Medium-Sized Carbocycles and Ethers from 4-Pyrones: A Photocyclization−Fragmentation Approach[1]

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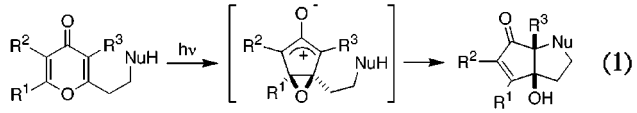
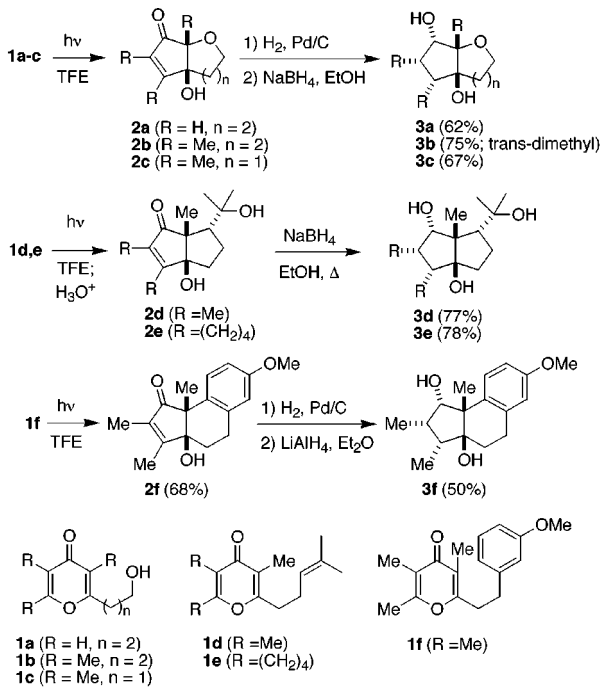
Eight- and nine-membered rings are prominently featured in many natural products. The well-known energetic penalties incurred in direct closure of medium rings[2] have prompted the development of a number of novel approaches to their formation by routes not involving direct ring closure.[3] Grob fragmentation has proven to be an effective strategy for the formation of medium rings,[4] but its application can be limited by the necessary complexity of the bicyclic precursor. We report here a concise approach to functionalized medium-sized ethers and carbocycles utilizing an efficient photocyclization of 4-pyrone derivatives followed by reduction and fragmentation of the resulting adduct.

We have shown that readily available 4-pyrones bearing pendant heteroatom or carbon nucleophiles undergo photochemical conversion to reactive bicyclic oxyallyl zwitterions. These intermediates are efficiently trapped by the internal nucleophile to directly form diquinane, hydrindan, benzohydrindene, oxabicyclo[3.3.0]octane, or oxabicyclo[4.3.0]nonane skeletons (eq 1).[5] In all cases, the bicyclic photoadduct contains an angular hydroxyl group in a 1,3-relationship to the cyclopentenone carbonyl, providing a handle for cleavage of the ring-fusing bond through a fragmentation approach. Direct cleavage via the well-precedented retro-aldol fragmentation[6] was deemed unlikely in these cases, since the ring strain inherent in the cyclopentenone would not be sufficient to drive the equilibrium toward the medium ring. On the other hand, an *irreversible* Grob-type fragmentation should be possible by reduction of the enone and selective activation of the resulting secondary hydroxyl group.



(1)

Scheme 1



Substrates examined included bicyclic ethers **2a**−**c**, diquinanes **2d**−**e**, and benzohydrindenone **2f**, prepared in good yield from the corresponding 4-pyrones **1a**−**f** (Scheme 1). The necessary cyclopentane-1,3-diols **3a**−**f** could be obtained by catalytic hydrogenation followed by metal hydride reduction of the resulting cyclopentanone or in some cases via one-pot reduction with $NaBH_4$ in hot EtOH.[7] It was difficult to prevent epimerization adjacent to the carbonyl during and after hydrogenation of **2b**,[8] and in this case, the major (trans) diastereomer was carried on. For ketone reduction in the preparation of **3f**, $LiAlH_4$ was found to be preferable to $NaBH_4$ due to slow reduction relative to enolization.

Tosylation was generally preferable to mesylation in order to better select for the secondary hydroxyl over the angular hydroxyl. However, in some cases (e.g., **2d**−**f**), tosylation was prohibitively slow, necessitating use of the mesylate (Scheme 2). After extensive experimentation using **3a**, it was determined that dimsylsodium in DMSO or KO-*t*-Bu in *t*-BuOH were the most effective fragmentation conditions. Unfortunately, the desired oxacyclononenone **4a** was accompanied by comparable amounts of the simple elimination product **5**. Nevertheless, formation of some of the functionalized nine-membered cyclic ether fragmentation product was encouraging and, to our knowledge, unprecedented. We reasoned that the fragmentation pathway might be enhanced by blocking elimination with an angular alkyl substituent. In the event, substrate **3b** gave the desired ether **4b** in good yield and in five steps overall from hydroxypropyl-4-pyrone starting material **1b**. Interestingly, **3c** gave none of the corresponding eight-membered ether, yielding instead acetylcyclohexanone **6** and bridged bicyclic ketone **7** in varying amounts (vide infra). All-carbon substrates **3d**−**f** all underwent clean fragmentation to yield cyclooctenone **4d**, bicyclo[6.4.0]dodecenone **4e**, and benzo-

(1) Presented in preliminary form: West, F. G.; Amann, C.; Fisher, P. V.; Pugh, M. *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO, March 1993; American Chemical Society: Washington, DC, 1993; ORGN 249.

(2) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(3) (a) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, pp 73−115. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (c) Moody, C. J.; Davies, M. J. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 201−239.

(4) (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485. (c) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991; pp 163−177. (d) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon: Oxford, 1991; Vol. 6, pp 1041−1070. (e) Ho, T.-L. *Heterolytic Fragmentation of Organic Molecules*; Wiley: New York, 1993.

(5) (a) West, F. G.; Fisher, P. V.; Willoughby, C. A. *J. Org. Chem.* **1990**, *55*, 5936. (b) West, F. G.; Fisher, P. V.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 1595. (c) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, *58*, 3796. (d) West, F. G.; Amann, C. M.; Fisher, P. V. *Tetrahedron Lett.* **1994**, *35*, 9653.

(6) (a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. (b) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135. (c) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541.

(7) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206.

(8) The tosylate derived from **3b** was subjected to X-ray diffraction analysis and the indicated stereochemistry confirmed: Amann, C. M.; Fisher, P. V.; Pugh, M.; Arif, A. M.; West, F. G. Manuscript in preparation.

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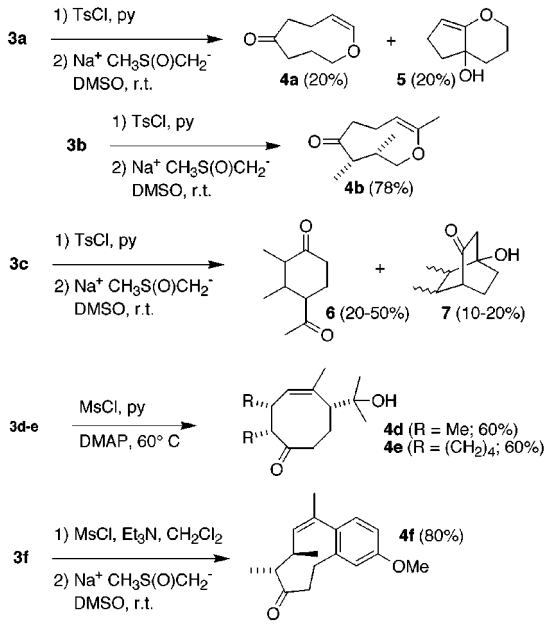
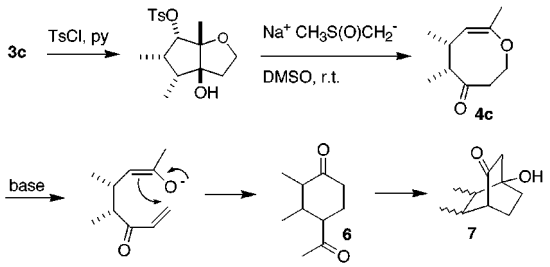
Scheme 2



cyclononadienone **4f**. Diquinane triols **3d**,**e** were found to undergo clean, in situ fragmentation when stirred with MsCl in hot pyridine.[9] *Thus, functionalized cyclooctenones* ***4d***,***e*** *are efficiently obtained in three steps from the simple 4-pyrone precursors* ***1d***,***e****. We believe this will serve as powerful methodology in the synthesis of cyclooctanoid targets.*[10]

In all cases, the *Z* stereochemistry shown for the double bonds was assumed by analogy to the well-precedented

Scheme 3



stereoselectivity seen in fragmentations of fused bicyclic substrates.[4] Although in each case three of the stereocenters of the substrate are sacrificed in the stereoselective formation of the medium-ring olefin, other centers set during the reduction of the double bond in **2b**−**f** were preserved. The disappointingly large amount of simple β-elimination seen with **3a** was surprising but could be rationalized in terms of the stability of the double bond in bicyclic enol ether **5**.[11] The unexpected cyclohexanone product **6** is assumed to result from desired fragmentation of **3c** to give oxocenone **4c**, followed by a retrograde Michael elimination of the enol ether oxygen from the newly formed ketone (Scheme 3). Recyclization by Michael addition of the resultant enolate into the enone through carbon instead of oxygen would then furnish **6**, while subsequent intramolecular aldol condensation would lead to **7**.[12] Unfortunately, use of a deficiency of base still resulted in formation of **6** and **7**, along with incomplete consumption of **3c**, while the MsCl/pyridine protocol used with **3d,e** did not effect fragmentation at all. Thus, at present it appears that eight-membered enol ethers may not be accessible via this route.

In summary, we have reported a short and efficient approach to medium-sized ethers or carbocycles by using a combination of 4-pyrone photocyclizations and Grob fragmentations. The substrates are easily prepared, and the fragmentation proceeds in most cases in good yield. Application of this methodology to the synthesis of medium-ring-containing natural products is under active investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and physical data for **3a**−**f**, **4a**,**b**,**d**−**f** and **5**−**7** and NMR spectra for **3a**,**d**,**f**, **4a**,**b**,**d**−**f**, and **5**−**7** (21 pages).

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(9) (a) A two-step procedure analogous to that used for **3f** could also be used, but was found inferior to the direct, one-pot protocol. (b) For an earlier report of a strain-driven in situ fragmentation mediated by MsCl/pyridine, see: Ikeda, M.; Ohno, K.; Takahashi, M.; Homma, K.; Uchino, T.; Tamura, Y. *Heterocycles* **1983**, *20*, 1005.

(10) Fragmentation approaches have been elegantly applied to construction of the B-ring of the taxanes: (a) Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 5389. (b) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558. (c) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878. (d) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (e) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755.

(11) Rhoads, S. J.; Waali, E. E. *J. Org. Chem.* **1970**, *35*, 3358.

(12) Upon subjection to reaction conditions, pure **6** was converted to a mixture of **6** and **7**. The relative stereochemistry of these unexpected products was not determined.