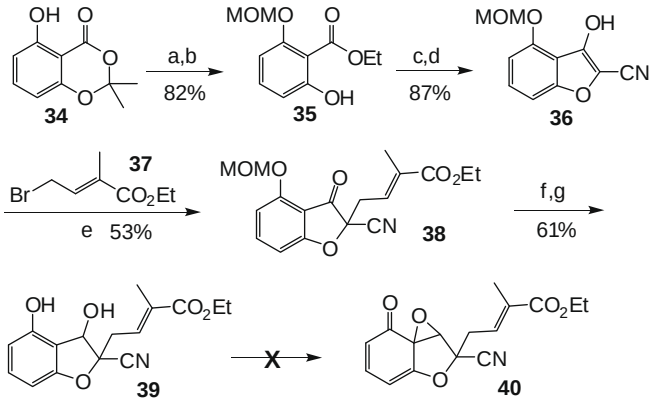
Scheme 5. Adler–Becker oxidation of chromanones. Reagents and conditions: (a) NaH, allyl bromide, DMF; (b) $Pd(OAc)_2$, TFA, EtOH, 50 °C; (c) $NaBH_4$, MeOH, (d) $NaIO_4$, MeOH, H_2O; (e) PhMe, 150 °C; (f) Cp_2TiCl, THF, rt.



Scheme 6. Adler–Becker oxidation of benzofuranone framework. Reagents and conditions: (a) LDA, THF, then TMSCl; (b) NBS, then KOH, MeOH, H_2O; (c) NaH, allyl bromide, DMF; (d) $Pd(OAc)_2$, TFA, EtOH; (e) $LiAlH_4$, THF, (f) $NaIO_4$, MeOH, H_2O; (g) PhMe, 150 °C.

oxidation of the resulting alcohol yielded desired dienone **23** in good yield. We were delighted to learn that, upon prolonged heating in toluene at 150 °C, the tetracyclic cycloadduct **24** was formed in excellent yield. Finally, Cp_2TiCl-mediated radical opening of the epoxide[4] gave the alcohol **25**. This simple model substrate contains much of the vinigrol pre-fragmentation core, with the all the challenging hydroxyl groups in their respective positions.

Catalyzed by this success, and in parallel with our chromanone model studies, we argued that a smaller fused framework might bring the dienophile closer to the dienone and hence enable cycloadditions at temperatures low enough to preclude decomposition of our sensitize *spiro*-quinols. Models and our calculations suggested a *spiro*-dienone product such as **30** would indeed bring the two cycloadduct components closer together, and thus a five-membered ring (benzofuran derivative, Scheme 6) variant of the chromanone model system was born. Our studies utilized known benzofuranone **28**[11] as a starting point, which is readily accessed in two high yielding steps from commercially available 2,6-dihydroxyacetophenone. Ketone **29** was obtained as **22** before, by first exhaustively allylating and then selectively deallylating to the free phenol. This new structure is both more rigid and more sterically



Scheme 7. Synthesis and evaluation of a more complex benzofuranone. Reagents and conditions: (a) MOMCl, *i*Pr_2NEt, DCM; (b) EtOH, K_2CO_3; (c) $ClCH_2CN$, K_2CO_3, MeCN, rt; (d) *t*BuOK, PhH, 0–25 °C; (e) NaH, THF, then NaI, 35, rt; (f) 5% aq HCl, EtOH; (g) $NaBH_4$, MeOH, 0 °C.

congested than its predecessor. This is reflected in a slower reduction and lower yielding Adler–Becker oxidation (**30**). Careful heating of the dearomatized core afforded the highly strained cycloadduct **31**, albeit in non-optimized yields. In order to better assess the scope of this approach we also accessed prenylated core **32** using an identical synthetic approach. This tetraene resisted all attempts to form **33**, with decomposition occurring at elevated temperatures.

Having realized moderate success in both the oxidative dearomatization and subsequent Diels–Alder cycloaddition to **31**, we investigated this benzofuran framework further using more advanced synthetic components (Scheme 7). Transesterification of the known benzodioxanone **34**[12] with EtOH gave **35**. Alkylation of the free phenol with chloroacetonitrile and subsequent condensation yielded the β-ketonitrile **36**. Keeping in mind the failure of the *bis*-prenyl derivative **32** to undergo Diels–Alder cycloaddition, we decided to use an electronically matched enoate dienophile in this route. Selective C-alkylation with bromo enoate **37**[13] was thus used, affording **38**. Deprotection of the phenolic MOM-group and reduction of the ketone set the stage for the critical dearomatization step. Unfortunately, diol **39** resisted all our attempts[14] to convert it to *spiro*-dienone **40**. Indeed, when any reaction at all occurred it was reoxidation to the ketone.

In summary, despite this route being a dead end for our vinigrol campaign it does serve to highlight both the incredible untapped synthetic potential of the Adler–Becker dearomatization in rapidly accessing complex structures and the need that still exists for reactive, selective oxidizing agents for such processes.

Acknowledgements

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Supplementary data

Supplementary data (experimental details and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.134.

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14. Conditions attempted include: $NaIO_4$, MeOH/H_2O; $NaIO_4$, AcOH; $NaBiO_3$, AcOH; $Cu(CH_3CN)_4PF_6$, morpholine, DIEA, CH_2Cl_2, O_2; $CuCl_2$–morpholine, MeCN, MeOH, O_2; $CuCl_2$, pyridine, MeOH, H_2O; $PhI(OAc)_2$, CF_3CH_2OH; H_5IO_6, wet MeOH; H_5IO_6, THF.