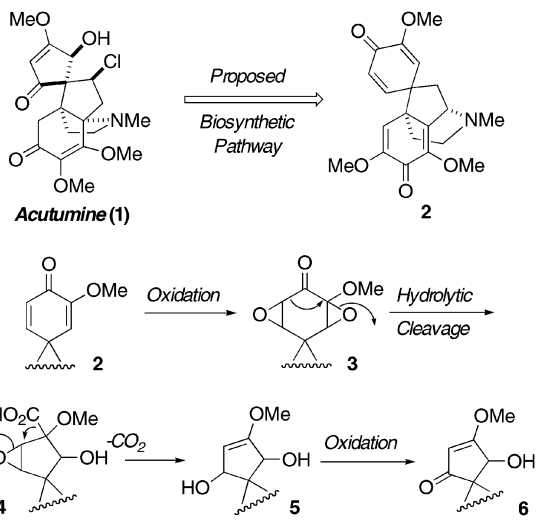
Spiroketals *via* oxidative rearrangement of enol ethers†

David L. Waller, Corey R. J. Stephenson and Peter Wipf*

Received 7th September 2006, Accepted 2nd November 2006
First published as an Advance Article on the web 14th November 2006
DOI: 10.1039/b612992g

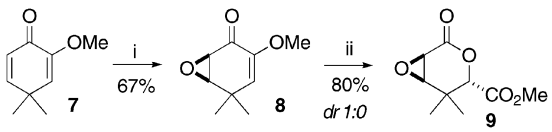
Oxidative rearrangement of cyclic enol ethers leads to α-alkoxyesters. In the presence of a neighboring spiroether, this approach provides a stereoselective access to spiroketals. A modified proposal for the biosynthesis of acutumine is presented.

As part of our research program on the synthesis of highly oxygenated spiroketal natural products and Trx inhibitors,[1] we attempted to model Barton's proposed biosynthesis of the spiro-fused vinylogous ester moiety of acutumine (**1**, Scheme 1).[2] In this proposal, Barton suggested spirodienone **2** as a possible biosynthetic branching point. Double epoxidation of **2** followed by a hydrolytic Favorskii-type rearrangement furnishes acid **4**. Decarboxylation and epoxide opening affords allylic diol **5**, which is only a single oxidation level apart from vinylogous ester **6**.[3]



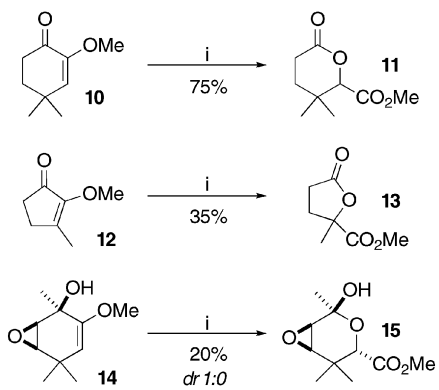
Scheme 1 Barton's proposal for the biosynthesis of acutumine (**1**).

Due to the ready access to dienones of type **2**,[4] this ring contraction provides an attractive, albeit hypothetical entry to acutumine alkaloid synthesis.[5] Our first approach to investigate this proposal began with model dienone **7**.[6] Treatment with basic hydrogen peroxide provided monoepoxide **8** in 67% yield (Scheme 2). When **8** was treated with 3 equivalents of *m*CPBA buffered with Na_2HPO_4, we expected that the intermediate bis-epoxide would undergo Barton's proposed cascade reaction; however we isolated only racemic epoxylactone **9** in 80% yield as a single diastereomer, characterized by X-ray crystallography. We found that the actual diastereoselectivity of this reaction in the absence of Na_2HPO_4 was only 2 : 1; the crude product then readily equilibrated to a single diastereomer while washing the organic layer with aqueous $NaHCO_3$.



Scheme 2 *Reagents and conditions*: (i) H_2O_2, K_2CO_3, THF, 40 °C, 6 h. (ii) *m*-chloroperbenzoic acid (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18 h.

While not entirely unprecedented,[7] the epoxide rearrangement of **8** to **9** offers new and intriguing opportunities for natural product and diversity-oriented synthesis.[8] In order to probe the mechanism and develop the scope of this transformation, we examined additional substrates, including five-and six-membered diosphenol ethers (**10**,[9] **12**[10]), and the highly functionalized hydroxy enol ether **14**. An epoxide (as in **8**) was clearly not necessary: enone **10** underwent rearrangement to lactone **11** in 75% yield (Scheme 3). In contrast, the yield for the conversion of five-membered enone **12** to lactone **13** was only 35%. A carbonyl functionality was also not needed to facilitate the rearrangement; the epoxy alcohol **14**, prepared by the addition of MeLi to ketone **8**, succumbed to the oxidative rearrangement to give hemiacetal **15** in 20% yield as a racemic single diastereomer which was again characterized by X-ray crystallography.

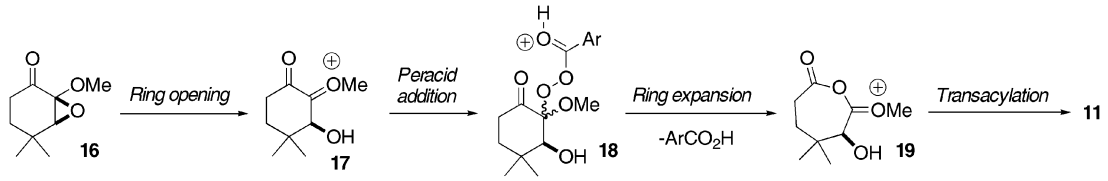


Scheme 3 *Reagents and conditions*: (i) *m*-chloroperbenzoic acid (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18 h.

A proposal for the oxidative rearrangement of **10** is outlined in Scheme 4. The epoxy ether intermediate **16** opens to the alkoxycarbenium ion **17** in the presence of a proton donor. This species is then intercepted by another equivalent of peracid to give peroxy ketal **18**. A methyl ether assisted acyl shift

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. E-mail: pwipf@pitt.edu; Fax: +1 412-624-0787; Tel: +1 412-624-8606

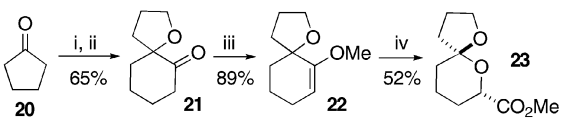
† Electronic supplementary information (ESI) available: Experimental details and spectral data for new compounds; X-ray data for compounds **9** and **15**. See DOI: 10.1039/b612992g



Scheme 4 Proposed mechanism for oxidative rearrangement.

generates the seven-membered lactone **19** which can undergo a ring contraction to generate the product lactone ester **20**, which is epimerizable at the α-position to the ester moiety, resulting in the thermodynamically more stable equatorial ester after basic workup and isolation. This sequence constitutes a net addition of two oxygen atoms concomitant with a skeletal rearrangement.[7]

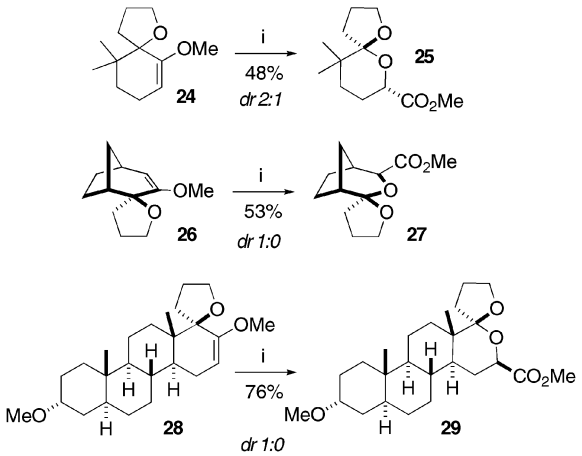
Even though the product forms in low yield, we were particularly interested in the possible use of highly functionalized substrates such as **14** in the oxidative enol ether rearrangement. Replacement of the tertiary hydroxy group with a cyclic ether would establish a novel access to spiroacetals, which are common features in biologically active natural products.[11,12] A procedure developed by Paquette *et al.* provided rapid access to the desired α-carbonyl functionalized cyclic ethers.[13] Addition of 5-lithio-2,3-dihydrofuran to cyclopentanone furnished an intermediate tertiary allylic alcohol which underwent an acid catalyzed pinacol rearrangement to give spirocyclic ketone **21**[13] in 65% overall yield (Scheme 5). While hard electrophiles such as Meerwein's reagent failed to give satisfactory yields of *O*-alkylation, generation of the enolate of **21** with KHMDS, followed by addition of DMF and dimethyl sulfate furnished the methyl enol ether **22** in 89% yield. When **22** was submitted to the oxidative rearrangement with *m*CPBA, the volatile spiroketal **23** was obtained as the sole product in 52% yield.



Scheme 5 *Reagents and conditions*: (i) 5-lithio-2,3-dihydrofuran, THF, −78 °C, 12 h. (ii) Dowex 50X, CH_2Cl_2, 18 h. (iii) KHMDS, Me_2SO_4, THF–DMF (4 : 1), −78 °C, 4 h. (iv) *m*-chloroperbenzoic acid (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18 h.

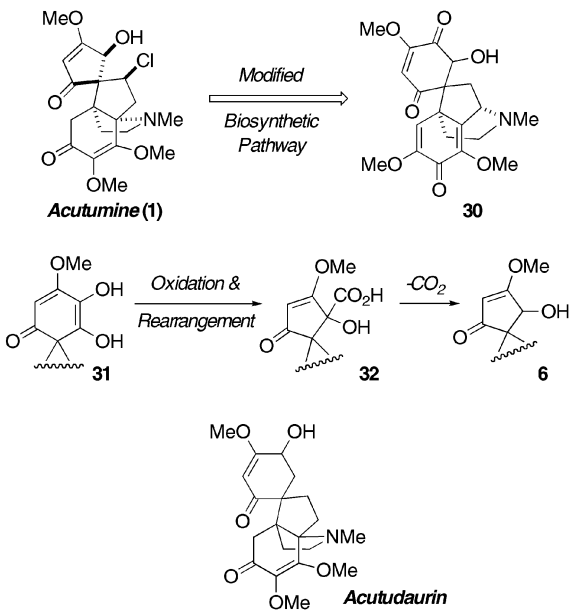
For a further expansion of this methodology, we prepared methyl enol ethers **24**, **26**[14] and androsterone-based **28**[14] in a fashion analogous to **22**.[15] When **24** was submitted to the rearrangement, the volatile spiroketal **25** was isolated in 48% yield as a modest 2 : 1 mixture of diastereomers (Scheme 6). The tricyclic methyl enol ether **26** smoothly underwent the rearrangement in 53% yield, and product **27** was isolated as a single diastereomer. Additionally, **28** was also converted to pentacyclic spiroketal **29** as a single diastereomer in 76% yield.[16]

In conclusion, we have demonstrated a new and efficient oxidative rearrangement of alkyl enol ethers to lactone and spiroketal esters. Our method allows a rapid access to these common structural subunits of natural products. We are currently exploring additional applications of this process towards biologically active molecules. This investigation was inspired by Barton's proposal for the biosynthesis of acutumine, but we have not been able to garner any experimental support for the dienone diepoxide



Scheme 6 *Reagents and conditions*: (i) *m*-chloroperbenzoic acid (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18 h.

rearrangement shown in Scheme 1. While an enzymatic pathway could easily take a different course, it appears that, chemically, α-epoxy ethers of type **3** prefer alternative rearrangements to a migratory ring contraction. In fact, the recent isolation of acutudaurin,[17] a possible precursor of acutumine-type natural products, supports a modified biosynthetic pathway (Scheme 7).



Scheme 7 Alternative proposal for the biosynthesis of acutumine (**1**).

The tricarbonyl tyrosine dimer **30** can be envisioned as a direct precursor of **1** after oxidation and benzilic acid rearrangement (**31** → **32**), followed by decarboxylation to give the cyclopentanone subunit **6**. This pathway is supported by experimental observations

in the literature,[18] and the oxygenation pattern on spirocycle **31** is in good agreement with the structure of acutudaurin.

Acknowledgements

This work has been supported the NIH/NIGMS CMLD program (GM067082). The authors thank Mr Alvarro Carraro and Dr Hidenori Takahashi (University of Pittsburgh) for preliminary synthetic studies, Dr Katsuhide Matoba (Otsuka Pharmaceutical Co. Ltd) for stimulating discussions, and Dr Steve Geib (University of Pittsburgh) for X-ray analysis.

References

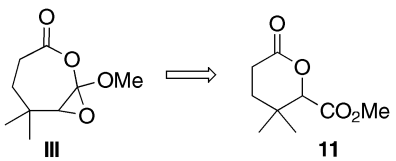
1 For recent examples, see: (*a*) G. Powis, P. Wipf, S. M. Lynch, A. Birmingham and D. L. Kirkpatrick, *Mol. Cancer Ther.*, 2006, **5**, 630; (*b*) P. Wipf, S. M. Lynch, G. Powis, A. Birmingham and E. E. Englund, *Org. Biomol. Chem.*, 2005, **3**, 3880; (*c*) P. Wipf, S. M. Lynch, A. Birmingham, G. Tamayo, A. Jimenez, N. Campos and G. Powis, *Org. Biomol. Chem.*, 2004, **2**, 1651; (*d*) P. Wipf and J.-K. Jung, *J. Org. Chem.*, 2000, **65**, 6319.

2 D. H. R. Barton, A. J. Kirby and G. W. Kirby, *J. Chem. Soc. C*, 1968, 929.

3 The biosynthetic pathways for acutumine have been investigated: H. A. A. Babiker, Y. Sugimoto, T. Saisho and S. Inanaga, *Phytochemistry*, 1999, **50**, 775; H. A. A. Babiker, Y. Sugimoto, T. Saisho, S. Inanaga, M. Hashimoto and A. Isogai, A., *Biosci., Biotechnol., Biochem.*, 1999, **63**, 515; Y. Sugimoto, S. Uchida, S. Inanaga, Y. Kimura, M. Hashimoto and A. Isogai, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 503.

4 P. Wipf and Y. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 11678.

5 Barton's proposal has been investigated before, although on a simpler model system: K. Matoba, N. Karibe and T. Yamazaki, *Chem. Pharm. Bull.*, 1984, **32**, 2639. This group assigned an enone oxidation product as a Baeyer–Villiger derived lactone. Based on our investigation presented herein, we believe that their assignment of **III** should be revised to **11**.



III **11**

6 K. Matoba, N. Karibe and T. Yamazaki, *Chem. Pharm. Bull.*, 1982, **30**, 3906.

7 To the best of our knowledge, this net transformation has been observed only twice; in both cases upon treatment of enones with basic hydrogen peroxide for extended periods of time: K. L. Bhat and G. Trivedi, *Synth. Commun.*, 1982, **12**, 585; M. Kocor, A. Kurek and J. Dabrowski, *Tetrahedron*, 1969, **25**, 4257.

8 For lead references on the concept of diversity-oriented synthesis, see: (*a*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74; (*b*) P. Wipf, C. R. J. Stephenson and M. A. A. Walczak, *Org. Lett.*, 2004, **6**, 3009; (*c*) P. Wipf, S. Werner, G. H. C. Woo, C. R. J. Stephenson, M. A. A. Walczak, C. M. Coleman and L. A. Twining, *Tetrahedron*, 2005, **61**, 11488.

9 (*a*) E. Wenkert, N. F. Golob, S. S. Sathe and R. A. J. Smith, *Synth. Commun.*, 1973, **3**, 205; (*b*) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, 1953, **18**, 1601.

10 B.-M. Kwon and C. S. Foote, *J. Org. Chem.*, 1989, **54**, 3878.

11 Reviews: (*a*) K. T. Mead and B. N. Brewer, *Curr. Org. Chem.*, 2003, **7**, 227; (*b*) M. A. Brimble and F. A. Fares, *Tetrahedron*, 1999, **55**, 7661; (*c*) S. Rodriguez and P. Wipf, *Synthesis*, 2004, 2767.

12 For recent synthetic work, see: (*a*) J. Hao, F. Matsuura, Y. Kishi, M. Kita, D. Uemura, N. Asai and T. Iwashita, *J. Am. Chem. Soc.*, 2006, **128**, 7742; (*b*) C. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 2997; (*c*) K. Meilert and M. A. Brimble, *Org. Biomol. Chem.*, 2006, **4**, 2184; (*d*) V. Rauhala, K. Nattinen, K. Rissanen and A. M. P. Koskinen, *Eur. J. Org. Chem.*, 2005, 4119. I; (*e*) I. Paterson, D. Gottschling and D. Menche, *Chem. Commun.*, 2005, 3568; (*f*) P. Wipf and T. D. Hopkins, *Chem. Commun.*, 2005, 3421.

13 L. A. Paquette, J. T. Negri and R. D. Rogers, *J. Org. Chem.*, 1992, **57**, 3947.

14 The assignment of the configuration of the tetrahydrofuran ring was based on previous studies conducted on these acid-mediated ring expansions: L. A. Paquette, J. F. P. Andrews, C. Vanucci, D. E. Lawhorn, J. T. Negri and R. D. Rogers, *J. Org. Chem.*, 1992, **57**, 3956.

15 See supporting information for experimental details.

16 The configurations of **25** and **27** were assigned in analogy to **9** and **15**, which were determined by X-ray analysis. CCDC reference numbers 624751 and 624752. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612992g. Further support for this assignment was obtained by ^{1}H NMR coupling constant analysis of the hydrogen α to the methyl ester. Compound **26** is the methyl enol ether of a known compound as noted in ref. 14.

17 T. Furumoto and Y. Sugimoto, *Planta Med.*, 2001, **67**, 194.

18 (*a*) V. Georgian and N. Kundu, *Tetrahedron*, 1963, **19**, 1037; (*b*) N. Greenhalgh, *J. Chem. Soc.*, 1954, 4699; (*c*) H. Liu, D. R. Siegel and S. J. Danishefsky, *Org. Lett.*, 2006, **8**, 423; (*d*) R. Holzel, A. P. Leftwick and B. C. L. Weedon, *J. Chem. Soc. D*, 1969, 128.

