Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cationic cascade cyclizations terminated by MOM ether derivatives of β-keto esters

Natalie C. Ulrich [a,b], Jose S. Yu [a], David F. Wiemer [a,*]

[a] Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, USA
[b] Department of Chemistry, Maryville University, St. Louis, MO 63141, USA

ARTICLE INFO

Article history:
Received 20 December 2022
Revised 27 February 2023
Accepted 13 March 2023
Available online xxxx

Keywords:
Cation cascade
Cyclization
Epoxide
MOM ether
Rearrangement

ABSTRACT

It has been known for some time that cationic cascade cyclizations initiated by Lewis acid mediated opening of an epoxide can be trapped by reaction with a β-keto ester. The studies reported here show that the efficiency of these cyclizations can be improved through preparation of a MOM enol ether from the β-keto ester. Furthermore, in both geranyl and farnesyl derivatives the stereochemistry of the enol ether controls formation of the major product. In both series, the *E*-enol ether leads to a cyclic vinylogous carbonate incorporating the oxygen originating in the ketone in the ring system, while the *Z*-enol ether leads to a cyclic enone incorporating the oxygen originating in the ester carbonyl group. Upon treatment with catalytic HCl, a facile rearrangement converts the enone product to the vinylogous carbonate. Because these cyclizations faithfully extend the stereochemistry of the original epoxide into multiple stereocenters, they have the potential to afford significantly more complex structures from relatively simple starting materials.

Cationic cascade cyclizations have the potential to generate a great deal of complexity from relatively simple precursors [1,2]. The quintessential biosynthetic cascade may be the production of lanosterol in animals and fungi from squalene via (3*S*)-squalene oxide and it has been studied extensively [3–6]. It also has inspired numerous efforts to exploit this strategy in chemical syntheses [1,2,7,8].

Our interest in cationic cascade cyclizations originated in an effort to prepare the natural meroterpenoids known as the schweinfurthins [9]. These synthetic efforts have been encouraged by the anti-proliferative activity of the schweinfurthins, especially against cell lines derived from the central nervous system, as well as their limited availability from natural sources. We now have published syntheses of schweinfurthin A [10], B (**1**, Figure 1) [11], C [12], E [11], F [13] (as each enantiomer separately to establish the absolute stereochemistry), G [14], and vedelianin [15]. In each case, the hexahydroxanthene ring system (**2**) was established by a cationic cascade initiated by ring opening of an epoxide. For example, when epoxide **3** was prepared in enantiomeric excess by Shi epoxidation [16], reagent level control of the epoxide stereochemistry was faithfully multiplied through the course of the cyclization to the tricyclic system of compound **2** [11]. After the methyl benzyl ether was converted to an aldehyde by DDQ oxidation, formation of the stilbene olefin of schweinfurthin B via HWE condensation was straightforward [11].

Apart from syntheses of the schweinfurthins, our most important application of this methodology has been the synthesis of angelichalcone (**6**) [17]. While neither the absolute nor the relative stereochemistry was assigned to the natural product, our analysis of the published data suggested the relative stereochemistry shown in structure **6**. We prepared the *2R,4aR,9aR*-enantiomer **6** as summarized in Figure 2 [16,17]. In this case, the cascade cyclization of epoxide **4** presumably generates a species equivalent to the $CH_3OCH_2^+$ cation, resulting in a tandem electrophilic aromatic substitution (EAS) to afford compound **5** as the sole product. This is a striking transformation, given that it proceeds in high yield and results in formation of two new stereocenters, two new rings, and a new aromatic substituent. In addition, the starting material **4** is symmetrical with respect to the aromatic ring, the EAS step has given an unsymmetrical aromatic system as a single regioisomer, and the new benzyl methyl ether serves as a latent aldehyde that allows further elaboration [18]. Insofar as one can determine through cross-over experiments with deuterium labels, the tandem EAS is an intramolecular process [17]. Finally, formation of compound **5** encouraged recognition that the MOM group can serve multiple functions, and led to this study of MOM derivatives of β-keto esters.

* Corresponding author.
E-mail address: david-wiemer@uiowa.edu (D.F. Wiemer).

https://doi.org/10.1016/j.tetlet.2023.154450
0040-4039/

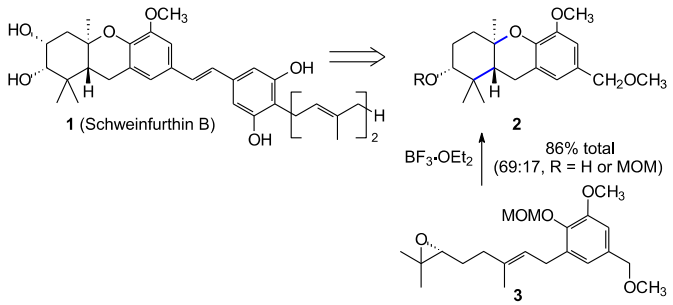


Figure 1. A cascade cyclization route to schweinfurthin B.

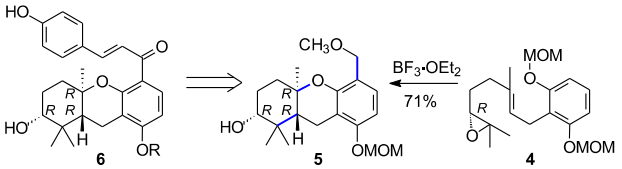


Figure 2. Synthesis of angelichalcone (**6**) via a cationic cascade cyclization.

The first use of a β-keto ester to trap a cation originating from a remote epoxide opening may be Parker's total synthesis of (±)-GERI-BP001, a pyripyropene type acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor (Figure 3) [19]. The modest yield (8%) of the $SnCl_4$-mediated conversion of epoxide **7** to tricycle **8** ultimately compelled them to pursue a route based on a $Hg(OTf)_2$ mediated cyclization that proceeded in better yield (~45% to the tricyclic organomercury compound) [19]. A similar strategy reported by Smith *et al.* used $BF_3{\cdot}OEt_2$ to induce an epoxide cyclization, and reported 20–30% yield for the reaction where the cyclized cation was trapped by a β-keto ester [20]. Despite the modest yields, these studies implied that a cationic cyclization might be trapped by the enol form of a β-keto ester, and suggested that locking an enol form in place through preparation of a MOM derivative might improve the transformation.

The studies reported herein were initiated with investigation of a geranylated β-keto ester. The alkylation of ethyl acetoacetate (**10**) with the known bromide **9** [17] proceeded in modest yield to provide the C-alkylated product **11** (Scheme 1). Conditions reported by Gibbs *et al.* for preparation of enol triflates [21,22], along with an effort to optimize the stereochemical course of this reaction [23], allowed preparation of both the *Z*- and *E*-enol ethers (**12** and **13** respectively). Reaction of β-keto ester **11** with LDA in THF at −78 °C followed by treatment with MOMCl led to the *Z*-enol ether **12**, while reaction of β-keto ester **11** with KHMDS in DMF at room temperature followed by treatment with MOMCl provided the desired *E*-enol ether **13**. Both of the stereoisomeric enol ethers were readily isolated by column chromatography. With both isomers available here, literature data for the spectra of the corresponding methyl ethers [24] and similar vinyl triflates [25], and

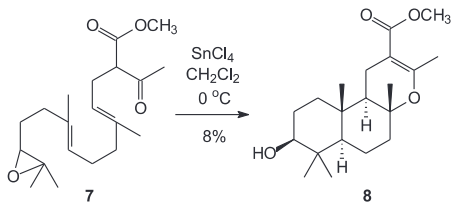
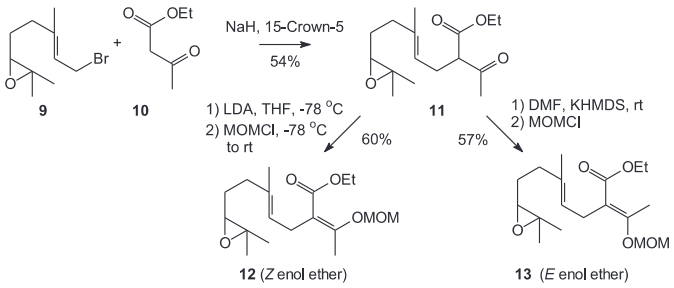


Figure 3. A cascade cyclization terminated by a β-keto ester [19].



Scheme 1. Synthesis of *E*- and *Z*-enol ethers.

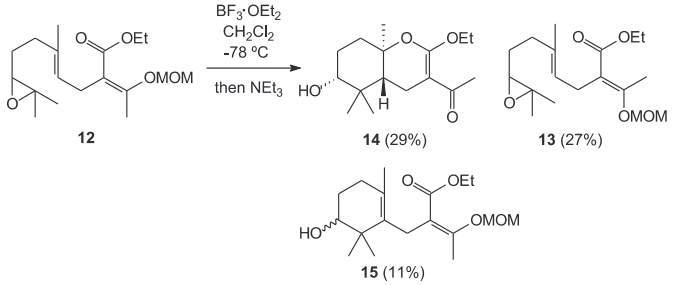
an NOE experiment on the *Z*-MOM ether derived from the prenyl β-keto ester (which has a less cluttered spectrum, cf SI), the ^1H NMR spectra of compounds **12** and **13** allowed unambiguous assignment of the olefin stereochemistry.

Both enol ethers **12** and **13** were subjected to the standard cyclization conditions employed in our labs [14,17,26]. Fortunately, the reaction products of these systems were readily purified and identified. The major product resulting from cyclization of the *Z*-enol ether **12** is the ketone **14** (Scheme 2). Rather surprisingly, the two other major products are the *E*-enol ether **13**, perhaps resulting from isomerization of the starting material, and compound **15** resulting from a single cyclization.

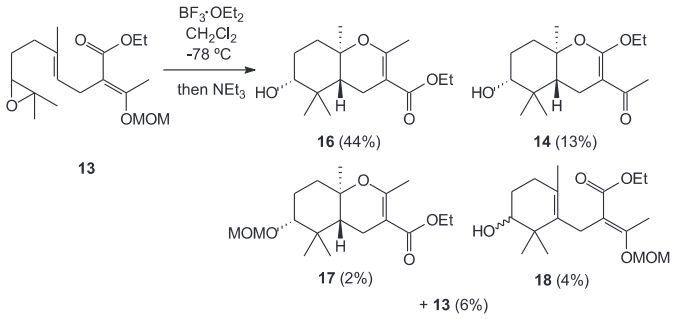
In contrast to the results from cyclization of the *Z*-enol ether **12**, the Lewis acid mediated cascade cyclization of the *E*-enol ether **13** afforded primarily the cyclic ester **16**, with a lesser amount of the ketone **14** (Scheme 3). In addition, small amounts of the A-ring MOM ester **17**, cyclohexene **18**, and recovered starting material **13** were obtained. The proposed *E* stereochemistry of the enol ether in cyclohexene **18** is based upon comparison of the chemical shift of its vinylic methyl hydrogens (2.17 ppm) to those of the *Z*-enol ether **12** (1.95 ppm).

During an attempt to prepare the MOM-protected derivative of ketone **14** an unexpected rearrangement was observed. When ketone **14** was treated with DIPEA and MOMCl, an A-ring MOM derivative was obtained but it was the rearranged ester **17** (Scheme 4) rather than the expected ketone derivative. To determine whether both ester **16** and ketone **14** rearrange under acidic conditions, both were treated with catalytic amounts of HCl in THF at room temperature (Scheme 4). Ester **16** proved to be stable to these conditions, and only recovered starting material was obtained as indicated by TLC and ^1H NMR analyses. Ketone **14** however immediately isomerized to ester **16** in excellent yield. These results indicate that ketone **14** is extremely acid labile, which may prove useful in further syntheses (*vide infra*).

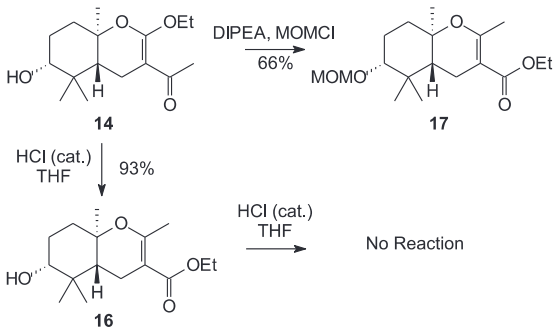
The experience gained in study of the geranyl system encouraged exploration of cascade cyclizations in the corresponding farnesyl compounds. To begin this study, a synthesis of the known farnesyl epoxy bromide **22** [27] was conducted (Scheme 5).



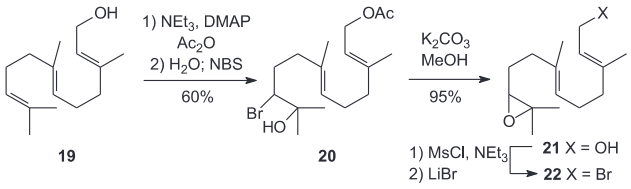
Scheme 2. Cyclization of the *Z*-enol **12**.



Scheme 3. Cyclization of the *E*-enol **13**.



Scheme 4. Rearrangement of ketone **14**.

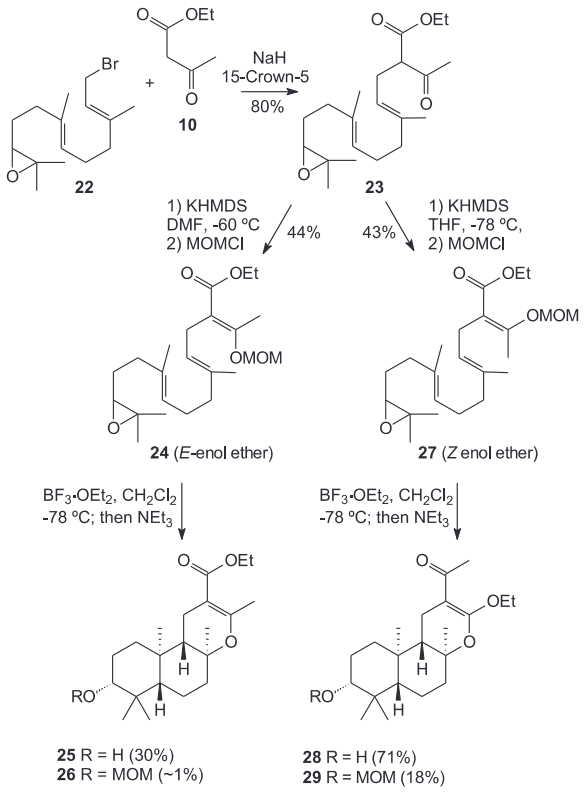


Scheme 5. Synthesis of the farnesyl derivative **22**.

Acetylation of *E*, *E*-farnesol (**19**) followed by treatment with NBS in H_2O provided bromohydrin **20** in modest yield. Simultaneous hydrolysis of the acetate and formation of the epoxide occurred smoothly under basic conditions to afford alcohol **21**, and final conversion to the bromide **22** was accomplished via the intermediate mesylate. To avoid potential decomposition, the bromide **22** immediately was used in the subsequent reaction.

Alkylation of ethyl acetoacetate (**10**) with bromide **22** proceeded in high yield to provide the β-keto ester **23** (Scheme 6) [19]. Because the *E*-enol ether **13** in the geranyl series favored formation of the ester **16** upon cyclization, while the *Z*-enol ether **12** favored formation of the isomeric ketone **14**, it was important to prepare both the *E*- and *Z*-enol ethers in the farnesyl series. Using conditions similar to those reported by Gibbs and coworkers [21,22], the isomeric enol ethers **24** and **27** were obtained in moderate yields.

With the requisite farnesyl-derived *E*- and *Z*-enol ethers in hand, the $BF_3{\cdot}OEt_2$ mediated cyclizations were performed (Scheme 6). As one might expect, these cyclizations produced more products than the geranyl system and isolated yields were more variable. In the case of the *E*-enol ether **24**, the major product isolated was the known ester **25** [28] along with trace amounts of its A-ring MOM derivative **26**, the isomeric *Z*-enol ether **27**, and the



Scheme 6. Preparation and cyclization of the farnesyl-derived *E*- (**24**) and *Z*-enol ethers (**27**).

isomeric ketone **28**. In the case of *Z*-enol ether **27**, the two major products that were obtained were the ketone **28** and its A-ring MOM derivative **29**. The structure of the ketone **28** initially was assigned based on its ^{13}C NMR spectrum which contained a resonance at 196 ppm, far downfield from the carbonyl resonance of the isomeric ester **25** (169 ppm). After column chromatography of the reaction mixture obtained from cyclization of the *Z*-enol ether, ketone **28** crystallized upon concentration of the hexane/ethyl acetate mixture which allowed a diffraction analysis of this product. The X-ray data clearly confirmed the assigned structure and established the relative stereochemistry (Figure 4). The A-ring

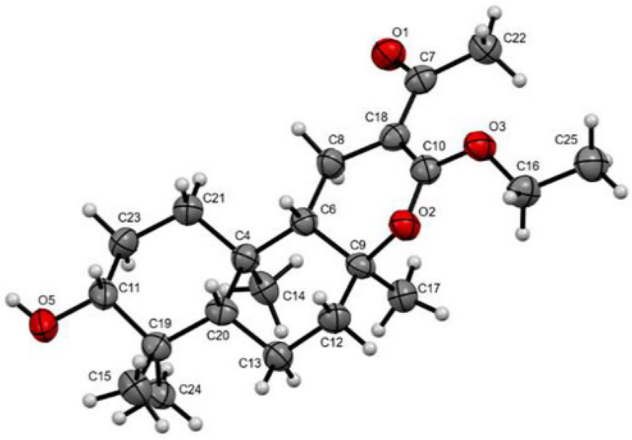
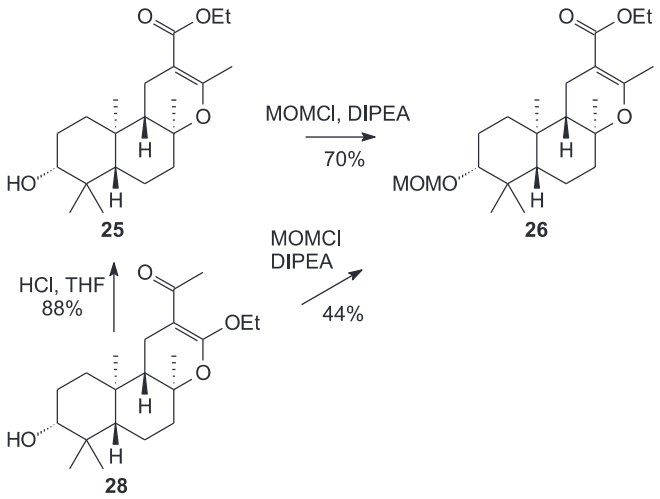


Figure 4. ORTEP of tricyclic ketone **28** based on diffraction analysis. The thermal ellipsoids are represented at 50% probability. Carbon, hydrogen and oxygen atoms are represented by gray, white, and red ellipsoids, respectively.



Scheme 7. MOM protection and rearrangement of the tricyclic compounds **25** and **28**.

alcohol is *syn* to the two bridgehead methyl groups, as observed in Parker's β-keto ester cascade cyclization [19]. Formation of ketone **28** represents the amplification of one stereocenter in the starting epoxide to provide four new stereogenic centers, three rings, two carbon-carbon bonds, and one carbon-oxygen bond.

In an effort to obtain the A-ring MOM derivatives, each of these two cascade products, compounds **25** and **28**, was treated with DIPEA and MOMCl (Scheme 7). Parallel to results encountered in the geranyl ester case (*vide supra*, **16**), the MOM protection of ester **25** proceeded smoothly to provide the MOM-protected tricycle **26**. However, attempted MOM protection of the ketone **28** resulted in rearrangement to the A-ring MOM ester **26**. Based on these results, ketone **28** was treated with a catalytic amount of HCl in THF at room temperature. Analysis of the reaction mixture by TLC and ^{1}H NMR indicated facile (<1 min) and complete conversion to the ester **25**, a rearrangement parallel to that observed in the geranyl series.

In conclusion, these studies have shown that use of a MOM derivative of a β-keto ester can significantly enhance the efficiency of a cationic cascade cyclization initiated by epoxide ring opening. While the yields can be variable, the substantial degree of complexity introduced in a single reaction makes this strategy well worth investigation. Furthermore, preparation of the ester **25** constitutes a formal total synthesis of racemic arisugacin F simply by treatment with LDA and methyl *p*-methoxybenzoate [28,29], and because the ketone **28** readily rearranges to the ester it could be employed in an arisugacin F synthesis as well. While the experiments reported here were conducted with racemic material, there is every reason to believe that enantioselective preparation of the epoxides used to initiate these cyclizations would afford non-racemic products, further enhancing the value of this strategy.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Dr. Dale C. Swenson and Dr. Daniel K. Unruh for their assistance with the diffraction analysis of compound **28**, and Dr. George Crull for his assistance with the NMR spectra. We thank the UI Graduate College for support in the form of a Presidential Fellowship (to NCU). Financial support from the Roy J. Carver Charitable Trust is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154450.

References

[1] A.G.M. Barrett, T.K. Ma, T. Mies, Recent developments in polyene cyclizations and their applications in natural product, Synthesis-Stuttgart 51 (2019) 67–82.
[2] R. Ardkhean, D.F.J. Caputo, S.M. Morrow, H. Shi, Y. Xiong, E.A. Anderson, Cascade polycyclizations in natural product synthesis, Chem. Soc. Rev. 45 (2016) 1557–1569.
[3] R.B. Woodward, K. Bloch, The cyclization of squalene in cholesterol synthesis, J. Am. Chem. Soc. 75 (1953) 2023–2024.
[4] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni. To Know the Triterpene. 190. A Stereochemical Interpretation of the Biogenetic Isoprene Rule in Triterpenes *Helv. Chim. Acta* **1955**, *38*, 1890-1904.
[5] R.K. Maudgal, T.T. Tchen, K. Bloch, 1,2-Methyl shifts in the cyclization of squalene to lanosterol, J. Am. Chem. Soc. 80 (1958) 2589–2590.
[6] J.W. Cornforth, R.H. Cornforth, C. Donninger, G. Popják, Y. Shimizu, S. Ichii, E. Forchielli, E. Caspi, The migration and elimination of hydrogen during biosynthesis of cholesterol from squalene, J. Am. Chem. Soc. 87 (1965) 3224–3228.
[7] E.E. Van Tamelen, B. Chemistry, Total synthesis of tetra- and pentacyclic triterpenoids, Acc. Chem. Res. 8 (1975) 152–158.
[8] S.K. Taylor, Biosynthetic, biomimetic and related epoxide cyclizations - a review, Org. Prep. Proced. Int. 24 (1992) 245–284.
[9] J.A. Beutler, R.H. Shoemaker, T. Johnson, M.R. Boyd, Cytotoxic geranyl stilbenes from *Macaranga schweinfurthii*, J. Nat. Prod. 61 (1998) 1509–1512.
[10] J.J. Topczewski, J.G. Kodet, D.F. Wiemer, Exploration of cascade cyclizations terminated by tandem aromatic substitution: total synthesis of (+)-Schweinfurthin A, J. Org. Chem. 76 (2011) 909–919.
[11] J.J. Topczewski, J.D. Neighbors, D.F. Wiemer, Total synthesis of (+)-Schweinfurthins B and E, J. Org. Chem. 74 (2009) 6965–6972.
[12] E.M. Treadwell, S.C. Cermak, D.F. Wiemer, Synthesis of Schweinfurthin C, a geranylated stilbene from *Macaranga schweinfurthii*, J. Org. Chem. 64 (1999) 8718–8723.
[13] N.R. Mente, A.J. Wiemer, J.D. Neighbors, J.A. Beutler, R.J. Hohl, D.F. Wiemer, Total synthesis of (R, R, R)- and (S, S, S)-Schweinfurthin F: differences of bioactivity in the enantiomeric series, Bioorg. Med. Chem. Lett. 17 (2007) 911–915.
[14] N.R. Mente, J.D. Neighbors, D.F. Wiemer, $BF_3{\cdot}Et_2O$-mediated cascade cyclizations: synthesis of Schweinfurthins F and G, J. Org. Chem. 73 (2008) 7963–7970.
[15] J.J. Topczewski, D.F. Wiemer, First total synthesis of (+)-Vedelianin, a potent antiproliferative agent, Tetrahedron Lett. 52 (2011) 1628–1630.
[16] L.H. Shu, Y. Shi, An efficient ketone-catalyzed epoxidation using hydrogen peroxide as oxidant, J. Org. Chem. 65 (2000) 8807–8810.
[17] J.J. Topczewski, M.P. Callahan, J.D. Neighbors, D.F. Wiemer, A tandem cascade cyclization-electrophilic aromatic substitution: application in the total synthesis of (+)-Angelichalcone, J. Am. Chem. Soc. 131 (2009) 14630–14631.
[18] P.A. Shah, D.F. Wiemer, Synthesis of bavachromanol from resorcinol via a tandem cationic cascade/EAS sequence, *Tetrahedron Lett.* 59 (2018) 1363–1365.
[19] K.A. Parker, L. Resnick, The first total synthesis of a pyripyropene-type ACAT inhibitor, (+/-)-GERI-BP001, J. Org. Chem. 60 (1995) 5726–5728.
[20] A.B. Smith, T. Kinsho, T. Sunazuka, S. Omura, Biomimetic total synthesis of the ACAT inhibitor (+)-Pyripyropene E, Tetrahedron Lett. 37 (1996) 6461–6464.
[21] Y. Shao, J.T. Eummer, R.A. Gibbs, Stereospecific synthesis and biological evaluation of farnesyl diphosphate isomers, Org. Lett. 1 (1999) 627–630.
[22] H.B. Xie, Y. Shao, J.M. Becker, F. Naider, R.A. Gibbs, Synthesis and biological evaluation of the geometric farnesylated analogues of the a-factor mating peptide of saccharomyces cerevisiae, J. Org. Chem. 65 (2000) 8552–8563.
[23] N.C. Ulrich, PhD Thesis, University of Iowa, 2010.
[24] B. Alcaide, L. Casarrubios, G. Dominguez, M.A. Sierra, Synthesis of 2-Acylvinyl ethers by reaction of chromium (Fischer) carbene complexes and stabilized sulfur ylides, *Organometallics* 15 (1996) 4612–4617.

[25] R.A. Gibbs, U. Krishnan, J.M. Dolence, C.D. Poulter, A stereoselective palladium copper-catalyzed route to isoprenoids - Synthesis and biological evaluation of 13-methylidenefarnesyl diphosphate, J. Org. Chem. 60 (1995) 7821–7829.

[26] J.D. Neighbors, J.J. Topczewski, D.C. Swenson, D.F. Wiemer, Synthesis of the Cis-fused hexahydroxanthene system via cationic cascade cyclization, *Tetrahedron Lett.* 50 (2009) 3881–3884.

[27] E.J. Corey, S.Z. Lin, A short enantioselective total synthesis of Dammarenediol II, J. Am. Chem. Soc. 118 (1996) 8765–8766.

[28] M. Handa, T. Sunazuka, A. Sugawara, Y. Harigaya, K. Otoguro, S. Omura, Total syntheses of the AChE inhibitors (+/-)-Arisugacins F and G, J. Antibiot. 56 (2003) 730–733.

[29] T. Sunazuka, M. Handa, K. Nagai, T. Shirahata, Y. Harigaya, K. Otoguro, I. Kuwajima, S. Omura, Absolute stereochemistries and total synthesis of (+)-Arisugacins A and B, potent, orally bioactive and selective inhibitors of acetylcholinesterase, Tetrahedron 60 (2004) 7845–7859.