

Synthesis of 8-Membered Ring Lactones from Dioxolenones

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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 laurenyne (2),³ laurepinnacin (3),⁴ and pinnatifidenyne (4).⁵

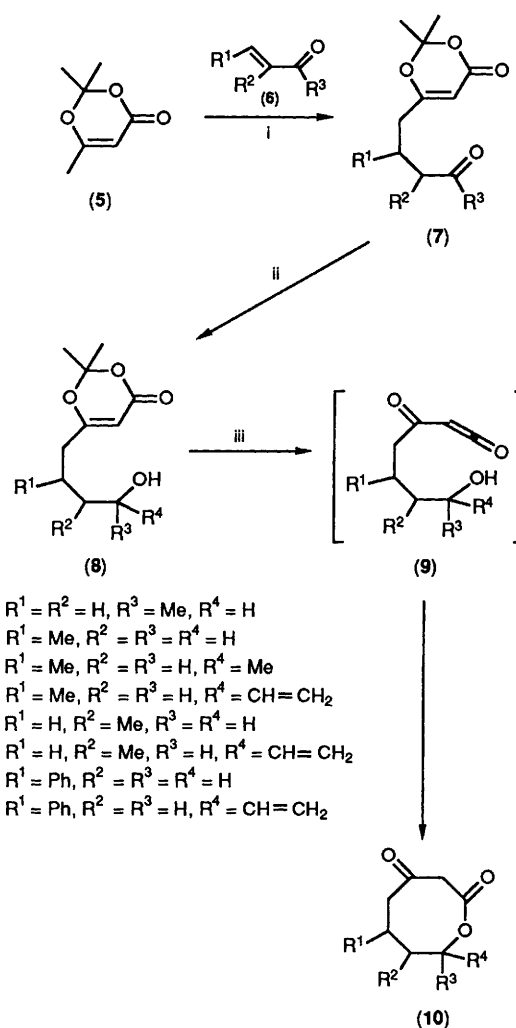
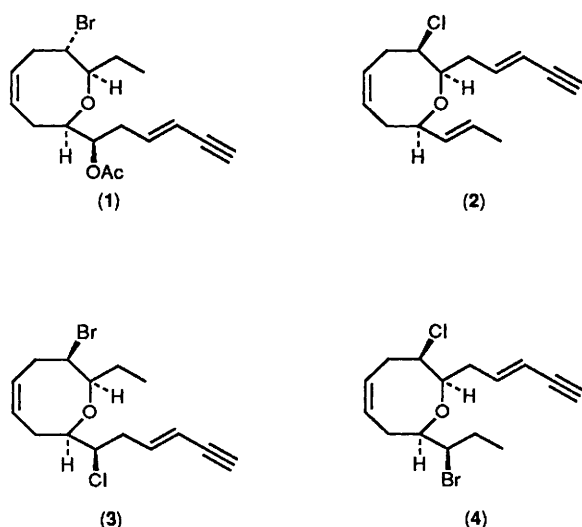
Due to the intrinsic difficulties associated with the formation of medium rings,⁶ the total synthesis of these molecules has remained a challenge. To date, only an early approach to (1)⁷ and a recent synthesis of (2)⁸ have been reported. In the past few years, however, considerable attention has focused 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.

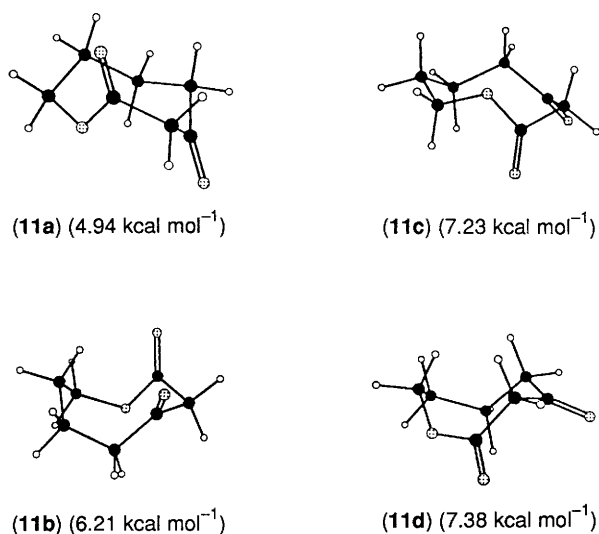
As shown in Scheme 1, commercially available dioxolenone (5) was readily converted to an organocuprate enolate species and then reacted with an α,β -unsaturated aldehyde or ketone (6) affording the conjugate addition product (7).¹⁶ Subsequent carbonyl reduction or addition of an organometallic reagent 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-



Scheme 1. Reagents and conditions: i, (5), lithium di-isopropylamide (LDA), CuI, tetrahydrofuran (THF), then (6); ii, R^4M ($R^4 = H, NaBH_4-MeOH; R^4 = Me, MeLi, THF; R^4 = CH=CH_2, CH_2=CHLi, THF$); iii, 100 °C, toluene.



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).

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