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SYNTHESIS OF FUNCTIONALIZED TETRAHYDROFURANS[1]

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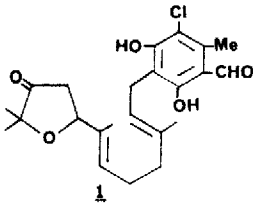
Abstract: *A novel cyclization reaction is described which affords readily manipulable 3(2H)-dihydrofuranone ethylene ketals, useful in the total synthesis of an ascofuranone model, bullatenone, and muscarine analogs.*

In connection with our studies directed towards the total synthesis of ascofuranone (1), an antibiotic and hypolipidemic agent,[2-6] as well as the natural product bullatenone (2) and muscarine analogs (3 and 4), we wish to describe a new method for the rapid and efficient construction of 3(2H)-dihydrofuranone ethylene ketals which possess manipulable functionality at C-5. Upon treatment with ethylene glycol and p-toluenesulfonic acid in refluxing benzene solution, readily accessible aldol condensation products such as 7, 16 or 17 afford high yields of the corresponding ketals which can be converted into a diverse array of tetrahydrofuranoid natural products and analogs.

Aldol condensation of 3-hydroxy-3-methyl-2-butanone (5) with α-methylcinnamaldehyde (6) (NaOEt, EtOH, 0°C) gave α'-hydroxydienone 7 in 89% yield.[7,8] Treatment of 7 under the cyclization conditions described above produced ketal 9 in 88% yield. We attribute the success of this cyclization to the formation of an extensively delocalized carbonium ion intermediate 8, which can be intercepted in a geometrically favorable manner[9a-c,10] by the proximate hydroxyl function. Ozonolysis of 9 (MeOH, -78°C) gave ketone 10 in 97% yield. The ketone was then coupled with the appropriate ylid as described. The reaction of isopropenylmagnesium bromide with phenylacetaldehyde produced allylic alcohol 11 which was directly transformed into (E)-olefinic ester 12 by the "ortho-acetate" Claisen rearrangement[11,12] in 37% overall yield.[13] Reduction of the ester ($LiAlH_4$, 99% yield), conversion of the corresponding alcohol to the bromide (CBr_4, $Ø_3P$, 92% yield),[14] followed by reaction of the bromide with triphenyl phosphine afforded phosphonium salt 13 which was utilized in the following Wittig reaction. Coupling of fragments 10 and 13 was achieved using potassium tert-amylate in refluxing benzene as the crucial base-solvent system. The choice of this system was based on the remarkable observation that reaction of "unstabilized" ylids derived from primary phosphonium salts with pregnenolone gave products exclusively possessing the (E)-olefin geometry.[15-17] Condensation of 10 and 13 under these conditions afforded olefin 14 in 54% yield.[18] Finally, deblocking of 14 produced the ascofuranone model 15.[19]



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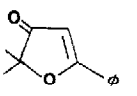

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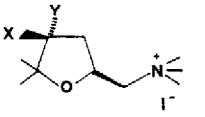
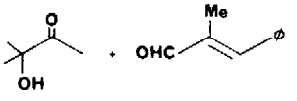


3, X = OH, Y = H
4, X = H, Y = OH



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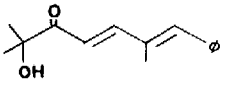

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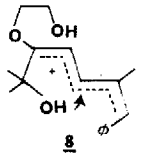

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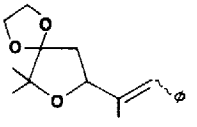

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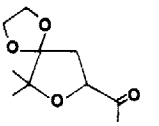

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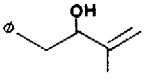

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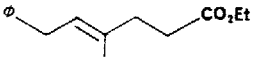

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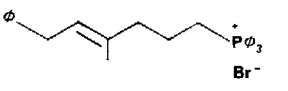

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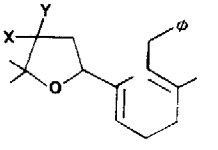
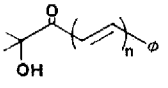
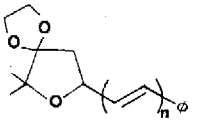
13 · 10



14, X = Y = OCH_2CH_2O
15, X = Y = O

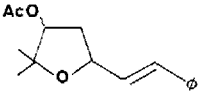


16, n = 0
17, n = 1



18, n = 0
19, n = 1

19



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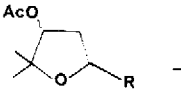
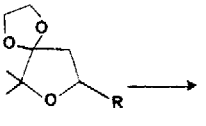
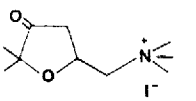


21, R = COOH
22, R = $CON(CH_3)_2$

3 and 4



23, R = COOH
24, R = $CON(CH_3)_2$



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Hydroxyenones 16 and 17, required in the synthesis of bullatenone and muscarine analogs, were obtained by the aldol condensation of 5 with benzaldehyde and trans-cinnamaldehyde[20] in 76% and 71% yields, respectively. Treatment of 16 and 17 under our cyclization conditions afforded ketals 18[21] and 19[22] in excellent yields. It should be noted that normal acid-catalyzed cyclization procedures gave disappointingly low yields (ca. 30%). Deblocking of ketal 18 afforded a known furanone[10,23] in 98% yield. This compound was then dehydrogenated (DDQ, toluene) to produce bullatenone 2 in 97% yield. The overall yield from 5 to 2 was 73%, the highest reported to date for the synthesis of this interesting substance.[10,24-27] Ketal 19 was deblocked, reduced ($NaBH_4$, EtOH), and acetylated (Ac_2O, pyr, DMAP) to give acetate 20 as a mixture (ca. 1:1) of cis and trans isomers. Ozonolysis of 20 followed by Jones oxidation afforded 21 (80% yield) which was converted to amide 22 (ca. 1:1 mixture of cis and trans isomers). Reduction of the individual isomers followed by quaternization of the corresponding amines gave 2-methylepimuscarine iodide (3) and 2-methylmuscarine iodide (4) respectively, in 88-93% overall yields.[28] Phase-transfer catalyzed oxidation[29] of ketal 19 gave carboxylic acid 23 which was converted via its mixed anhydride into amide 24. Reduction, ketal deblocking, and quaternization of the resultant amine afforded 2-methylmuscarone iodide (25).[30]

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References and Footnotes.

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7. IR (neat): 3390, 1590, and 1680 cm^{-1}; UV: λ_{max}EtOH (log ε): 225 (4.0), 318 nm (4.4); ^1H NMR ($CDCl_3$, 60 MHz): δ 1.41 (s, 6H), 2.07 (d, J = 1.1 Hz, 1H), 3.97 (s, 1H), 6.56 (d, 1H, J = 16 Hz), 6.95 (m, 1H), 7.33 (br s, 5H), 7.66 (d, 1H, J = 16 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz): δ 13.7, 26.5, 75.5, 118.0, 127.9, 128.3, 129.5, 134.2, 136.4, 141.2, 150.4, 202.6.
8. All new compounds gave satisfactory spectroscopic and analytical values.
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   (c) J. E. Baldwin, ibid., 738 (1976).
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13. bp 103-106°C/0.25 mm; IR (neat): 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 60MHz): δ 1.18 (t, 3H, J = 7 Hz), 1.72 (s, 3H), 2.38 (s, 4H), 3.32 (d, 2H, J = 7 Hz), 4.11 (q, 2H, J = 7 Hz), 5.42 (t, 1H, J = 7 Hz), 7.21 (br s, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ 14.2, 16.0, 33.2, 34.1, 34.7, 60.2, 123.9, 125.7, 128.3, 134.4, 141.3, 173.1.
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18. ^1H NMR ($CDCl_3$, 60 MHz): δ 1.23 (s, 6H), 1.71 (br s, 6H), 2.23 (m, 6H), 3.33 (d, 2H, J = 7 Hz), 3.93 (s, 4H), 4.93 (t, 1H, J = 8 Hz), 5.33 (distorted t, 2H), 7.24 (s, 5H). Since the chemical shifts of both olefin-bound methyl groups are coincident at δ 1.71, and since the "ortho-acetate" Claisen rearrangement produces (E)-trisubstituted olefins with a high degree of stereoselectivity, we believe that this material possesses the desired (E,E) olefin geometry.
19. IR (CCl_4 solution): 1758 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.24 (s, 3H), 1.30 (s, 3H), 1.71 (br s, 3H), 1.73 (d, 3H, J = 1.1 Hz), 2.16 (m, 4H), 2.43 (d, 2H, J = 8.3 Hz), 3.36 (d, 2H, J = 7.4 Hz), 5.07 (t, 1H, J = 8.3 Hz), 5.05 (t of minor isomer), 5.35 (dt, 1H, J = 7.4 Hz J = 1.1 Hz), 5.41 (m, 1H), 7.22 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ 16.1, 17.2, 21.7, 24.2, 25.9, 34.2, 39.3, 39.7, 70.1, 80.2, 123.8, 125.6, 128.2, 129.5, 132.9, 133.1 (minor isomer), 135.1, 135.2 (minor isomer), 141.3, 216.7. This spectral data indicates the presence of some isomerized material (approximately 20%) which could have been formed during the ketal hydrolysis.
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21. bp 101-103°C/0.08 mm, ^1H NMR ($CDCl_3$, 60 MHz): δ 1.26 (s, 3H), 1.29 (s, 3H), 2.23 (m, 2H), 3.82 (s, 4H), 4.99 (dd, 1H), 7.27 (m, 5H).
22. bp 150-155°C/0.45 mm; ^1H NMR ($CDCl_3$, 60 MHz): δ 1.22 (s, 3H), 1.23 (s, 3H), 2.17 (m, 2H), 3.88 (s, 4H), 4.61 (dt, 1H, X of ABX, $J_{BX} \simeq 6.4$ Hz, $J_{AX} \simeq 0$ Hz), 6.16 (dd, 1H, B of ABX, $J_{BA} \simeq 15.7$ Hz, $J_{BX} \simeq 6.4$ Hz), 6.58 (d, 1H, A of ABX, $J_{AB} \simeq 15.7$ Hz, $J_X \simeq 0$ Hz), 7.28 (m, 5H).
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29. A. W. Herriott and D. Picker, Tetrahedron Lett., 1511 (1974).
30. The melting points of compounds 3, 4, and 24 (152.0-152.5°C, 128.5-129.5°C and 236.5-237.5°C respectively) differed somewhat from previous literature values but spectroscopic and analytical data for these compounds were in full accord with the assigned structures.

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