

Formation of 9,10-Unsaturation in the Mitomycins: Facile Fragmentation of β -Alkyl- β -aryl- α -oxo- γ -butyrolactones

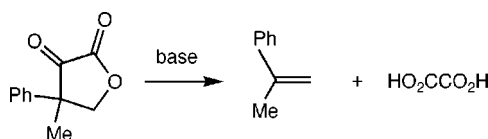
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ABSTRACT

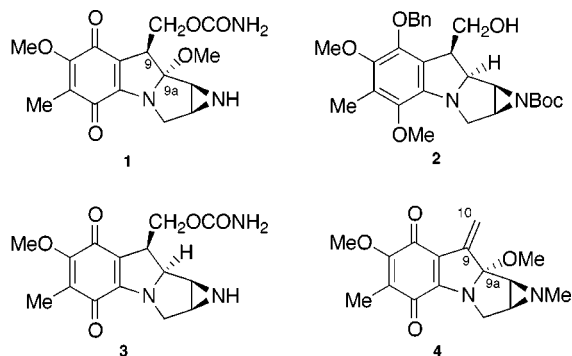


A facile fragmentation of β -alkyl- β -aryl- α -oxo- γ -butyrolactones is reported. A study to assist in the elucidation of the mechanism of the reaction is also revealed.

In studies directed toward the synthesis of mitomycin A (**1**), we demonstrated that the enantiomerically pure tetracycle **2** could be formed by a highly stereoselective aziridinyl radical cyclization. Subsequent transformations led to (+)-9a-desmethoxymitomycin A.¹ Eventual oxidative introduction of the requisite C_{9a} methoxy group requires suppression of indole formation by protection of the C₉ position with a removable protecting group. A formyl group, removed by decarbonylation, had served this end in a previous, related study.²

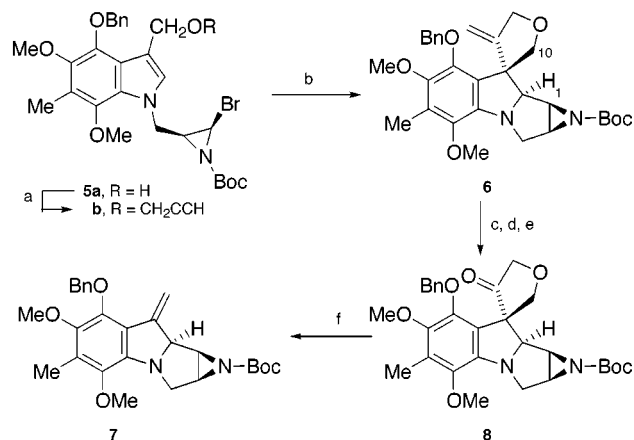
To apply a similar strategy to a synthesis of mitomycin K (**4**),³ a protecting group was sought, which upon liberation would reveal the C_{9,10} double bond. This communication details a mild method to achieve this goal.

The hydroxyl group of *cis*-3-indolyl alcohol **5a**,⁴ prepared by NaBH₄ reduction of the aldehyde, was exchanged with



propargyl alcohol, and the crude product **5b** was subjected to tandem radical cyclization to afford pentacycle **6** in 39% overall yield from the aldehyde (Scheme 1).¹ The cyclization

Scheme 1



a) propargyl alcohol, p-TsOH, PhH, rt, 1 h. b) 0.01M **6** in toluene, 0.02M n-Bu₃SnH, ACN, reflux, 2h.; 39%, 3 steps. c) MCPBA, 0 °C, CH₂Cl₂. d) O₃, MeOH, -78 °C. e) Me₂S, 3h, 25 °C; 93%, from **6**. f) KHMDS (2 equiv.), (EtO)₃P (2 equiv.), dry O₂, THF, 25 °C; 85%.

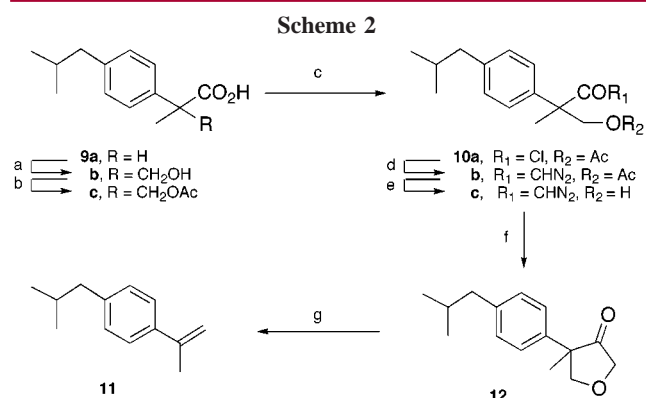
worked with the *trans*-bromide equally well. The stereochemistry of **6** was inferred from the stereochemistry obtained in the formation of tetracycle **2** wherein hydrogen

atom delivery occurred on the convex face of the intermediate tetracyclic benzylic radical. Cyclization of a benzylic radical with the acetylene to form **6** was expected to occur in a similar fashion.⁵ Moreover, an NOE (6.7%) was observed between the C₁-H and the proximate C₁₀-H.

Prior to exploring the introduction of oxygen at C_{9a}, prudence dictated that a method be developed first for excising the atoms of the allyl ether moiety of **6** to produce a styrene. Although the exocyclic double bond of **6** could be readily isomerized to the endo cyclic position [cat. (Ph₃P)₃-RhCl, DABCO, aqueous EtOH, 95 °C, 83%], efforts to functionalize or cleave oxidatively the endo cyclic double bond were unsuccessful. However, olefin **6** was converted to ketone **8** by ozonolysis with the proviso that the basic nitrogen of **6** was first protected as its *N*-oxide. Direct ozonolysis led to decomposition. Not only did dimethyl sulfide serve its usual role of reducing the ozonide, but it also effected reduction of the *N*-oxide.

After several unsuccessful attempts to oxygenate the carbon adjacent to the carbonyl group in spiro dihydrofuranone **8**, treatment of the furanone under the Gardner protocol⁶ [KHMDS, (EtO)₃P, and O₂] also failed to give any α -ketol but rather surprisingly and rewardingly afforded the desired styrene **7** in excellent yield! Moreover, the reaction proceeded in the absence of the phosphite. Olefin **7** had been prepared previously by Martin sulfurane dehydration (70%)⁷ where other more conventional elimination techniques proved unsuccessful.⁸

The generality of the reaction was explored on the less complex, racemic furanone **12**, prepared from (*S*)-ibuprofen (**9a**) as described in Scheme 2. The model retained a



a) 2 equiv. LDA, THF, -78 \rightarrow 0 °C, gaseous CH₂O; 96%. b) Ac₂O, pyr., CH₂Cl₂; 68%. c) DMF, (COCl)₂, CH₂Cl₂, reflux. d) CH₂N₂, Et₂O, rt., 12 h; 64% (2 steps). e) K₂CO₃, MeOH, rt., 3 h; 89%. f) Rh₂(OAc)₄ (cat.), CH₂Cl₂, r.t., 5 h; 70%. g) KHMDS (2 equiv.), THF, 0 °C; O₂, 5 min.; 90%.

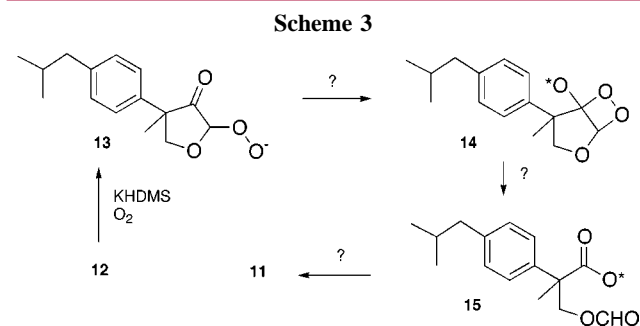
quaternary carbon and an aromatic ring. The orange enolate solution of **12** was bleached immediately by O₂ to give olefin **11** in the absence of phosphite.

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(3) For total syntheses of mitomycin K, see: (a) Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305. (b) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049.

To elucidate the mechanism of the reaction, the hypothesis of Scheme 3 was tested. Intermediate dioxetane **14**,⁹ as a



radical or anion, could fragment to the carboxylate anion or radical **15**, which could undergo elimination. The β -formyloxy carboxylic acid of **15** was readily accessible from β -hydroxy acid **9a**. Treatment of the formate ester under simulated reaction conditions led only to hydroxy acid **9b**, saponification occurring presumably as the result of adventitious hydroxide.

The possibility of a radical decarboxylation of acyloxy radical **15** to an intermediate benzyl radical prior to elimination was considered less likely because such radical species are the product of acyloxy group migration from the benzylic position to a primary radical.¹⁰ Nonetheless, the formyloxy carboxylic acid was activated as its thiohydroxamate ester and photolyzed with visible light.¹¹ No styrene was observed, but stereoisomeric benzyl dimers were identified along with sulfur-containing products of radical origin.

An α -keto- γ -butyrolactone was considered as a likely intermediate in the elimination procedure. To explore this possibility, ketolactone **18** was prepared as outlined in Scheme 4. Upon exposure of this material to K₂CO₃ in aqueous THF at room temperature, α -methylstyrene and oxalic acid were formed. Oxalic acid was identified by ¹³C NMR and by ¹H NMR of its dimethyl ester.

McMurry has reported the formation of α -methylene cyclohexanone from oxalocyclohexanone **20** (Scheme 5) upon exposure of the latter compound to gaseous formaldehyde in aqueous NaHCO₃ at 0 °C.^{12,13} The presumed

(4) New compounds were characterized by ¹H and ¹³C NMR spectroscopy, combustion analysis, and/or HRMS.

(5) For an example of stereocontrol in spiroalkylation, see: Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414.

(6) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (b) Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695.

(7) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

(8) For a related elimination, see: Jones, G. B.; Guzel, M.; Mathews, J. E. *Tetrahedron Lett.* **2000**, *41*, 1123.

(9) For examples of the fragmentation of 1,2-dioxetanes, see: *Singlet Oxygen*; Schaap, P. A., Zaklika, K. A., Eds.; Academic Press: New York, 1979; Vol. 40, Chapter 6, p 173.

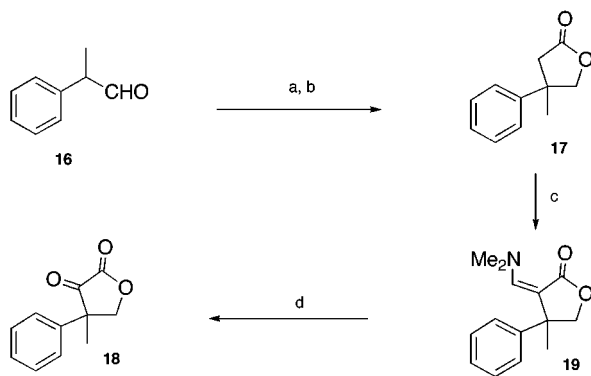
(10) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273.

(11) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(12) Ksander, G. M.; McMurry, J. E.; Johnson, M. J. *Org. Chem.* **1977**, *42*, 1180.

(13) See also, Nield, C. H. *J. Am. Chem. Soc.* **1945**, *67*, 1145.

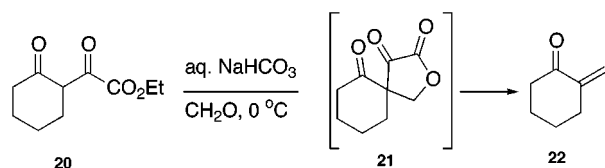
Scheme 4



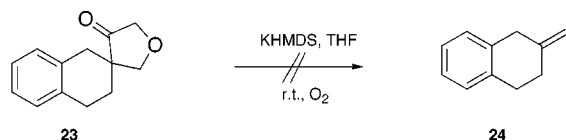
a) NaH, DMSO; BrCH₂CO₂Me, r.t.; 88% b) NaBH₄, MeOH, r.t.; 95%.
c) (Me₂N)₃CH, neat, 70 °C, 12h; 85% d) O₃, -78 °C, CH₂Cl₂; Me₂S; 63%.

intermediate, nonenolic β -dicarbonyl **21** suffers retro-Claisen cleavage and subsequent β -elimination. Undoubtedly, this reaction can be considered of the E1cB type, owing to the presence of the cyclohexanone carbonyl.

Scheme 5



The aromatic ring clearly facilitates the elimination because furanone **23**, prepared by the method of Scheme 2 from tetrahydro- β -naphthoic acid, did not lead to olefin **24**.

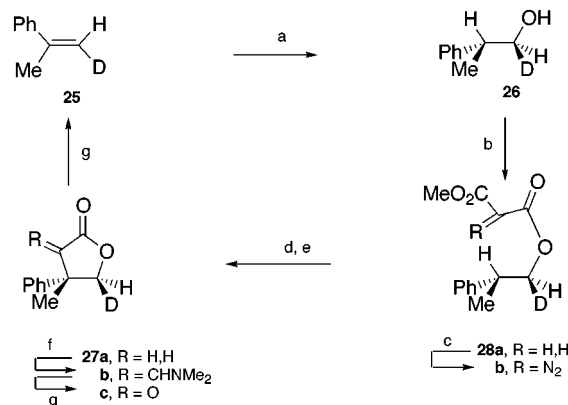


A deuterium labeling experiment was designed to determine if the elimination reaction of ketolactone **18** was concerted or stepwise. (*E*)-Styrene-*d*₁¹⁴ was hydroborated and ultimately converted into diazomalonnate **28b** (Scheme 6). Stereocontrolled, rhodium-mediated C–C bond formation¹⁵ afforded a mixture of lactone esters, which was decarboxy-

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Scheme 6



a) BH₃ THF, aq. NaOOH; 81%. b) methyl malonyl chloride, Et₃N, rt; 76%. c) PABSA, Et₃N, CH₂Cl₂, rt; 94%. d) 2 mol % Rh₂(OAc)₄, CH₂Cl₂, reflux, 2.5h. e) conc. HCl/HOAc, reflux; 52 % (2 steps). f) (Me₂N)₃CH, neat, 70 °C, 12h; 85%. g) O₃, -78 °C, CH₂Cl₂; Me₂S; 68%.

lated under vigorous acidic conditions. That the decarboxylation conditions did not alter the labeling pattern in lactone **27a** was confirmed by integration¹⁶ of the diastereotopic methylene protons (¹H NMR) of the derived vinylogous amide **27b**. Exposure of **27c** to KHMDS or K₂CO₃ in THF containing 1.5 equiv of water at room temperature gave rise to a 4.67:1.00 mixture of (*E*)- α -methylstyrene **25** and its (*Z*)-isomer, respectively, or an 82% “retention of configuration”. Assuming that inversion occurs via a process that permits free bond rotation, then 18% of the retained configuration arises by bond dissociation. Thus, 64% of the product can be demonstrated to form by a concerted, syn-elimination.

The product arising from isomerization may be the result of a concerted elimination if the isomerization is prior to the product determining step, or it may be the result of a stepwise elimination. The clarification of this issue has not, as yet, been addressed. No product of C–C bond cleavage and protonation was detected.

Paquette¹⁷ has observed both retention and inversion in the Haller–Bauer (NaNH₂, C₆H₆, reflux) cleavage (protonolysis) of α,α -dialkyl deoxybenzoins and elimination to α -methylstyrene with α -methyl- α -allyloxymethyl desoxybenzoins.¹⁸

The facility with which this fragmentation occurs is reflected in the pyruvate nature of the carbonyl group and the syn arrangement of the elimination. α -Ketolactones of this type may serve as useful synthetic templates from which α -alkyl styrenes may be synthesized.

Acknowledgment. This research was supported by PHS grant GM-54499.

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(16) (*E*)- α -Methylstyrene-*d*₁ (**25**) contained 16% *d*₀-compound.

(17) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044.

(18) Paquette, L. A.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5054.