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A Remarkable Multicomponent Cascade Sequence for the Formation of a Spirocyclic Polyether

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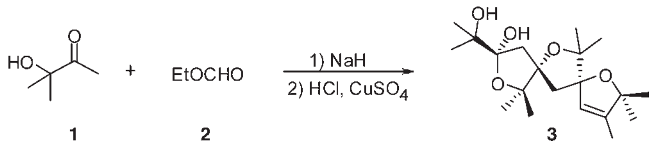
ABSTRACT



A reaction of 2-hydroxy-2-methylbutan-3-one with sodium hydride in the presence or absence of ethyl formate after acid workup gave the spirocyclic ether 3.

The phenolic ketone ascofuranone **4**[1] is an antifungal agent isolated from the fungus *Ascochyta visiae* (Figure 1).

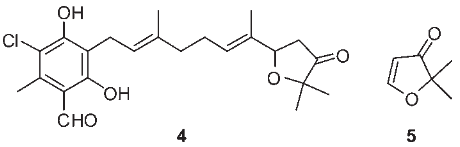
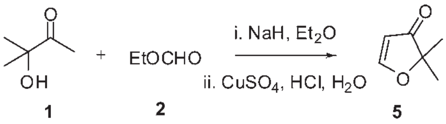


Figure 1

In our approach to the synthesis of ascofuranone **4** we required the vinylogous ester **5** as a starting material. A survey of the literature revealed that Margaretha et al.[2] in 1971 had reported the preparation of furanone **5** using a base mediated condensation of 2-methyl-2-hydroxy-3-butanone **1** with ethyl formate **2** (Scheme 1).

Smith[3] and his co-workers in 1981 reported that they were unable to repeat this reaction, and we have also failed to repeat the results reported by Margaretha et al.[2] Careful analysis of the reaction reported by Margaretha et al.[2] which was repeated using a range of different conditions indicated a different reaction pathway to that reported, which led to the formation of the tricyclic ether **3**. When the reaction was carried out in the absence of ethyl formate using the conditions outlined in Margaretha's paper, the tricyclic ether **3** was the only product isolated (Scheme 2).

Scheme 1



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(1) (a) Mori, K.; Fujioka, T. *Tetrahedron Lett*. **1983**, *24*, 1547–1548. (b) Guthrie, A. E.; Semple, J. E.; Joullié, M. M. *J. Org. Chem*. **1982**, *47*, 2369–2376.

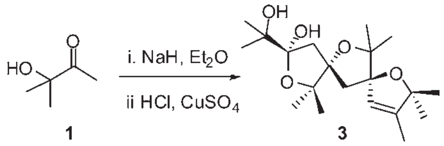
(2) Margaretha, P. *Tetrahedron Lett*. **1971**, *12* (51), 4891–4892.

(3) Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc*. 1981, Vol. *103*, 1501-1513.

(4) (a) Diels, O.; Jost., H. *Ber* **1902**, *35*, 3290. (b) Cresswell, R. M.; Smith, W. D. R.; Wood, H. C. S. *J. Chem. Soc*. **1961**, 4882. (c) Hudec, J.; Turner, D. L. *J. Chem. Soc., Perkin Trans*. **1982**, *2*, 951. (d) Poje, M.; Perina, I.; Vockovic, I.; Bruno, M. *Tetrahedron* **1985**, *41*, 1985. (e) Baldenius, K.; Dallman, P.; Hudec, J. *Tetrahedron Lett*. **1993**, *34*, 1517. (f) Hudec, J.; Crabb, T. A.; Patel, A. V. *Heterocycles* **1996**, *43*, 3125.

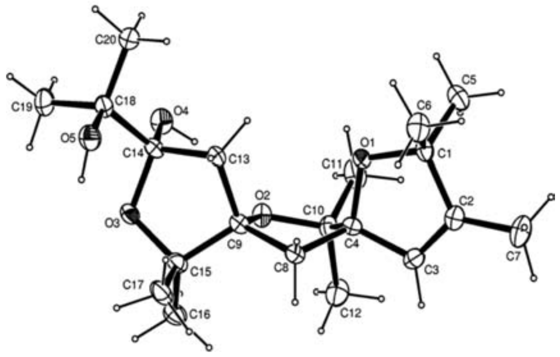
10.1021/ol201354k

Scheme 2



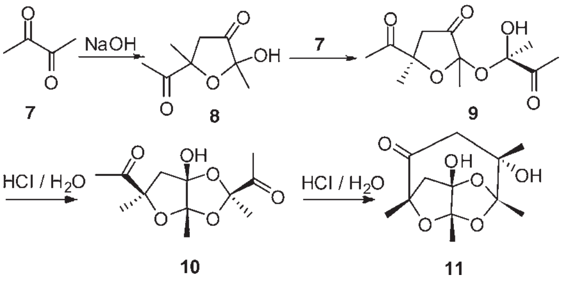
The reaction outlined in Scheme 2 was performed using different bases (LDA and ^{t}BuOK) followed by a simple acid workup in the presence or absence of copper II sulfate; the crystalline tricyclic ether **3** was again isolated in good yield.

X-ray structure for 3



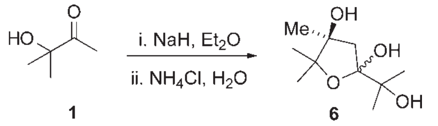
The acid and base catalyzed reactions of biacetyl have been published, and Hudec et al.[4] have shown that the acid catalyzed trimerization of biacetyl **7** results in the formation of the ketol **11** together with other interesting dimers and trimers of biacetyl (Scheme 3).

Scheme 3

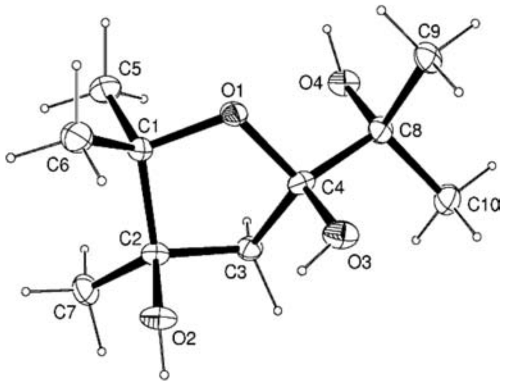


Treatment of 2-hydroxy-2-methylbutan-3-one **1** with sodium hydride in ether, followed by workup with aqueous ammonium chloride, gave a crystalline product. This was shown by NMR spectroscopy and X-ray analysis to be the aldol dimer **6** which is consistent with literature reported on similar systems[5] (Scheme 4).

Scheme 4

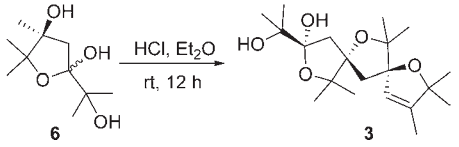


X-ray structure for 6



These data indicate that the starting material **1** reacts with itself under base catalyzed conditions much faster than with ethyl formate **2**. We have shown that when the dimer **6** is exposed to aqueous ethereal hydrochloric acid, the spirocyclic ether **3** is formed in 30% yield (Scheme 5).[6]

Scheme 5



The formation of **3** could result from the series of condensations outlined in Scheme 6.

Dehydration of **7** will furnish the enone **8** which in turn will undergo an acid catalyzed aldol condensation with the starting material **1** (Scheme 6).

An acid catalyzed reaction of the enone **8** with the ketol **1** will give the tetraol **10** which will undergo loss of water to form the diene **11**. Acid mediated intramolecular Michael addition will give the dihydrofuran **12**. The intermediate **12** will react again with the ketol **1** in acid to give the enone **14** (Scheme 7).

The enone **14** could undergo a further acid catalyzed intramolecular Michael addition to give the spirocycle **15** which will ring close to afford the spirocycle **16**. The

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(5) Favorskaya, T. A.; Shevchenko, Z. A.; Kuznetsova, T. A. *Russ. J. Gen. Chem.* **1962**, *33*, 2909–2916.

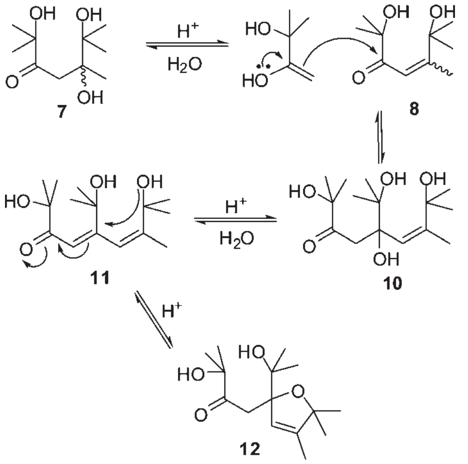
(6) The yield of **3** from **1** was 18% due to competing dehydration of **1** and the formation of polymeric material.

(7) Saimoto, H.; Shinoda, M.; Matsubara, S.; Oshima, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3088–3092.

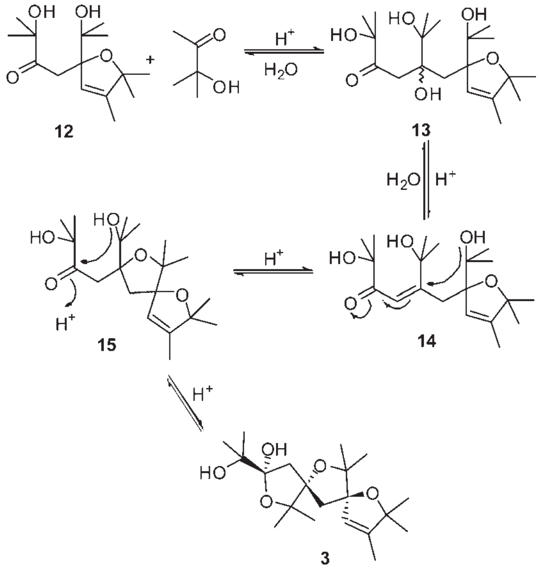
(8) Williams, D. R.; Abbaspour, A.; Jacobsen, R. M. *Tetrahedron Lett.* **1981**, *22*, 3565–3568.

(9) We thank one of the referees for pointing out this alternative pathway.

Scheme 6



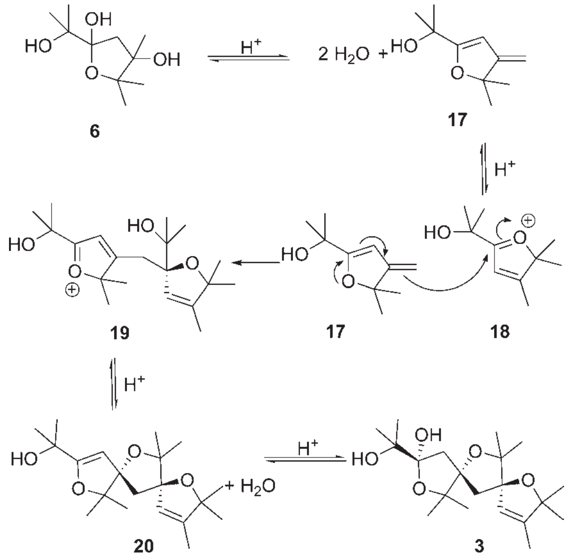
Scheme 7



desired enone has now been prepared by the reliable procedures of Hiyama et al.[7] and Williams et al.[8]

The observed yield of **3** was higher (30%) when the dimer **6** was used as the starting material. This gives credence to the mechanistic pathway outlined in Scheme 8.[9] We will attempt to distinguish between the mechanisms outlined in Schemes 6, 7, and 8 using O^{18} labeled water.

Scheme 8



We are currently investigating the theory of this interesting observation using a DFT approach.[10] These results will be published in full at a later stage.

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Supporting Information Available. Experimental procedures and spectroscopic data for **3** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. The structure of compound **1** was corrected in the Abstract graphic, Scheme 2, and Scheme 4; the correct version reposted July 1, 2011.

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(10) Seminario, J. M.; Politzer, P. *Modern Density Functional Theory: A Tool for Chemistry*; Elselvier: Amsterdam, 1995.