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REACTIONS OF γ-ACYLOXY-β-KETOPHOSPHONATES: NEW ROUTES TO 3(2H)- AND 2(3H)-DIHYDROFURANONES

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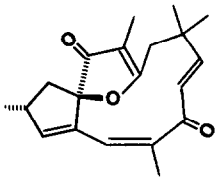
Abstract: Depending on the reaction conditions, γ-acyloxy-β-ketophosphonate anions can undergo either an intramolecular Wittig-like condensation or an unexpected rearrangement which affords an enol ester product.

The 3(2H)-dihydrofuranone structure is a feature of a number of naturally occurring compounds[1], and interest in their total synthesis has spurred development of methods for 3(2H)-dihydrofuranone formation.[2,3] However, our approach to the total synthesis of (+)-jatrophone (1)[4] was predicated upon the conversion of a lactone such as compound 2 into the final 3(2H)-dihydrofuranone, and known methods are not readily applicable to this system.



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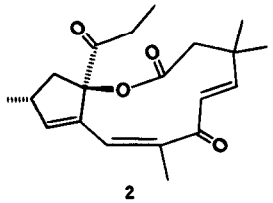

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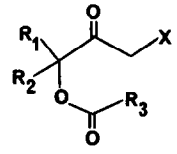


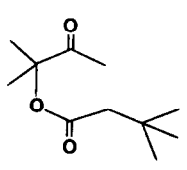
3 $R_1 = R_2 = R_3 = CH_3$; X = H.

4 X = $P(O)(OCH_2CH_3)_2$

From studies of simple ketoesters (e.g. compound 3) it is known that the protons alpha to the ketone are considerably more acidic than those adjacent to the ester carbonyl. Nevertheless, when treated with a strong base an equilibrium concentration of the ester enolate is formed and the favored process[2,5] is formation of a butenolide product via condensation of this ester enolate with the ketone carbonyl. We hypothesized that by addition of a second activating group to enhance the stability of the ketone enolate

these equilibria might be shifted toward formation of the 3(2H)-dihydrofuranone product. Use of a phosphonate moiety for the second activating group was especially attractive because of the precedence for an intramolecular Wadsworth-Emmons condensation of β-ketophosphonates with ester carbonyls.[6,7] The model studies we have conducted show that this is a viable route to 3(2H)-dihydrofuranones, but under certain conditions an unexpected rearrangement occurs which leads to an isomeric product. In this communication we report one route to compounds of the general structure 4, and the conversion of one such compound to both the 3(2H)-dihydrofuranone and the unexpected isomer, a 2(3H)-dihydrofuranone.

Our route to the model phosphonate ketoester 8 is shown below. The ketoester 5, prepared from 3-hydroxy-3-methylbutanone and t-butylacetyl chloride in 62% yield, is smoothly converted to the enol silyl ether 6 upon reaction with trimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undecene (87% yield).[8] When treated with iodine and silver acetate[9] this enol ether affords the iodoketone 7 (53%), and a subsequent reaction with triethylphosphite[10] affords the desired phosphonate 8 (78%).



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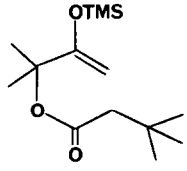

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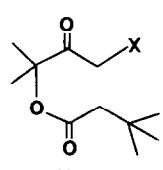
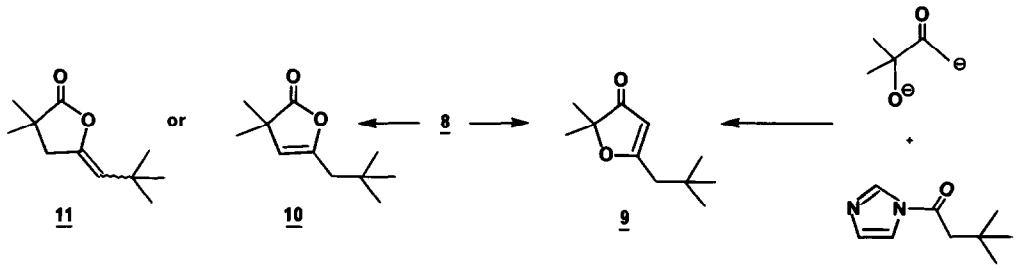


7 X = I

8 X = $P(O)(OCH_2CH_3)_2$

When compound 8 is treated with sodium hydride in dimethoxyethane and the resulting anion is heated at reflux, a major product is formed (59% by GC) which has both ^1H NMR and mass spectra consistent with our expectations for the 3(2H)-dihydrofuranone.[11] However, the ^{13}C NMR spectrum clearly would not allow assignment of this structure, but was consistent with several isomeric structures. The 3(2H)-dihydrofuranone 9 was synthesized by an unambiguous route using a variation of the procedure of Smith et al.[2] While this authentic 3(2H)-dihydrofuranone gave ^1H NMR and mass spectra very similar to those obtained for the condensation product, the ^{13}C NMR spectrum was clearly different.[12] The structure of the isomeric product became more evident when an FT-IR spectrum confirmed the presence of an enol ester group (1817 cm^{-1})[13] suggested by the ^{13}C NMR data. This focused our attention on the two structures 10 and 11. The difference NOE spectra of the

condensation product show both enhancement of the methylene protons (7%) upon irradiation of the t-butyl group and enhancement of the vinylic proton (4%) upon irradiation of the gem-dimethyl group. These results support assignment of structure 10 to this compound. Final confirmation of this structural assignment was obtained by degradative experiments. Catalytic hydrogenation of compound 10 gives a lactone product. In the ^{1}H NMR spectrum of this lactone the proton geminal to the ring oxygen appears as a quintet indicating two adjacent methylene groups. Ozonolysis of compound 10, followed by reductive work-up and treatment of the reaction products with diazomethane, gives methyl t-butylacetate (identified by GC and GC-MS comparisons with an authentic sample). This ester is an expected product from the ozonolysis of the 2(3H)-dihydrofuranone 10, but would not be expected from degradation of compound 11.



Even without a complete understanding of the mechanism which leads to the rearranged carbon skeleton of compound 10, it appears clear that this rearrangement has some potential as a synthetic method in its own right. There are a limited number of synthetic methods applicable to the formation of quaternary centers,[14] and formally this rearrangement has given a quaternary carbon from a tertiary alcohol. We plan to explore the potential of this novel reaction in more detail.

Our original objective was a route to 3(2H)-dihydrofuranones from these γ-acyloxy-β-ketophosphonates, and we have found that this condensation can be accomplished. When the phosphonate 8 is treated with potassium carbonate and dicyclohexyl-18-crown-6 in refluxing toluene[15], the 3(2H)-dihydrofuranone 9 becomes a major product (27% isolated yield after column chromatography vs. 35% yield for compound 10). Treatment of compound 8 with potassium carbonate in DMF at 110° gives the 3(2H)-dihydrofuranone as the only isolable product (47% yield). Apparently, product distribution between the 3(2H)- and 2(3H)-dihydrofuranones can be controlled through simple changes in the reaction conditions.

Application of these methods of dihydrofuranone formation to natural products synthesis will be the subject of future communications.

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11) ^{1}H NMR spectrum ($CDCl_3$) δ 5.15 (s, 1, =CH-), 2.12 (s, 2, $-CH_2-$), 1.30 (s, 6, $C(CH_3)_2$), 0.98 (s, 9, $(CH_3)_3$); EI GC-MS (70 eV) M/z 182 (M^+, 10), 154 (5), 126 (81), 111 (100), 83 (81); ^{13}C NMR spectrum ($CDCl_3$) δ 182.9 (s), 152.6 (s), 113.4 (d), 44.4 (s), 42.0 (t), 30.9 (s), 29.7 (q), 24.5 (q).

12) ^{1}H NMR spectrum ($CDCl_3$) δ 5.34 (s, 1, =CH-), 2.37 (s, 2, $-CH_2-$) 1.38 (s, 6, $C(CH_3)_2$), 1.02 (s, 9, $C(CH_3)_3$); EI GC-MS M/z 182 (M^+, 34), 154 (1), 126 (100), 111 (68), 83 (18), 81 (32), 68 (34), 57 (79)); ^{13}C NMR spectrum ($CDCl_3$) δ 207.4, 190.2, 103.2, 88.6, 44.6, 31.8, 29.7, 22.9.

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