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PII: S0040-4039(18)30230-2
DOI: https://doi.org/10.1016/j.tetlet.2018.02.041
Reference: TETL 49726

To appear in: *Tetrahedron Letters*

Received Date: 26 January 2018
Revised Date: 13 February 2018
Accepted Date: 15 February 2018

Please cite this article as: Shah, P.A., Wiemer, D.F., Synthesis of bavachromanol from resorcinol via a tandem cationic cascade/EAS sequence., *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.02.041

Graphical Abstract

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Synthesis of bavachromanol from resorcinol via a tandem cationic cascade/EAS sequence.

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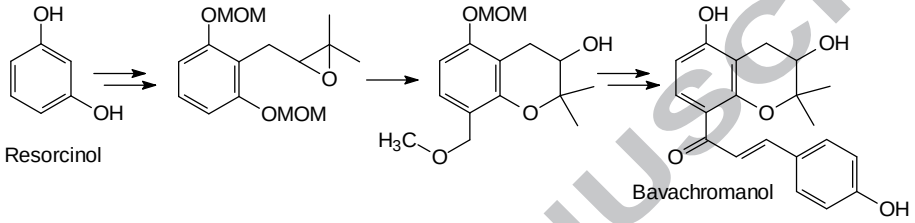
Parin A. Shah and David F. Wiemer*
Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, U.S.A.



Pergamon

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LETTERS

Synthesis of bavachromanol from resorcinol via a tandem cationic cascade/EAS sequence.

Parin A. Shah and David F. Wiemer*

Department of Chemistry, The University of Iowa, Iowa City, Iowa, 52242-1294, USA

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Abstract— The natural chalcone bavachromanol has been prepared through a tandem reaction sequence that joins cationic cyclization of an epoxide to an adjacent MOM-acetal with electrophilic aromatic substitution by a presumed methoxymethylene cation. Only a single regioisomer of the tandem product was observed, with substitution taking place exclusively ortho to the position of the original acetal. This regiocontrol provided a key intermediate from a symmetrical precursor, and allowed preparation of the meroterpenoid through a short reaction sequence.

Keywords: tandem reaction, cationic cascade, electrophilic aromatic substitution, epoxide

The chalcone bavachromanol (**1**, Figure 1) was first reported in 1980 as a component of the seeds of *Psoralea corylifolia*,[1,2] a plant which is widely used in both traditional Chinese medicine (where it is known as "bu gu zhi") and Ayurvedic medicine.[3] It also was identified during a recent, and more exhaustive, study of this plant.[4] The structure of this meroterpenoid caught our attention because introduction of the ketone substituent through chemical modification of a bicyclic precursor containing the aromatic ring would be required adjacent to the ether functionality rather than the free phenol. While there are synthetic methods that allow ortho C-alkylation of phenolate anions,[5,6] regiospecific introduction of an alkyl group adjacent to the ether linkage might be expected to be more challenging.

Recently we have reported the synthesis of angelichalcone (**2**)[7,8] and schweinfurthin A (**3**)[9-11] through sequences based on tandem cyclization/electrophilic aromatic substitution reactions, where a geranyl epoxide was employed to initiate a cationic cascade.[12] Tandem reactions can afford an attractive strategy for synthesis of complex natural products,[13] perhaps especially when the reactions follow a biomimetic pathway,[14-16] and linking ring formation to electrophilic aromatic substitution is highly conservative in terms of atom economy. If a strategy similar to those we have used with geranyl-substituted compounds could be employed with a resorcinol bearing only a 5-carbon chain, and more importantly if the high ortho regioselectivity in the electrophilic aromatic substitution component still held true, it could afford an efficient strategy for preparation of bavachromanol. In this report the synthesis of this meroterpenoid through an application of this strategy is described.

* Corresponding author: david-wiemer@uiowa.edu

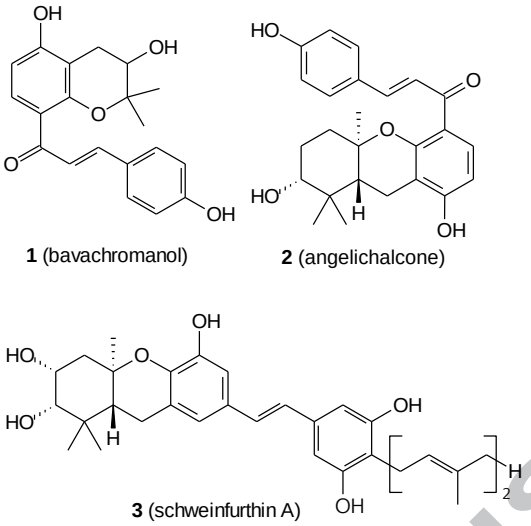


Figure 1. Bavachromanol and some related meroterpenoids.

From a retrosynthetic perspective (Figure 2), the enone of the target compound could be seen arising from an intermediate such as compound **4** through oxidation of the benzyl methyl ether to the corresponding aldehyde followed by transformation to the methyl ketone and ultimately an aldol condensation. The keystone of the sequence would be to convert the symmetrical resorcinol derivative **5** to the unsymmetrical ether **4**. This transformation could be envisioned through a tandem cationic cyclization followed by electrophilic aromatic substitution of the cation released upon cyclization, as long as the substitution reaction proceeded at the position ortho to the newly formed ether. While this regiochemical outcome would be consistent with the major product found in one geranyl-substituted system we have studied,[8] in another system the liberated MOM group was either lost (presumably to reactions with solvent) or found on a distant alcohol.[17] Thus, while it might be challenging to predict the course of the reaction sequence with the epoxide **5**, given that this epoxide can be easily derived from readily available and inexpensive resorcinol (**6**) it was reasonable to explore the viability of a tandem process in this system.

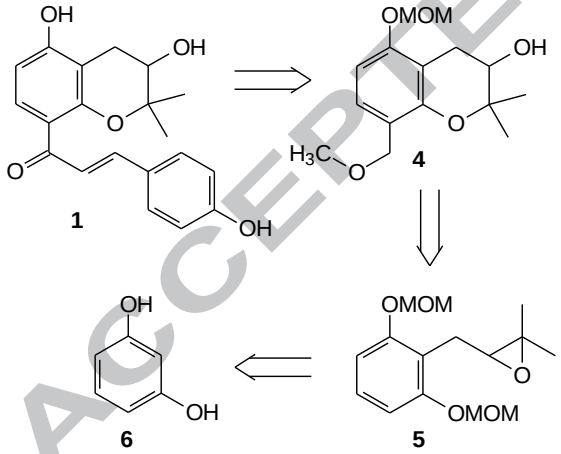
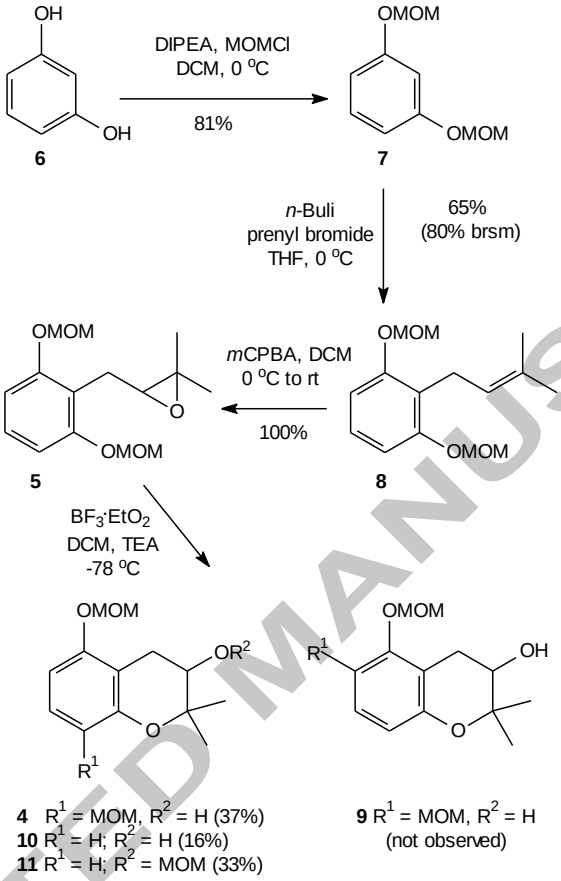


Figure 2. Retrosynthesis of bavachromanol.

Synthesis of the key intermediate **5** began with protection of resorcinol (**6**) as the di-MOM acetal **7** (Scheme 1). Directed ortho metalation[18,19] of compound **7** was achieved in good yield upon treatment with *n*-BuLi, and subsequent reaction of the resulting anion with prenyl bromide gave the symmetrical aromatic system **8** in good yield.[20] Epoxidation was accomplished in quantitative yield upon treatment with *m*CPBA to give compound **5**. Brief treatment of compound **5** with $BF_3{\cdot}OEt_2$ at low temperature yielded three products; one tandem cyclization-electrophilic aromatic substitution product in 37% yield, and compounds **10** and **11** in yields of 16% and 33% respectively. The structures of compounds **10** and **11** were readily apparent. For both compounds three aromatic hydrogens were observed in the ^{1}H NMR spectrum. Furthermore, the spectrum of compound **10** showed only the aromatic MOM substituent (5.19 and 3.49 ppm), while the spectrum of compound **11** revealed

the presence of both an aromatic MOM acetal and an aliphatic MOM acetal (5.20 and 3.50; 4.84 and 4.69, two doublets from the diastereotopic methylene hydrogens and 3.42, respectively).



Scheme 1. Synthesis of the key intermediate **5** and its tandem cyclization/EAS products.

Assignment of the structure of the tandem reaction product required a more detailed analysis of its spectral data. In the ^{1}H NMR spectrum of this compound, two aromatic hydrogens are apparent as coupled doublets (J = 8.4 Hz), requiring the product to display two ortho hydrogens (i.e. isomers **4** and **9**). Assuming that compound **10** is an intermediate in the reaction sequence, *a priori* both positions ortho to oxygen might be expected to be comparably activated for an electrophilic aromatic substitution reaction. Two methyl groups bearing oxygen also are observed. The more downfield of the two methyl groups (3.47 ppm) could be assigned to the methoxy component of the MOM acetal, while the more upfield of the two methoxy groups (3.38 ppm) was assigned as the benzyl methyl ether. Each of these methyl groups was correlated to an aromatic hydrogen in the NOESY spectrum, leaving the isomer **4** as the only reasonable structure assignment (Figure 3). Fortunately, this isomer is the one required for synthesis of bavachromanol. The isolated yield of this tandem product was moderate, but both the short sequence and the formation of a single regioisomer encouraged continuation of the effort. Furthermore, it may be possible to recycle compound **10** and/or compound **11** into the main sequence, although in this case the brevity of the synthetic design suggested that such efforts were unnecessary and they were not pursued.

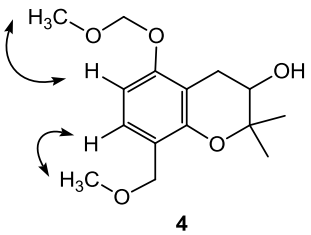
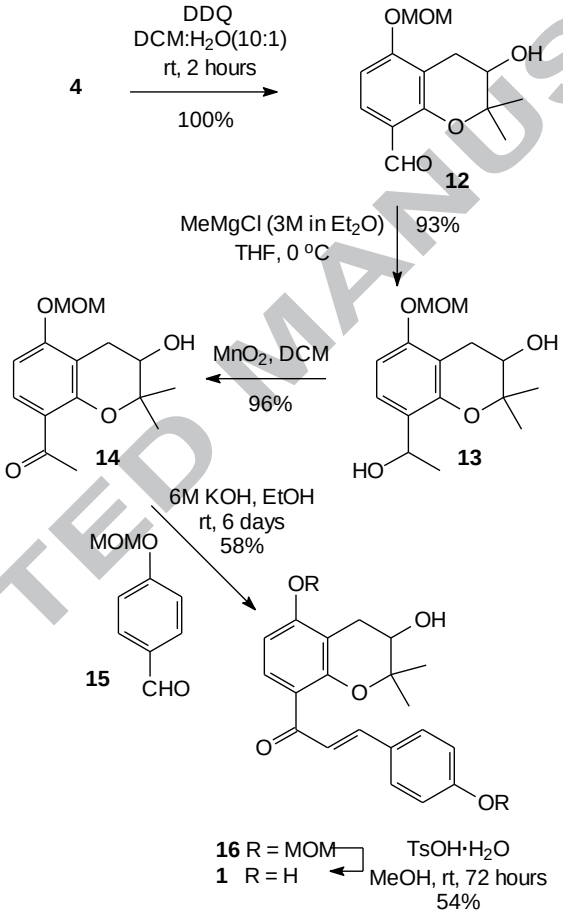


Figure 3. NOESY correlations in the tandem reaction product **4**.

* Corresponding author: david-wiemer@uiowa.edu

Completion of the synthesis was accomplished through relatively straightforward transformations (Scheme 2). From the outset, we viewed the benzyl methyl ether as a latent aldehyde, and treatment of the ether **4** with DDQ gave the expected aldehyde **12** in quantitative yield. Reaction of this aldehyde with excess methyl lithium was complicated by a competing dehydration reaction, but reaction with excess methyl magnesium chloride, where excess was employed to circumvent the need to protect the free alcohol, gave the benzylic alcohol **13** in very good yield. While compound **13** was clearly a mixture of diastereomers based on the ^{1}H NMR spectrum, this was of no long-term importance given that the stereocenter was destroyed by smooth oxidation to the ketone **14** in the next step (96%). A base-mediated aldol condensation with *p*-hydroxybenzaldehyde was exceedingly slow, but condensation with the MOM-protected benzaldehyde **15** proceeded smoothly, albeit still slowly, to afford the enone **16**. Final deprotection of both MOM groups by treatment with *p*TsOH in methanol gave the desired product **1**. While the yield for hydrolysis of the two MOM groups is only moderate, it is consistent with other reports for hydrolysis of two aromatic MOM acetals.[21] Despite this yield, the final step gave sufficient material for characterization, and the spectra of this material proved to be identical with those reported for the natural product bavachromanol.[1]



Scheme 2. Completion of the bavachromanol synthesis.

In conclusion, the meroterpenoid bavachromanol has been prepared in 9 steps and 7% yield. The key step, a tandem cationic cyclization/electrophilic aromatic substitution reaction, gave a single regioisomer determined to have undergone substitution only ortho to the newly formed ether, despite the probability that the para position is equally activated. While this product was obtained in moderate yield, the short sequence needed to prepare the intermediate as well as the short sequence needed to complete the natural product allowed reasonably efficient access to this natural product. Perhaps more importantly, this new example of the tandem reaction sequence extends its ortho selectivity to a new system, and thus supports planning similar routes to other meroterpenoids. Given that the number of meroterpenoids continues to grow rapidly,[22] further applications of the tandem cationic cascade/electrophilic aromatic substitution strategy will follow.

Acknowledgments

We thank the University of Iowa Graduate College for summer fellowships (to PAS). Financial support from the Roy J. Carver Charitable Trust through its Research Program of Excellence (to DFW) is gratefully acknowledged.

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Supplementary data

Experimental procedures and/or spectral data for compounds **4**–**8**, **10**–**14**, and **16** are available. Supplementary data associated with this article can be found in the online version at doi:

* Corresponding author: david-wiemer@uiowa.edu

Highlights

- A tandem reaction sequence converts a symmetrical resorcinol derivative to a single bicyclic substitution product.
- Only a single regioisomer of the tandem cyclization/EAS product was observed.
- The meroterpenoid bavachromanol has been prepared in 9 steps and 7% yield.