Oxonium Ions in Organic Synthesis: Condensation of 2,3-Dihydrofuran and 3,4-Dihydro-2*H*-pyran with 1,3-Dicarbonyl Compounds

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Received December 30, 1988

2,3-Dihydrofuran (**3a**) and 3,4-dihydro-2*H*-pyran (**3b**) condense with a variety of β-keto esters and cyclic or acyclic β-diketones (or their enol tautomers), in the presence of trifluoroacetic acid, to form 2-(tetrahydrofuran-2-yl)-1,3-dicarbonyl (**6**) and 2-(tetrahydropyran-2-yl)-1,3-dicarbonyl adducts (**7**). Cyclic β-diketones **6b**, **6c**, **7b**, and **7c** exist predominantly as their enol tautomers. A mechanism is proposed in which oxonium ion **2** condenses with the enol tautomer of the ketones.

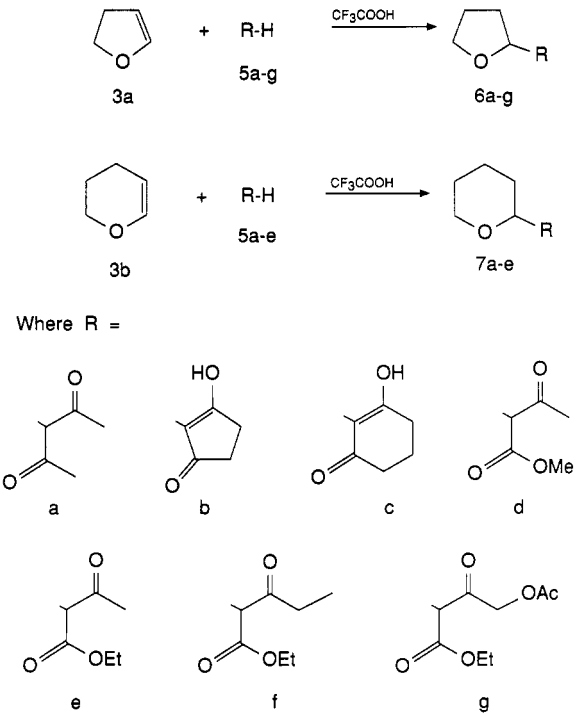
Attempts to C-alkylate the enolates derived from β-keto esters and β-diketones with α-halo ethers are frequently frustrated by low yields and significant O-alkylation.[1] Accordingly, we have been interested in alternative acid-catalyzed methods for the preparation of 2-(tetrahydrofuran-2-yl)-1,3-dicarbonyl (**6**) and 2-(tetrahydropyran-2-yl)-1,3-dicarbonyl compounds (**7**). In the course of synthesizing the antihypertensive fungal metabolite oudenone, we found that tetrahydrofuran-2-ol (**1**) condensed with 3-hydroxy-2-cyclopenten-1-one (**5b**, the predominant enol tautomer of 1,3-cyclopentanedione) under acidic conditions to form 3-hydroxy-2-(tetrahydrofuran-2-yl)-2-cyclopenten-1-one (**6b**).[2] Since this reaction presumably proceeds via oxonium ion **2**[1b,3,4] (Scheme I), we anticipated that the same product would also be formed if oxonium ion **2** were produced by protonation of 2,3-dihydrofuran (**3a**).

Isolated literature precedent was found for similar reactions: 3,4-dihydro-2*H*-pyran (**3b**) reacts with 3-hydroxy-2-cyclohexen-1-one (**5c**) in the presence of catalytic sulfuric acid to afford a modest yield of **7c**.[5] 2-Chlorotetrahydropyran reacts similarly with 3-hydroxy-2-cyclohexen-1-one (**5c**) to give a lower yield of **7c**. However, yields from 2-chlorotetrahydrofuran are dismal, and acyclic β-diketones and 3-hydroxy-2-cyclopenten-1-one (**5b**) fail to react.[5] Acetylated glycals are reported to react with acyclic β-diketones and β-keto esters in the presence of boron trifluoride, with elimination of the allylic acetoxy group.[6] In this case, however, 3-hydroxy-2-cyclohexen-1-one (**5c**) failed to react.

Results and Discussion

As shown in Table I, both 2,3-dihydrofuran (**3a**) and 3,4-dihydro-2*H*-pyran (**3b**) readily condense with a variety of β-keto esters and β-diketones (or their enol tautomers), in the presence of trifluoroacetic acid, to form the desired 2-(tetrahydrofuran-2-yl)-1,3-dicarbonyl (**6**) and 2-(tetrahydropyran-2-yl)-1,3-dicarbonyl adducts (**7**). The reaction is general, tolerating both cyclic and acyclic ketones. The current method for preparing adducts such as **6** and **7** is easier to perform and more direct than the approach from lactols (i.e., **1**)[2] and will often be the preferred route.

All of the acyclic β-diketone and β-keto ester products exist predominantly as keto tautomers. However, the ^1H NMR and ^{13}C NMR spectra of **6b**, **6c**, **7b**, and **7c** demonstrate that these cyclic β-diketones exist predominantly as their enol tautomers in $CDCl_3$. This is in accord with previous observations that enols of cyclic β-diketones are more favorable than enols of acyclic β-diketones, which are more favorable than enols of β-keto esters in nonpolar to moderately polar solvents.[7] Two new asymmetric centers are generated in the formation of **6d–g** and **7e**. Accordingly, two diastereomers of **6d–g** and **7e** were observed by ^{13}C NMR. Although a preparative separation of the diastereomeric pairs was not practical because of facile interconversion,[8] analytical TLC and GC separation was observed.



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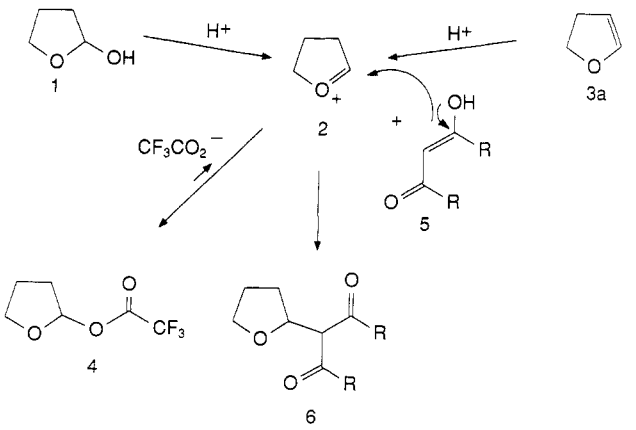
0022-3263/89/1954-4291$01.50/0

Table I. Reactions of 2,3-Dihydrofuran (3a) and 3,4-Dihydro-2*H*-pyran (3b) with β-Diketones and β-Keto Esters (5)

β-diketone or β-keto ester	mol % 3a or 3b	CF_3CO_2H, mol %	time, h	yield,[a] %	product
5a	200 3a	100	24	72	6a
5b	115 3a	200	3	60	6b
5c	115 3a	150	1	64	6c
5d	115 3a	200	24	70	6d
5e	115 3a	200	12	71	6e
5f	200 3a	30[b]	1[b]	53	6f
5g	115 3a	200	72	60	6g
5a	115 3b	200	48	22	7a
5b	115 3b	200	17	51	7b
5c	115 3b	200	7	56	7c
5e	115 3b	200	24	29	7e

[a] Isolated yield after purification as described in the text. [b] $BF_3 \cdot Et_2O$ was utilized as the catalyst.

Scheme I



Initially, boron trifluoride was utilized as the catalyst, but trifluoroacetic acid produced a superior yield of **6d** and was used in all subsequent reactions. In all cases, 2,3-dihydrofuran (**3a**) or 3,4-dihydro-2*H*-pyran (**3b**) was added slowly to the mixture of ketone **5** and trifluoroacetic acid in order to minimize the chance of acid-catalyzed polymerization of **3**. As noted in Table I, the reactions with 2,3-dihydrofuran (**3a**) seem to be more rapid and higher yielding than the corresponding reactions with 3,4-dihydro-2*H*-pyran (**3b**). This is consistent with previous observations that 2,3-dihydrofuran (**3a**) forms oxonium ions more readily than 3,4-dihydro-2*H*-pyran (**3b**).[3,9]

Interestingly, we found it necessary to use at least 100 mol % of trifluoroacetic acid in order to obtain optimal yields and reaction rates. For example, the isolated yield of **6d** was only 35% when 50 mol % trifluoroacetic acid was utilized, and no **6d** was isolated when 10 mol % trifluoroacetic acid was utilized. The requirement for stoichiometric trifluoroacetic acid appears curious, since it is not consumed in the overall transformation. This can be explained by the observation that trifluoroacetic acid reacts very rapidly and quantitatively with 2,3-dihydrofuran under the reaction conditions to produce tetrahydro-2-furanyl trifluoroacetate (**4**), readily identified by ^1H NMR.[1g,4b,4c,10] Tetrahydro-2-furanyl trifluoroacetate (**4**) partially dissociates to provide a low concentration of oxonium ion **2**, which presumably condenses with the enol tautomer of the ketones, as shown in Scheme I. The mechanism depicted in Scheme I is in accord with our observation that diethyl malonate, which does not easily enolize, fails to react with 2,3-dihydrofuran in the presence of trifluoroacetic acid. The failure of malonate to react in a related condensation has been noted previously.[6] Also consistent with this mechanism, tertiary alkyl halides capable of forming relatively stable carbonium ions have been reported to react with 1,3-dicarbonyl compounds in the presence of Lewis acid catalysts.[11]

Experimental Section

Low-resolution mass spectra were obtained with 70-eV electron-impact ionization. Gas chromatography was performed on a 10% SE-30 column in a HP-5830A chromatography. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on EM 5539 silica gel 60 plates, and preparative flash chromatography was performed on EM silica gel 60 (0.040–0.063 mm). Solvents were evaporated in vacuo on a rotary evaporator. All enols, β-keto esters, and β-diketones gave characteristic purple, red, or brown colors when added to a 1% aqueous $FeCl_3$ solution. The purity of all new compounds was judged to be greater than 95% by NMR spectroscopy and GC or TLC.

Tetrahydro-2-furanyl Trifluoroacetate (4). Trifluoroacetic acid (120 mol %) was added to 2,3-dihydrofuran (**3a**) dissolved in $CDCl_3$ at 0 °C and then warmed to 20 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (2 H, m), 2.19 (2 H, t, J = 10 Hz), 4.13 (2 H, br t, J = 10 Hz), 6.45 (1 H, br s).[10]

3-Hydroxy-2-cyclopenten-1-one (5b) was obtained commercially: ^{13}C NMR (acetone-d_6) δ 32.09, 106.48, 197.99.

Ethyl 4-acetoxy-3-oxobutanoate (5g) was prepared from ethyl 4-bromo-3-oxobutanoate as described:[12] bp 55–58 °C, 0.5 Torr (lit. bp 84–86 °C, 0.7 Torr); 12.10 g, 28% yield; R_f 0.44 (1:1 EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3 H, t, J = 7.2 Hz), 2.17 (3 H, s), 3.50 (2 H, s), 4.22 (2 H, q, J = 7.2 Hz), 4.79 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96 (q), 20.26 (q), 46.05 (t), 61.63 (t), 67.74 (t), 166.23 (s), 169.50 (s), 196.50 (s).

General Procedure for Condensations. The following general procedure was followed, with the modifications shown in Table I. 2,3-Dihydrofuran (**3a**) or 3,4-dihydro-2*H*-pyran (**3b**) (5.75 mmol) was added very slowly (>15 min) with stirring to a soltuion of the β-keto ester or β-diketone (**5**) (5.0 mmol) and trifluoroacetic acid (0.77 mL, 1.14 g, 10.0 mmol) in dichloromethane (3 mL) under nitrogen. Reactions were followed by ^1H NMR, TLC, or GC (10% SE-30). After the reaction appeared to be complete, the mixture was diluted with CH_2Cl_2, rinsed with water and saturated aqueous sodium chloride, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to afford the crude product, which was purified by flash chromatography on silica gel or by Kugelrohr distillation.

3-(Tetrahydrofuran-2-yl)-2,4-pentanedione (6a) was purified by Kugelrohr distillation, 55–58 °C, 0.1 Torr (lit.[1g] bp 96 °C, 1 Torr): ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (1 H, ddd, J = 8, 8, 18 Hz), 1.85 (2 H, quintet, J = 7 Hz), 2.10 (1 H, m), 2.15 (3 H, s), 2.22 (3 H, s), 3.75 (3 H, m), 4.44 (1 H, ddd, J = 7, 7, 10 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 25.37, 29.64, 30.31, 30.43, 67.87, 73.87,

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77.70, 202.21, 202.87; mass spectrum m/e 170 (0.4, M^+), 127 (100), 113 (18), 97 (16), 85 (49), 71 (45), 43 (56); IR (neat) 2950, 2860, 1725, 1700, 1420, 1355, 1275, 1200, 1155, 1070 cm^{-1}; HRMS calcd for $C_9H_{14}O_3$ m/e 170.0943, found 170.0940. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 64.03; H, 8.40.

3-Hydroxy-2-(tetrahydrofuran-2-yl)-2-cyclopenten-1-one (6b) was purified by chromatography (CH_2Cl_2–acetone, 50:50): mp 107–108 °C (lit.[2] mp 115–116 °C); ^1H NMR data consistent with literature;[2] ^{13}C NMR (20 MHz, $CDCl_3$) δ 25.52, 26.94, 31.72, 33.38, 68.28, 77.81, 116.72, 185.04, 203.23; mass spectrum m/e 168 (21, M^+), 125 (100), 70 (40), 43 (30); IR ($CHCl_3$) 3000, 2940, 1725, 1630, 1400, 1290, 1255, 1215, 1090 cm^{-1}.

3-Hydroxy-2-(tetrahydrofuran-2-yl)-2-cyclohexen-1-one (6c) was purified by chromatography (EtOAc–hexane, 75:25): ^1H NMR (80 MHz, $CDCl_3$) δ 1.3–2.8 (10 H, m), 3.94 (2 H, m), 4.96 (1 H, dd, J = 6, 9 Hz), 10.71 (1 H, br s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 20.48, 25.08, 29.16, 32.80, 36.48, 67.90, 79.37, 112.81, 174.19, 197.15; mass spectrum m/e 182 (23, M^+), 165 (20), 154 (100), 139 (93), 137 (31), 126 (96), 112 (22), 111 (28), 108 (28), 98 (42), 84 (34); IR ($CHCl_3$) 2950, 2880, 1715, 1625, 1430, 1420, 1380, 1325, 1295, 1260, 1235, 1145, 1030 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_3$ m/e 182.0943, found 182.0940.

Methyl 2-(tetrahydrofuran-2-yl)-3-oxobutanoate (6d)[13] was prepared according to the above general procedure and also by the following larger scale procedure: Trifluoroacetic acid (22.80 g, 0.20 mol, 200 mol %) was added to a stirred solution of methyl acetoacetate (11.60 g, 0.10 mol, 100 mol %) in methylene chloride (75 mL) under a nitrogen atmosphere. 2,3-Dihydrofuran (8.05 g, 115.0 mmol, 115 mol %) was added to this mixture over 2 h. After 24 h, methylene chloride (150 mL) was added, and the reaction mixture was cooled to 0–5 °C and washed with 10% sodium bicarbonate solution (150 mL) to pH 9. The organic layer was then washed with saturated sodium chloride and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product (19.7 g), which was distilled (85–90 °C, 0.4 mm) to afford 12.98 g (70% yield). TLC (1:1 hexane–EtOAc) revealed a 65:35 mixture of diastereomers with R_f values 0.42 and 0.32: ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (1 H, m), 1.90 (2 H, m), 2.16 (1 H, m), 2.25 (1.2 H, s), 2.31 (1.8 H, s), 3.50 (0.6 H, d, J = 10 Hz), 3.57 (0.4 H, d, J = 8.5 Hz), 3.73 (1.8 H, s), 3.77 (1.2 H, s), 3.84 (2 H, m), 4.43 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.02 (t), 25.28 (t), 29.59 (t), 29.6 (q), 30.17 (t), 52.07 (q), 52.27 (q), 64.46 (d), 64.87 (d), 67.80 (t), 67.94 (t), 76.78 (d), 77.06 (d), 167.87 (s), 168.30 (s), 201.18 (s), 201.84 (s); mass spectrum m/e 143 (43), 127 (27), 111 (31), 71 (100), 43 (41); IR (neat) 2950, 2860, 1740, 1710, 1425, 1350, 1190, 1140, 1060; HRMS calcd for $C_7H_{11}O_3$ m/e 143.0708, found 143.0707.

Ethyl 2-(tetrahydrofuran-2-yl)-3-oxobutanoate (6e) was purified by Kugelrohr distillation (70–73 °C, 0.05 Torr). GC indicated a 60:40 diastereomeric mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 and 1.30 (3 H, 2 t, J = 7 Hz), 1.6 (1 H, m), 1.90 (2 H, ddd, J = 3, 7, 15 Hz), 2.16 (1 H, m), 2.25 (1.2 H, s), 2.33 (1.8 H, s), 3.51 (0.6 H, d, J = 9 Hz), 3.58 (0.4 H, d, J = 8 Hz), 3.80 (2 H, m), 4.19 (0.8 H, q, J = 7 Hz), 4.25 (1.2 H, q, J = 7 Hz), 4.45 (1 H, m); ^{13}C NMR (20 MHz, $CDCl_3$) δ 14.50, 25.74, 25.97, 30.16, 30.27, 30.82, 61.81, 61.93, 65.51, 65.79, 68.48, 68.63, 77.51, 77.72, 168.00, 168.39, 201.87, 202.87; mass spectrum m/e 157 (39), 127 (32), 112 (12), 111 (27), 85 (19), 71 (100), 69 (16), 43 (52); IR (neat) 2990, 2880, 1760, 1615, 1500, 1420, 1410, 1350, 1250, 1210, 1118, 1090 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.69; H, 8.12.

Ethyl 4-Oxo-2-(tetrahydrofuran-2-yl)pentanoate (6f). 2,3-Dihydrofuran (290 mg, 4.14 mmol) was added over 1 h with stirring to a solution of ethyl 3-oxopentanoate (300 mg, 2.07 mmol) and $BF_3{\cdot}Et_2O$ (75.3 mg, 0.53 mmol, 26 mol %). After 1 h of reaction, the mixture was diluted with CH_2Cl_2, rinsed with aqueous sodium carbonate and water, and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the product was purified by Kugelrohr distillation (85–95 °C, 0.05 Torr) to afford a mixture of diastereomers (55:45): ^1H NMR (80 MHz, $CDCl_3$) δ 0.96 (3 H, t, J = 7 Hz), 1.17 (3 H, t, J = 7 Hz), 1.8 (4 H, m), 2.45 (2 H, m), 3.3–4.0 (4 H, m), 4.0–4.5 (2 H, m); ^{13}C NMR (20 MHz, $CDCl_3$) δ 7.02, 13.63, 24.88, 25.09, 29.36, 30.02, 35.81, 60.82, 60.94, 63.63, 63.85, 67.54, 67.68, 76.78, 167.17, 167.56, 203.66, 204.12. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.23; H, 8.39.

Ethyl 4-acetoxy-2-(tetrahydrofuran-2-yl)-3-oxobutanoate (6g) was purified by chromatography (40:60 EtOAc–hexane) followed by Kugelrohr distillation (120–140 °C) to afford a (50:50) mixture of diastereomers: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3 H, m), 1.68 (1 H, m), 1.90 (2 H, m), 2.10 (1 H, m), 2.15 (3 H, s), 3.56 (0.5 H, d, J = 9 Hz), 3.69 (0.5 H, d, J = 8 Hz), 3.80 (2 H, m), 4.20 (2 H, m), 4.46 (1 H, m), 4.79 (1 H, s), 4.89 (1 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.61 (q), 13.99 (q), 19.97 (q), 20.26 (q), 25.05 (t), 25.27 (t), 29.20 (t), 30.27 (t), 60.60 (d), 60.98 (d), 61.47 (t), 61.59 (t), 67.63 (t), 67.84 (t), 67.99 (t), 68.14 (t), 76.70 (d), 76.73 (d), 166.55 (s), 166.80 (s), 169.72 (s), 169.79 (s), 197.31 (s), 197.42 (s); IR (neat) 2980, 2880, 1747, 1726, 1410, 1370, 1230, 1060 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.65; H, 6.90.

3-(Tetrahydropyran-2-yl)-2,4-pentanedione (7a) was purified by chromatography (EtOAc–hexane, 10:90 to 50:50) followed by Kugelrohr distillation (70–72 °C, 0.5 Torr): ^1H NMR (80 MHz, $CDCl_3$) δ 1.3–2.0 (6 H, m), 2.10 (3 H, s), 2.13 (3 H, s), 3.2–4.4 (4 H, m); ^{13}C NMR (20 MHz, $CDCl_3$) δ 23.21, 25.81, 29.32, 30.04, 30.89, 68.91, 75.18, 76.99, 202.20, 203.08; mass spectrum m/e 184 (0.2, M^+), 141 (100), 127 (12), 97 (7), 85 (38); IR (neat) 2925, 2840, 1720, 1690, 1420, 1350, 1285, 1210, 1160, 1040 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_3$ m/e 184.1100, found 184.1108.

3-Hydroxy-2-(tetrahydropyran-2-yl)-2-cyclopenten-1-one (7b) was purified by chromatography (hexane–EtOAc, 50:50, then EtOAc): mp 87–89 °C, white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–2.2 (6 H, m), 2.5 (4 H, m), 3.58 (1 H, dt, J = 3, 11 Hz), 4.16 (1 H, dt, J = 2, 11 Hz), 4.45 (1 H, d, J = 11 Hz), 10.2 (1 H, br s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 22.63, 26.01, 26.70, 31.10, 33.18, 69.20, 76.92, 117.18, 184.70, 203.00; mass spectrum m/e 182 (84, M^+), 164 (18), 153 (33), 152 (22), 151 (33), 139 (22), 136 (25), 135 (41), 125 (100), 112 (30), 111 (28), 107 (24), 98 (62); IR (neat) 2930, 1780, 1690, 1630, 1410, 1310, 1290, 1260, 1200, 1170, 1080, 1050, 1035 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_3$ m/e 182.0943, found 182.0944.

3-Hydroxy-2-(tetrahydropyran-2-yl)-2-cyclohexen-1-one (7c)[5] was purified by chromatography (hexane–EtOAc, 75:25) or by Kugelrohr distillation (155–165 °C, 0.4 Torr (lit.[5] bp 116–117 °C, 2.5 Torr)): ^1H NMR (300 MHz, $CDCl_3$) 1.3–2.1 (8 H, m), 2.38 (4 H, m), 3.54 (1 H, dt, J = 3, 11 Hz), 4.13 (1 H, dd, J = 3, 11 Hz), 4.64 (1 H, dd, J = 2, 11 Hz), 10.0 (1 H, br s); ^{13}C NMR (20 MHz, $CDCl_3$) δ 20.90, 23.04, 26.06, 29.37, 31.47, 36.68, 69.48, 77.21, 114.71, 174.54, 196.43; mass spectrum m/e 196 (69), 178 (24), 167 (100), 139 (48), 137 (39), 112 (40), 55 (33); IR (neat) 2935, 2855, 1725, 1700, 1425, 1360, 1290, 1265, 1215, 1190, 1090, 1015 cm^{-1}; HRMS calcd for $C_{11}H_{16}O_3$ m/e 196.1099, found 196.1103.

Ethyl 2-(tetrahydropyran-2-yl)-3-oxobutanoate (7e) was purified by Kugelrohr distillation (65–70 °C, 0.1 Torr). GC indicated a 60:40 diastereomeric mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3 H, m), 1.45–1.9 (6 H, m), 2.23 (1.2 H, s), 2.26 (1.8 H, s), 3.35–3.6 (2 H, m), 3.9–4.0 (2 H, m), 4.1–4.3 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.99, 23.00, 23.04, 25.61, 25.66, 29.45, 29.68, 29.76, 29.83, 61.24, 61.26, 65.55, 65.97, 68.64, 68.77, 76.07, 76.63, 167.21, 167.75, 201.01, 202.10; mass spectrum m/e 171 (60, M – 43), 141 (37), 125 (46), 85 (100), 84 (20), 43 (58); IR (neat) 2935, 2870, 1740, 1710, 1440, 1365, 1355, 1290, 1260, 1165, 1085 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.46; H, 8.55.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the New York State Science and Technology Foundation for partial support of this research.

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