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

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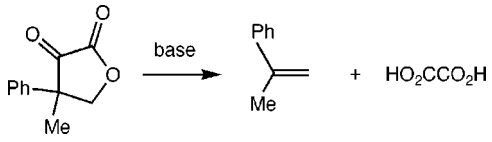
ABSTRACT

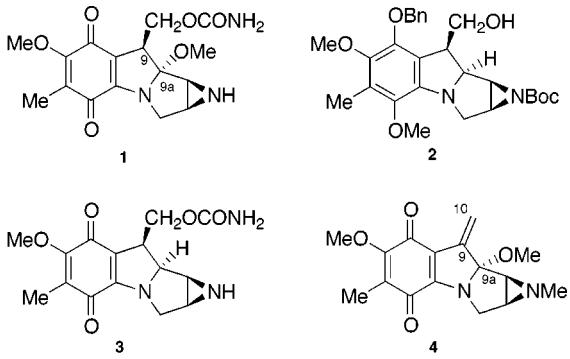


A facile fragmentation of β-alkyl-β-aryl-α-oxo-γ-butyrolactones is reported. A study to assist in the elucidation of the mechanism of the reaction is also revealed.

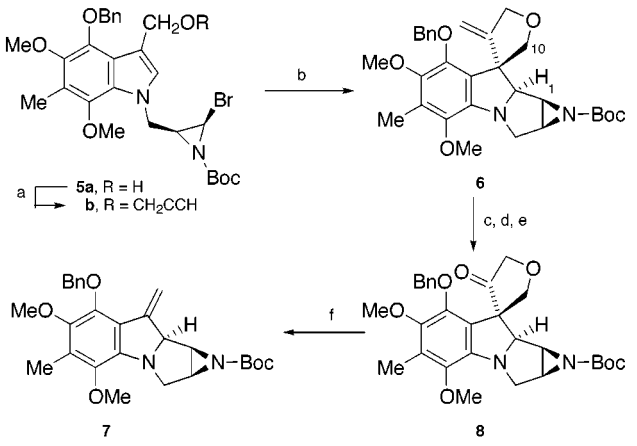
In studies directed toward the synthesis of mitomycin A (**1**), we demonstrated that the enantiomerically pure tetracycle **2** could be formed by a highly stereoselective aziridinyl radical cyclization. Subsequent transformations led to (+)-9a-desmethoxymitomycin A.[1] Eventual oxidative introduction of the requisite C_{9a} methoxy group requires suppression of indole formation by protection of the C_9 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 $NaBH_4$ 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 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



Scheme 1



a) propargyl alcohol, p-TsOH, PhH, rt, 1 h. b) 0.01M **6** in toluene, 0.02M n-Bu_3SnH, ACN, reflux, 2h.; 39%, 3 steps. c) MCPBA, 0 °C, CH_2Cl_2. d) O_3, MeOH, -78 °C. e) Me_2S, 3h, 25 °C; 93%, from **6**. f) KHMDS (2 equiv.), $(EtO)_3P$ (2 equiv.), dry O_2, THF, 25 °C; 85%.

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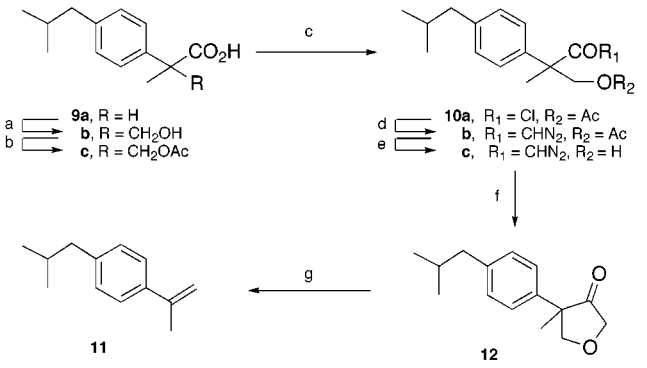
atom delivery occurred on the convex face of the intermediate tetracyclic benzylic radical. Cyclization of a benzylic radical with the acetylene to form **6** was expected to occur in a similar fashion.[5] Moreover, an NOE (6.7%) was observed between the C_1-H and the proximate C_{10}-H.

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. $(Ph_3P)_3$-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 protocol[6] [KHMDS, $(EtO)_3P$, and O_2] 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

Scheme 2

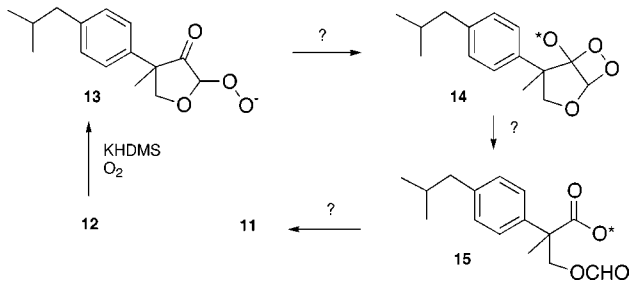


a) 2 equiv. LDA, THF, -78 --> 0 °C, gaseous CH_2O; 96%. b) Ac_2O, pyr., CH_2Cl_2; 68%. c) DMF, $(COCl)_2$, CH_2Cl_2, reflux. d) CH_2N_2, Et_2O, rt., 12 h; 64% (2 steps). e) K_2CO_3, MeOH, r.t., 3 h; 89%. f) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, r.t., 5 h; 70 %. g) KHMDS (2 equiv.), THF, 0 °C; O_2, 5 min.; 90%.

quaternary carbon and an aromatic ring. The orange enolate solution of **12** was bleached immediately by O_2 to give olefin **11** in the absence of phosphite.

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

Scheme 3



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 K_2CO_3 in aqueous THF at room temperature, α-methylstyrene and oxalic acid were formed. Oxalic acid was identified by ^{13}C 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 $NaHCO_3$ at 0 °C.[12,13] The presumed

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(2) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083.
(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.
(4) New compounds were characterized by ^1H and ^{13}C 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.
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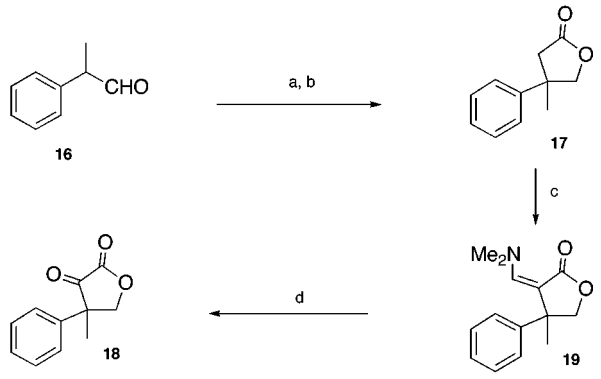
(13) See also, Nield, C. H. *J. Am. Chem. Soc.* **1945**, *67*, 1145.

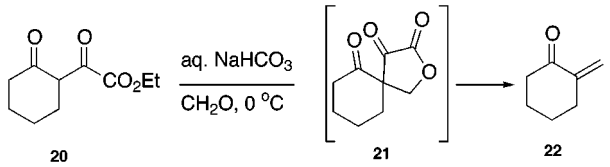
Scheme 4



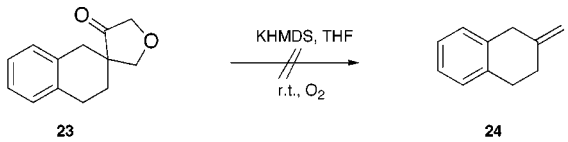
a) NaH, DMSO; $BrCH_2CO_2Me$, r.t.; 88% b) $NaBH_4$, MeOH,r.t.; 95%. c) $(Me_2N)_3CH$, neat, 70 °C, 12h; 85% d) O_3,-78 °C, CH_2Cl_2; Me_2S; 63%.

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

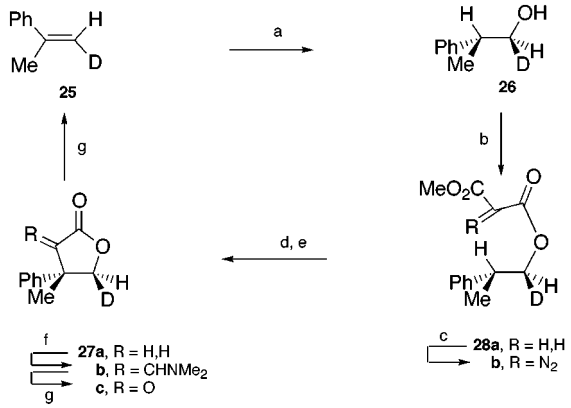


The aromatic ring clearly facilitates the elimination because furanone **23**, prepared by the method of Scheme 2 from tetrahydro-β-naphthoic acid, did not lead to olefin **24**.



A deuterium labeling experiment was designed to determine if the elimination reaction of ketolactone **18** was concerted or stepwise. (*E*)-Styrene-d_1[14] was hydroborated and ultimately converted into diazomalonate **28b** (Scheme 6). Stereocontolled, rhodium-mediated C−C bond formation[15] afforded a mixture of lactone esters, which was decarboxy-

Scheme 6



a) BH_3·THF, aq. NaOOH; 81%. b) methyl malonyl chloride, Et_3N, rt; 76%. c) PABSA, Et_3N, CH_2Cl_2, rt; 94%. d) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 2.5h. e) conc. HCl/HOAc, reflux; 52 % (2 steps). f) $(Me_2N)_3CH$, neat, 70 °C, 12h; 85%. g) O_3, -78 °C, CH_2Cl_2; Me_2S; 68%.

lated under vigorous acidic conditions. That the decarboxylation conditions did not alter the labeling pattern in lactone **27a** was confirmed by integration[16] of the diastereotopic methylene protons (^{1}H NMR) of the derived vinylogous amide **27b**. Exposure of **27c** to KHMDS or K_2CO_3 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.

Paquette[17] has observed both retention and inversion in the Haller−Bauer ($NaNH_2$, C_6H_6, reflux) cleavage (protonolysis) of α,α-dialkyl deoxybenzoins and elimination to α-methylstyrene with α-methyl-α-allyloxymethyl desoxybenzoin.[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.

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(16) (*E*)- α-Methylstyrene-d_1 (**25**) contained 16% d_0-compound.

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