

Synthesis of 8-Membered Ring Lactones from Dioxolenones

Nicos A. Petasis* and Michael A. Patane

Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0744, USA

Thermolysis of hydroxy-dioxolenones affords 8-membered ring β -keto-lactones, which may be suitable for the synthesis of naturally occurring 8-membered ring cyclic ethers.

A variety of 8-membered ring cyclic ethers (oxocenes) have been isolated from marine organisms, particularly from the genus *Laurencia*.¹ This intriguing family of natural products includes many halogenated derivatives with novel structures, such as laurencin (1),² laurenynes (2),³ laurepinnacin (3),⁴ and pinnatifidenyne (4).⁵

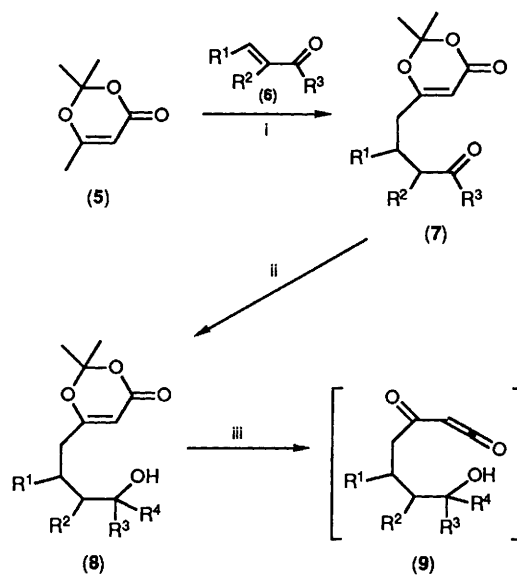
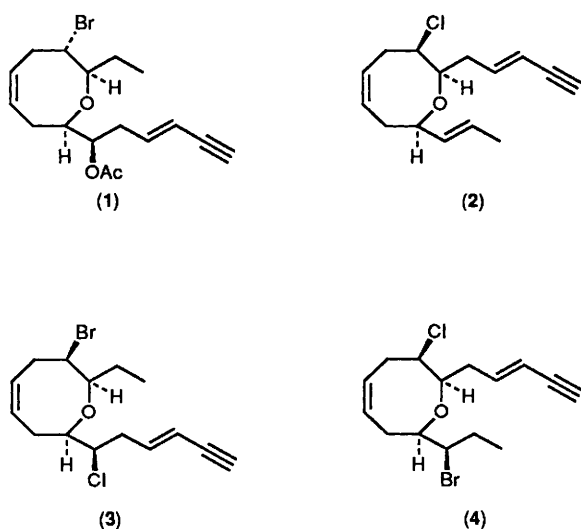
Due to the intrinsic difficulties associated with the formation of medium rings,⁶ the total synthesis of these molecules has remained a challenge. To date, only an early approach to (1)⁷ and a recent synthesis of (2)⁸ have been reported. In the past few years, however, considerable attention has focused on this class of compounds and significant synthetic advances have been made by a number of groups.^{9–14}

We are currently developing a new approach to this family of natural products based on properly functionalized 8-membered ring lactones. The usual lactonization methodology is most difficult for this particular ring size primarily due to ring strain and transannular interactions.¹⁵ In this paper we report a new and efficient three-step strategy for the construction of such compounds from dioxolenones.

As shown in Scheme 1, commercially available dioxolenone (5) was readily converted to an organocuprate enolate species and then reacted with an α,β -unsaturated aldehyde or ketone (6) affording the conjugate addition product (7).¹⁶ Subsequent carbonyl reduction or addition of an organometallic reagent to (7) led to hydroxy-dioxolenones (8) in high yields. Finally, thermolysis of (8) at 100 °C gave the β -keto-lactones (10) in excellent yields (>90%). Presumably, thermal extrusion of acetone under these conditions¹⁷ formed the highly unstable acyl ketene intermediate (9), which was trapped intramolecularly by the hydroxy group.

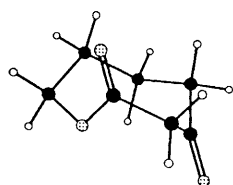
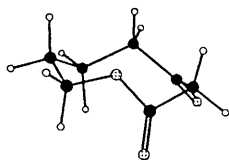
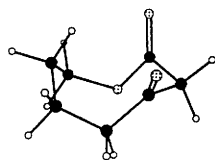
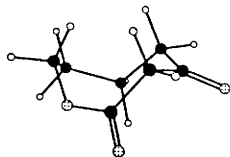
Both primary and secondary alcohols worked very well in this lactonization,¹⁸ although similar reactions with tertiary alcohols were not observed, probably for steric reasons.

The success of this 8-membered ring forming process may be partly attributed to a substantially lower strain energy of β -keto-lactones relative to the corresponding lactones. As shown in Scheme 2, molecular mechanics calculations¹⁹ indicated that the most stable conformation for the parent β -keto-lactone is the *twist-boat-chair* (11a). Several other conformations common in 8-membered ring derivatives,²⁰ including the *boat-chairs* (11b, 11d) and *crown* (11c), have higher energies. The same conformations of the corresponding unsubstituted 8-membered ring lactone are higher in energy by 9–10 kcal mol⁻¹. The presence of the β -keto group apparently modifies the torsional strain of the ring and limits the 1,2-, 1,3-, and transannular steric interactions. Further-



- a; R¹ = R² = H, R³ = Me, R⁴ = H
 b; R¹ = Me, R² = R³ = R⁴ = H
 c; R¹ = Me, R² = R³ = H, R⁴ = Me
 d; R¹ = Me, R² = R³ = H, R⁴ = CH=CH₂
 e; R¹ = H, R² = Me, R³ = R⁴ = H
 f; R¹ = H, R² = Me, R³ = H, R⁴ = CH=CH₂
 g; R¹ = Ph, R² = R³ = R⁴ = H
 h; R¹ = Ph, R² = R³ = H, R⁴ = CH=CH₂

Scheme 1. Reagents and conditions: i, (5), lithium di-isopropylamide (LDA), CuI, tetrahydrofuran (THF), then (6); ii, R⁴M (R⁴ = H, NaBH₄-MeOH; R⁴ = Me, MeLi, THF; R⁴ = CH=CH₂, CH₂=CHLi, THF); iii, 100 °C, toluene.

(11a) (4.94 kcal mol⁻¹)(11c) (7.23 kcal mol⁻¹)(11b) (6.21 kcal mol⁻¹)(11d) (7.38 kcal mol⁻¹)

Scheme 2. Calculated conformations and energies of the 8-membered β -ketolactone.

more, this versatile functionality may allow access to the substitution pattern found in many naturally occurring 8-membered ring O-heterocycles, such as (1)–(4).

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society for financial support. M. A. P. thanks the USA Department of Education for a National Needs Fellowship.

Received, 26th February 1990; Com. 0/00863J

References

- 1 K. L. Erickson, in 'Marine Natural Products,' ed. P. J. Scheuer, Academic Press, New York, 1983, vol. V, p. 131; D. J. Faulkner, *Nat. Prod. Rep.*, 1984, **1**, 251; 551; 1986, **3**, 1; 1987, **4**, 539; 1988, **5**, 613.
- 2 T. Irie, M. Suzuki, and T. Masamune, *Tetrahedron Lett.*, 1965, 1091; A. F. Cameron, K. K. Cheung, G. Erguson, and J. M. Robertson, *J. Chem. Soc., Chem. Commun.*, 1965, 638; T. Irie, M. Suzuki, and T. Masamune, *Tetrahedron*, 1968, **24**, 4193.
- 3 C. P. Falshaw, T. J. King, S. Imre, S. Islimyeli, and R. H. Thomson, *Tetrahedron Lett.*, 1980, 4951. The absolute configuration of (2) has been corrected to the reverse of the one reported in this paper. See ref. 8(b).
- 4 A. Fukuzawa and T. Masamune, *Tetrahedron Lett.*, 1981, **22**, 4081.
- 5 A. G. Gonzalez, J. D. Martin, V. S. Martin, M. Norte, R. Perez, and J. Z. Ruano, *Tetrahedron*, 1982, **38**, 1009.
- 6 J. A. Moore and F. A. L. Anet, in 'Comprehensive Heterocyclic Chemistry,' eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 7, ch. 5.19, p. 653.
- 7 T. Masamune, H. Murase, H. Matsue, and A. Murai, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 135.
- 8 (a) L. E. Overman, T. A. Blumenkopf, A. Castaneda, and A. S. Thompson, *J. Am. Chem. Soc.*, 1986, **108**, 3516; (b) L. E. Overman and A. S. Thompson, *ibid.*, 1988, **110**, 2248.
- 9 G. S. Cockerill and P. Kocienski, *J. Chem. Soc., Chem. Commun.*, 1983, 705; G. S. Cockerill and P. Kocienski, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2093; M. Mortimore, G. S. Cockerill, P. Kocienski, and R. Treadgold, *Tetrahedron Lett.*, 1987, **28**, 3747.
- 10 S. L. Schreiber and S. E. Kelly, *Tetrahedron Lett.*, 1984, **25**, 1757; S. L. Schreiber, S. E. Kelly, J. A. J. Porco, T. Sammakia, and E. M. Suh, *J. Am. Chem. Soc.*, 1988, **110**, 6210.
- 11 K. C. Nicolaou, M. E. Duggan, and C. K. Hwang, *J. Am. Chem. Soc.*, 1986, **108**, 2468; K. C. Nicolaou, C. K. Hwang, M. E. Duggan, and R. K. Bal, *Tetrahedron Lett.*, 1987, **28**, 1501; K. C. Nicolaou, D. G. McGarry, P. K. Somers, C. A. Veale, and G. T. Furst, *J. Am. Chem. Soc.*, 1987, **109**, 2504; K. C. Nicolaou, C. V. C. Prasad, C. K. Hwang, M. E. Duggan, and C. A. Veale, *ibid.*, 1989, **111**, 5321.
- 12 R. W. Carling and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1986, 325; 1986, 565; J. S. Clark and A. B. Holmes, *Tetrahedron Lett.*, 1988, **29**, 4333.
- 13 M. C. Pirrung and J. A. Werner, *J. Am. Chem. Soc.*, 1986, **108**, 6060.
- 14 J. C. Heslin, C. J. Moody, A. M. Z. Slawin, and D. J. Williams, *Tetrahedron Lett.*, 1986, **27**, 1403; C. J. Moody and R. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1989, 721.
- 15 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95. See however: B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4743.
- 16 In some cases, small amounts of 1,2-addition products, as well as α -conjugate addition adducts were also formed, which were removed by chromatography. For related studies see: A. B. Smith III, and R. M. J. Scarborough, *Tetrahedron Lett.*, 1978, 4193; D. Seebach, U. Miszlitz and P. Uhlmann, *Angew. Chem.*, 1989, **101**, 484.
- 17 R. J. Clemens and J. A. Hyatt, *J. Org. Chem.*, 1985, **50**, 2431; R. J. Clemens and J. S. Witzeman, *J. Am. Chem. Soc.*, 1989, **111**, 2186.
- 18 R. K. Boeckman, Jr., and J. R. Pruitt, *J. Am. Chem. Soc.*, 1989, **111**, 8286.
- 19 Calculations were performed with the program Macromodel Version 2.0, using the MM2 force field.
- 20 'Conformational Analysis of Medium-Sized Heterocycles,' ed. R. S. Glass, VCH, New York, 1988.