

Photochemical Ring-Contraction of Fused Bicyclic 4-Pyrones: A Novel 2-Step Cyclopentannulation Approach

F. G. West*, P. V. Fisher, G. U. Gunawardena and Scott Mitchell†

Department of Chemistry, University of Utah, Salt Lake City, UT 84112

Key words: 4-pyrones, oxyallyl zwitterions, cyclopentenones

Abstract: Fused bicyclic 4-pyrones were prepared by condensation of enamines derived from cyclic ketones with diketene or substituted 1,3-dioxin-4-ones. Photolysis in a hydroxylic medium led to bicyclo[n.3.0]alkenones bearing oxygenation at both angular positions. This process occurs via regioselective nucleophilic solvent attack on the intermediate tricyclic oxyallyl zwitterion. The efficiency of the transformation was found to be dependent upon the size of the ring fused to the 4-pyrone.

Numerous biologically important natural products contain substructures consisting of a bicyclo[n.3.0]alkane nucleus. Hydrindane, hydrazulene and bicyclo[6.3.0]undecane skeletons are particularly common. Given the prevalence of these skeletons, the development of approaches for the annulation of a new 5-membered ring fused to an existing ring remains a subject of intense interest.¹ The bridgehead oxygenation present in some natural products containing bicyclo[n.3.0]alkane skeletons (Figure 1) poses a special challenge. We report here a new route to such structures.

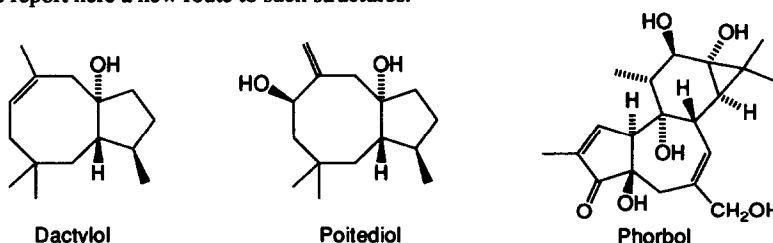
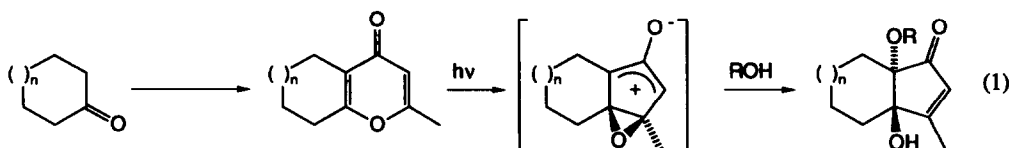


Figure 1. Natural products containing bicyclo[n.3.0]alkane subunits and bridgehead oxygenation.

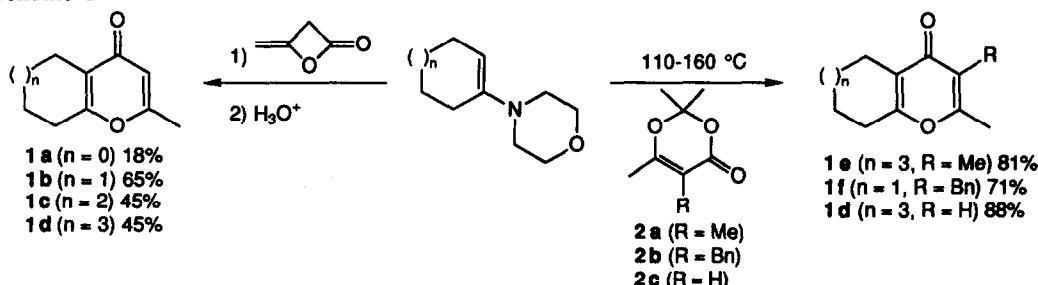
An attractive strategy for cyclopentannulation would be a 5-membered version of the well-known Robinson annulation approach² to attach cyclohexenones to existing cycloalkanones. We have reported the use of 4-pyrones as precursors to new cyclopentenone rings via photochemical ring contraction and subsequent intramolecular capture of the resultant oxyallyl zwitterion by pendant nucleophiles.³ Intermolecular zwitterion trapping could be potentially efficient with use of a hydroxylic solvent.^{4,5} Thus, given a means of preparing fused bicyclic 4-pyrones, an overall annulation of a cyclopentenone to a starting cycloalkanone would be possible, with introduction of oxygenation at both bridgehead positions (eq 1). This letter describes the



successful realization of such a route, employing simple reactants and leading to the target bicyclo[n.3.0]alkenones in two steps from readily available enamines.⁶

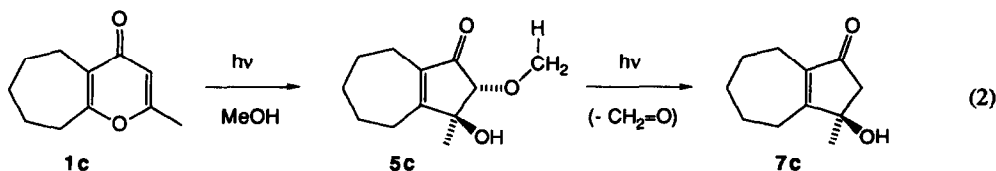
A homologous series of fused bicyclic 4-pyrones **1a-d** could be assembled in one step using a variation of the condensation of morpholine enamines with diketene first reported by Hünig and coworkers (Scheme I).⁷ Given the structure of the 3-carbon diketene fragment, the product 4-pyrones necessarily bore a 2,5,6-trisubstitution pattern, with no substituent at C-3. Preparation of 3-substituted 4-pyrones **1e-f** could be effected by use of "diketene equivalents," dioxinones **2a-b**, which release acetone and transient acylketenes when heated at 110-160 °C.⁸ In the case of trisubstituted substrate **1d**, a significantly higher yield could be obtained by use of parent dioxinone **2c** in place of diketene.

Scheme I



With substrates **1a-f** in hand, we sought to examine the efficiency of the solvent trapping reaction, using methanol or water as the trap. As depicted in Table 1, the bicyclic 4-pyrones were all converted with one exception to the desired bicyclo[n.3.0]alkenones **3b-g** and **4b-d** in modest to good yield. Both solvents served as traps, although methanol was more convenient.⁹ Efforts to use water were hampered by the low solubility of the substrates, and initial attempts led to destruction. However, it was found that inclusion of catalytic sulfuric acid dramatically improved trapping efficiency.^{10,11} Typical photolyses were run using 50-100 mg of 4-pyrone, but reactions employing up to 1 g of substrate showed no diminution in yield.

It is important to note the apparent dependence of yield on ring size. Thus, in the series **1a-d**, in which the size of the ring fused to the pyrone was varied, the yield decreased significantly in going from an eight-membered to a six-membered ring, and cyclopentano-fused substrate **1a** failed to give any of the corresponding diquinane. We reason that the initial photochemical ring contraction to form the strained tricyclic zwitterion is sensitive to the size of the neighboring ring, with a six-membered ring being the apparent minimum size for effective closure.



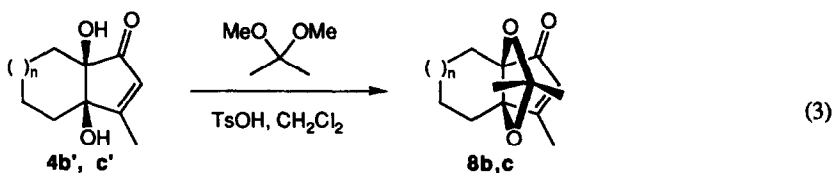
For trisubstituted substrates **1a-d**, good regioselectivity was observed in all but one case, with solvent attacking at the more highly substituted (bridgehead) end of the zwitterion to give **3** or **4** in preference to **5**. Not surprisingly, tetrasubstituted substrates **1e-f** showed little regioselectivity. Formal reduction product **7c**

Table 1. Photolysis of fused bicyclic 4-pyrones in hydroxylic media.^a

Substrate	n	R	R'	Yield, % ^b	Product(s)	Ratio
1a	0	H	Me	0	3a	--
1b	1	H	Me ^c	10	3b	--
"	1	H	H ^c	32	4b, 4b'	1 : 1
1c	2	H	Me	70	3c, 3c', 7c	4 : 1 : 2
"	2	H	H ^c	43	4c, 4c', 6c	4 : 2 : 1
1d	3	H	Me	59	3d	--
"	3	H	H ^c	32	4d	--
1e	3	Bn	Me	52	3e, 5e	ca. 1 : 1
1f	1	Me	Me	40 ^d	3f, 5f	2 : 3

^aStandard procedure: Substrates (50–100 mg) were dissolved in H₂O or MeOH (ca. 5×10^{-3} M) and photolyzed using a Hanovia medium pressure Hg lamp (quartz) until starting material was consumed (0.5–2 h). Higher concentrations of s.m. led to longer reaction times and lower yields. Solvent was removed (MeOH) or extracted with EtOAc (H₂O) and the crude product was purified by flash chromatography (silica gel). ^bIsolated yields after chromatography. Satisfactory IR, ¹H and ¹³C NMR and combustion analysis or HRMS were obtained for all substrates and products. ^cPhotolyses were carried out with 10–20 mol% H₂SO₄. ^dOptimum results were obtained using a 3W low pressure Hg lamp.

is presumed to arise from **5c** (which was not observed), via a Norrish type II fragmentation with loss of formaldehyde (eq 2).¹² Finally, the stereoselectivity of solvent attack must be considered. In most cases, only one diastereomeric adduct was isolated, with the angular hydroxyl and OR' groups trans in analogy to earlier solvent trapping studies.⁴ However, **1b** and **1c** also gave cis isomers **3c'**, **4b'** and **4c'**, with the stereochemistry of the latter two confirmed by their conversion to acetones **8b** and **8c** (eq 3). In these cases, the incipient strain of solvent trapping transition states leading to trans hydrindenones or hydrazulenones may cause some erosion of the inherent trans selectivity seen with monocyclic 4-pyrones.¹³



In summary, we have reported a new method for attachment of a cyclopentenone onto an existing six-membered or larger ring. This can be accomplished in two steps by condensation of an enamine with either diketene or a thermally generated acylketene to give a fused bicyclic 4-pyrone, followed by photochemical generation of a tricyclic oxyallyl zwitterion and nucleophilic capture by solvent to give a bicyclo[n.3.0]alkenone. The photochemical step proceeds in most cases with good regio- and stereoselectivity, particularly in the case of cyclooctanoid derivative **1d**, and moderate yields are mitigated by the conciseness and

procedural simplicity of the sequence. Application of this route to fused bicyclic natural products will be reported in due course.

Acknowledgement. We thank the National Institutes of Health (GM44720-01) for generous support of this work, along with the University of Utah Research Committee, the American Cancer Society for a Junior Faculty Research Award (F.G.W.), the University of Utah for a Graduate Research Fellowship (P.V.F.) and the NSF-REU program for a summer stipend (S.M.).

References and Notes

[†]NSF-REU participant, University of Utah, 1991.

1. (a) Fu, X.; Cook, J. M. *Aldrichimica Acta* **1992**, *25*, 43. (b) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820. (c) Ramaiah, M. *Synthesis* **1984**, 529.
2. Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
3. (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.
4. For extensive mechanistic studies of 4-pyrone photochemistry, including solvent trapping experiments, see: a) Barltrop, J. A.; Day, A. C.; Samuel, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 7521. (b) Pavlik, J. W.; Pauliukonis, L. T. *Tetrahedron Lett.* **1976**, 1939. (c) Keil, E. B.; Pavlik, J. W. *J. Heterocycl. Chem.* **1976**, *13*, 1149.
5. Related synthetic applications of oxyallyl zwitterions derived photochemically from cyclic dienones: (a) Schultz, A. G. *Pure Appl. Chem.* **1988**, *60*, 981. (b) Pirrung, M. C.; Nunn, D. S. *Tetrahedron Lett.* **1988**, *29*, 163. (c) Matlin, A. R.; Kim, K. *Ibid.* **1989**, *30*, 637.
6. For a complementary cyclopentannulation using enamines + oxyallyl zwitterions, see: Hayakawa, H.; Yokoyama, K.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1799.
7. Hünig, S.; Benzing, E.; Hübner, K. *Chem. Ber.* **1961**, *94*, 486.
8. (a) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1990**, *31*, 3677. (b) Sato, M.; Ogasawara, H.; Kato, K.; Sakai, M.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 4300. (c) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896.
9. Trapping with ethanol was also possible, but with substantially lower efficiency.
10. Inclusion of protic or Lewis acids has improved cyclization efficiency in some examples of intramolecular nucleophilic trapping: (a) West, F. G.; Willoughby, D. W. submitted for publication. (b) West, F. G.; Fisher, P. V. manuscript in preparation.
11. For a similar enhancement by acid in the case of tropone [6+2]-photocycloadditions, see: Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M.-J. *J. Org. Chem.* **1989**, *54*, 592.
12. A similar Norrish type II fragmentation of the trifluoroethanol adduct of 2,6-dimethyl-4-pyrone has previously been reported.^{4c}
13. Complete selectivity in favor of trans-fused bicyclo[6.3.0]undecenones from cyclooctanone derivatives **1d** and **1e** may reflect greater stability of the trans-fused 8-5 skeleton. For other examples of preferred trans ring-fusion, see: (a) Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676. (b) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875. (c) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541.

(Received in USA 27 April 1993; accepted 18 May 1993)