J|A|C|S COMMUNICATIONS

Published on Web 09/25/2009

A Tandem Cascade Cyclization−Electrophilic Aromatic Substitution: Application in the Total Synthesis of (+)-Angelichalcone

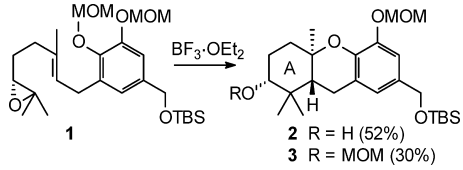
Joseph J. Topczewski, Michael P. Callahan, Jeffrey D. Neighbors, and David F. Wiemer*

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

Received July 31, 2009; E-mail: david-wiemer@uiowa.edu

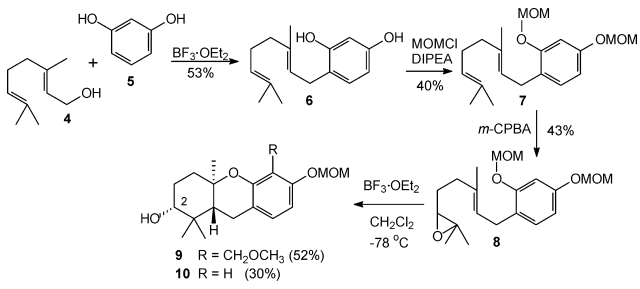
Cascade reactions offer an attractive strategy for efficient synthesis of complicated natural products, especially when the cyclization is a biomimetic process.[1,2] Our previous reports on schweinfurthin synthesis[3,4] have shown that cascade cyclizations provide a particularly appealing means of generating the hexahydroxanthene core when methoxymethyl (MOM)-protected phenols are employed to terminate the reaction.[4] During synthesis of schweinfurthin G,[4] it was noted that even though tricyclic material was obtained in very good yield when $BF_3{\cdot}OEt_2$ was used to mediate the reaction of epoxide **1**, the product contained significant amounts of the A-ring MOM acetal **3** along with the expected product **2** (Scheme 1). Because formation of the unexpected product **3** must be associated with loss of the MOM group upon cyclization, it became of interest to determine whether the intermediate electrophile itself could be harnessed in a more productive reaction. In this report, a novel process that extends the central cascade cyclization of a MOM-"protected" phenol to include a tandem electrophilic aromatic substitution is described, and an application of this strategy in the synthesis of a natural chalcone is reported.

Scheme 1. Formation of an A-ring Acetal upon Cyclization



To test the concept of a tandem cascade cyclization−electrophilic aromatic substitution in a simple system, epoxide **8** was prepared through a short sequence of standard reactions from compounds **4** and **5** (Scheme 2). The initial cascade product of epoxide **8** could undergo electrophilic aromatic substitution at either or both of the two positions meta to the geranyl chain, because these two positions would both be activated by the oxygen substituents. Upon brief treatment of epoxide **8** with $BF_3{\cdot}OEt_2$, tricyclic products were obtained in an overall yield of 82%. In both of the products **9** and **10**, the equatorial orientation of the hydroxyl group was apparent from the diaxial coupling in the resonance of the C2 hydrogen,[3,4] and a trans ring fusion was clear from the shifts of the aliphatic methyl groups.[5] Significantly, the major product **9** had undergone both cyclization and electrophilic aromatic substitution at a single position and was isolated in 52% yield. The regiochemistry of this product was clear because of the obvious ortho coupling between the remaining aromatic hydrogens. This reaction is reminiscent of the novel electrophile-induced ether transfer reported by Taylor[6] but differs significantly in that the entire MOM group becomes part of the product, resulting in the formation of an additional carbon−carbon bond.

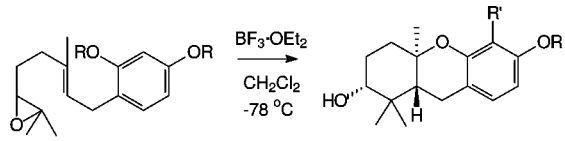
Scheme 2. Tandem Cascade Cyclization−Electrophilic Aromatic Substitution



The regioselectivity observed in the conversion of compound **8** into compound **9** might be considered surprising, especially because resorcinol (**5**) itself typically undergoes electrophilic aromatic substitution at C4 rather than C2.[7−9] In addition, despite the observed formation of the distal acetal **3**, an analogous A-ring MOM derivative was not observed in this series, which suggests that this process can be conducted in the presence of a free hydroxyl group.

To probe this reaction in more detail, the hexadeuterated compound **11** was prepared by an analogous reaction sequence through the use of the trideuterated reagent CD_3OCH_2Cl.[10,11] When a mixture of epoxides **8** (*m*/*z* 350) and **11** (*m*/*z* 356) was treated with $BF_3{\cdot}OEt_2$ under typical reaction conditions, analysis of the products by GC−MS indicated no significant amount of the crossover products **13** (*m*/*z* 353), consistent with an intramolecular process (Scheme 3). Thus, the tandem reaction appears to offer significant advantages over a stepwise approach to the same target in terms of both regioselectivity and efficiency.

Scheme 3. Crossover Experiment with Epoxides **8** and **11**

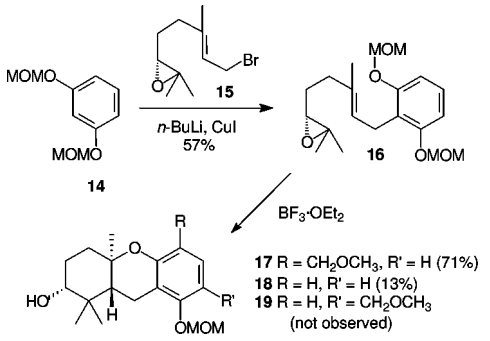


The tandem process observed in the formation of compound **9** utilizes one of the original MOM protecting groups to install a new benzylic methyl ether on the aromatic core, is formally a rearrangement, and thus has high atom economy.[12,13] To display the utility of this tandem process, a synthesis of the natural chalcone **25**[14] was initiated. This compound, which we would name angelichalcone, was reported to exhibit various medicinal properties after its isolation from *Angelica keiskei,* a Japanese herb used in traditional medicine.[15,16] Other reports on the medicinal properties of this species have described a number of related geranylated chalcones with identical aromatic substitution patterns and various oxidation states along the geranyl chain.[15,16]

10.1021/ja906468v CCC: $40.75

The synthesis of compound **25** began with the protected resorcinol **14** (Scheme 4).[17] Compound **14** underwent a highly regioselective lithiation upon treatment with strong base, and the presumed organolithium intermediate was converted to the corresponding cuprate through reaction with CuI.[18] When the resulting anion was allowed to react with (*R*)-6,7-epoxygeranyl bromide (**15**),[19] compound **16** was obtained rapidly as a single regioisomer along with recovered **14** (13%).

Scheme 4. Synthesis and Cyclization of Epoxide **16**

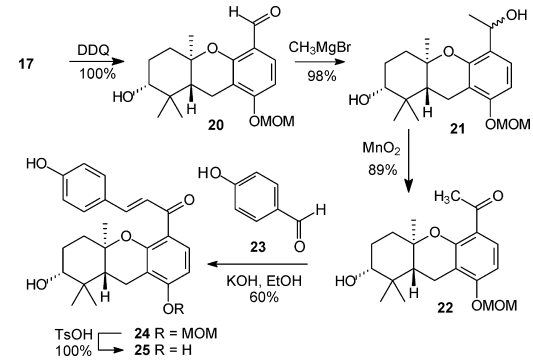


With epoxide **16** in hand, exploration of the cascade process was conducted (Scheme 4). Brief exposure of compound **16** to $BF_3 \cdot OEt_2$[4] gave the tricyclic benzyl methyl ether **17** in 71% yield along with a small amount of the tricyclic compound **18**. In a single operation, this reaction sequence formed two rings plus two additional stereogenic centers and utilized the original MOM protecting group to forge a new carbon−carbon bond. In addition, the reaction proceeded with stereochemical integrity. For example, cyclization of epoxide **16** with 88% ee gave both **17** and **18** in 88% ee as measured by chiral HPLC analysis. The **17**/**18** ratio appeared to be dependent on both concentration and the duration of the reaction. However, the other likely regioisomer, **19**, was not observed under any reaction conditions examined. In addition, attempts to convert compound **18** into compound **17** through reaction with MOMCl and $BF_3 \cdot OEt_2$ were unsuccessful and resulted only in complex mixtures. This difficulty only emphasizes the unique utility of this tandem process.

While one might view a benzyl methyl ether as an unattractive motif for further transformation, it can be employed as a latent aldehyde. Elaboration of ether **17** (Scheme 5) proceeded in excellent yield through DDQ-induced oxidation[20,21] to afford aldehyde **20**. Treatment of aldehyde **20** with methylmagnesium bromide generated the diastereomeric alcohols **21**, which converged to ketone **22** upon exposure to MnO_2. Conclusion of the synthesis proceeded when ketone **22** was allowed to condense with *p*-hydroxybenzaldehyde (**23**) under standard Claisen−Schmidt conditions, which afforded the MOM-protected chalcone **24**. This condensation proved to be sluggish even in concentrated base, presumably because of the free phenol, but unreacted starting material could be recovered fully. Acidic hydrolysis of the remaining MOM acetal proceeded in superb yield to afford (+)-angelichalcone (**25**). Both the ^1H and ^{13}C NMR spectra of the synthetic material were identical to data reported for the natural product, confirming both the structure and relative configuration of this chalcone.[22]

In summary, the cascade cyclization of a "MOM-protected" phenol has been extended to include a tandem electrophilic aromatic substitution of a group equivalent to the $CH_3OCH_2^+$ cation. This tandem reaction allowed the first synthesis of (+)-angelichalcone (**25**) in just seven steps and ∼21% overall yield. The results of the crossover experiments on a related resorcinol are consistent with an intramolecular process, and the tandem reaction affords a single regioisomer that has been difficult to obtain by simple electrophilic aromatic substitution. Further investigations of the mechanism and scope of this process are underway and will be reported in due course.

Scheme 5. Synthesis of (+)-Angelichalcone (**25**)



Acknowledgment. We thank Mr. Kelly Boss for preparation of CD_3OCH_2Cl, the UI Mass Spectrometry Facility for their assistance with analysis of the crossover experiments, and the Roy J. Carver Charitable Trust for their financial support.

Supporting Information Available: Experimental details and the ^1H and ^{13}C NMR spectra for compounds **6**−**12**, **16**−**18**, **20**−**22**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.
(2) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564.
(3) Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. *J. Org. Chem.* **2005**, *70*, 925–931.
(4) Mente, N. R.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2008**, *73*, 7963–7970.
(5) Neighbors, J. D.; Topczewski, J. J.; Wiemer, D. F. *Tetrahedron Lett.* **2009**, *50*, 3881–3884.
(6) Kartika, R.; Frein, J. D.; Taylor, R. E. *J. Org. Chem.* **2008**, *73*, 5592–5594.
(7) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Spagna, R. *J. Am. Chem. Soc.* **1988**, *110*, 546–552.
(8) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, 2877–2881.
(9) Selvam, J. J. P.; Suresh, V.; Rajesh, K.; Reddy, S. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 2507–2509.
(10) Reggelin, M.; Doerr, S. *Synlett* **2004**, 1117.
(11) Buschek, J. M.; Holmes, J. L.; Terlouw, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7321–7325.
(12) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
(13) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281.
(14) Ohnogi, H.; Sugiyama, K.; Muraki, N.; Sagawa, H.; Kato, I. U.S. Patent US20060039998, Feb 23, 2006.
(15) Akihisa, T.; Tokuda, H.; Ukiya, M.; Iizuka, M.; Schneider, S.; Ogasawara, K.; Mukainaka, T.; Iwatsuki, K.; Suzuki, T.; Nishino, H. *Cancer Lett.* **2003**, *201*, 133–137.
(16) Aoki, N.; Muko, M.; Ohta, E.; Ohta, S. *J. Nat. Prod.* **2008**, *71*, 1308–1310.
(17) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888.
(18) Gansauer, A.; Justicia, J.; Rosales, A.; Rinker, B. *Synlett* **2005**, 1954–1956.
(19) Neighbors, J. D.; Mente, N. R.; Boss, K. D.; Zehnder, D. W., II; Wiemer, D. F. *Tetrahedron Lett.* **2008**, *49*, 516–519.
(20) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699–702.
(21) Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965–6972.
(22) The relative stereochemistry of the cyclization was assigned in a fashion parallel to that for compound **9**. Neither the absolute stereochemistry nor the rotation was reported for angelichalcone in the original report. The synthetic material described here has (2*R*,4*aR*,9*aR*) stereochemistry.

JA906468V