washed 3 times with 10 mL of ether. The combined organic layers were dried ($MgSO_4$) and evaporated to give 0.918 g of crude product. Purification of 0.519 g by medium-pressure chromatography on silica gel with 1:1 pentane–ether as eluent gave 83.5 mg (15%) of a mixture of cyclobutanes and ene adducts, 6.6 mg (1%) of dihydropyran **5** ($R_1 = R_2 = R_3 = CH_3$), 12.5 mg (2%) of **10b** and **11b**, and 59.0 mg (10%) of **8** ($R_1 = R_2 = R_3 = CH_3$).

The first fraction was purified by preparative GC on 0.25 in. × 9 ft, 10% DEGS on Chromosorb PNAW at 145 °C with a flow rate of 70 mL/min. All four cyclobutanes and two ene adducts were isolated. Yields shown in Table I are based on analysis of the chromatogram. ^{13}C NMR data are given in Table II.

The spectral data for **12c** follow: NMR ($CDCl_3$) δ 3.79 (s, 3), 2.4 (m, 3), 1.81 (q, 2, J = 7.5 Hz), 0.96 (s, 3), 0.90 (m, 3 virtually coupled), 0.92 (t, 3, J = 7.5 Hz); IR (CCl_4) 2970, 2235, 1747, 1255 cm^{-1}; GC t_R 51 min.

The spectral data for **13b** follow: NMR ($CDCl_3$) δ 3.79 (s, 3), 2.91 (dd, 1, J = 7, 11.7 Hz), 2.18 (m, 1), 1.89 (dd, 1, J = 11.7, 6.2 Hz), 1.77 (q, 2, J = 7 Hz), 1.12 (d, 3, J = 7 Hz), 1.06 (s, 3), 0.98 (t, 3, J = 7 Hz); IR (CCl_4) 2970, 2235, 1747, 1255 cm^{-1}; mass spectrum, m/e (relative intensity, %) 166 (M^+ - 31, 6), 155 (6), 154 (64), 122 (13), 110 (8), 94 (9), 85 (9), 84 (100), 80 (9), 70 (5), 69 (59), 67 (10), 56 (16), 55 (24), 41 (29); GC t_R 55.0 min.

The spectral data for **12b** follow: NMR ($CDCl_3$) δ 3.78 (s, 3), 2.39 (m, 3), 1.50 (q, 2, J = 7.2 Hz), 1.39 (s, 3), 0.98–1.05 (m, 3, virtually coupled), 0.79 (t, 3, J = 7 Hz); IR (CCl_4) 2985, 2235, 1745, 1255 cm^{-1}; mass spectrum, m/e (relative intensity, %) 166 (M^+ - 29, 1), 164 (M^+ - 31, 5), 163 (2), 155 (5), 154 (44), 120 (8), 95 (11), 85 (7), 84 (100), 80 (10), 69 (53), 56 (14), 55 (14), 42 (8), 41 (30); GC t_R 59.8 min.

The spectral data for **13c** follow: NMR ($CDCl_3$) δ 3.81 (s, 3), 2.75 (dd, 1, J = 8, 10 Hz), 2.1–2.6 (m, 1), 1.94 (dd, 1, J = 9, 10 Hz), 1.39 (q, 2, J = 7 Hz), 1.33 (s, 3), 1.00 (d, 3, J = 6.8 Hz), 0.82 (t, 3, J = 7 Hz); IR (CCl_4) 2970, 2235, 1740 cm^{-1}; GC t_R 62.5 min. Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.50; H, 9.07.

The spectral data for **11a** follow: NMR ($CDCl_3$) δ 4.83 (br s, 2), 3.78 (s, 3), 3.42 (m, 1), 2.4 (m, 1), 1.7–2.2 (m, 2), 1.58 (br, 2), 0.95–1.13 (m, 6); IR (CCl_4) 3095, 2970, 2250, 1755, 1644, 1260, 895 cm^{-1}; GC t_R 80.4 min.

The spectral data for **10a** follow: NMR ($CDCl_3$) δ 5.3 (m, 1), 3.78 (s, 3), 3.41 (m, 1), 2.0–2.5 (m, 1), 1.7–2.0 (m, 2), 1.4–1.7 (m, 6), 1.04 and 1.02 (2 d, 3, J = 7 Hz, CH_3 of two diastereomers); IR (CCl_4) 2960, 2250, 1755, 1260 cm^{-1}; GC t_R 85.2 min.

The spectral data for dihydropyran **5** ($R_1 = R_2 = R_3 = CH_3$) follow: NMR ($CDCl_3$) δ 3.76 (s, 3), 1.2–2.3 (m, 5), 1.32 (s, 3), 0.95 (d, 3, J = 6 Hz), 0.92 (t, 3, J = 6 Hz); IR (neat) 2975, 2200, 1760 (sh), 1640 cm^{-1}; UV max (ETOH) 298 nm (ε 195), 230 (2755).

The spectral data for **10b** (obtained pure from (*E*)-3-methyl-2-pentene) follow: NMR ($CDCl_3$) δ 5.30 (m, 1), 3.83–3.90 (several s, 3), 3.77 (t, 1 J = 7 Hz), 2.1–2.6 (m, 2), 1.8–2.1 (m, 3), 1.4–1.6 (m, 6), ~1.0 (2 d, 3, J = 7 Hz); IR (neat) 2960, 2200, 1750 cm^{-1}; mass spectrum, m/e (relative intensity, %) 307 (5), 306 (M^+, 25), 294 (2), 291 (7), 280 (2), 276 (2), 275 (12), 274 (3), 266 (2), 265 (11), 264 (29), 248 (9), 247 (18), 243 (8), 233 (6), 220 (6), 219 (5), 215 (8), 211 (33), 210 (33), 209 (8), 208 (46), 206 (11), 205 (8), 196 (10), 195 (46), 194 (16), 180 (24), 179 (29), 178 (14), 176 (43), 167 (11), 166 (74), 164 (23), 163 (13), 162 (11), 148 (26), 141 (10), 140 (14), 136 (30), 135 (12), 134 (20), 132 (11), 127 (25), 126 (24), 122 (14), 121 (25), 120 (22), 112 (95), 109 (24), 107 (24), 105 (24), 100 (41), 99 (39), 98 (57), 97 (79), 96 (79), 95 (29), 94 (22), 93 (33), 87 (72), 84 (83), 83 (95), 82 (36), 81 (95), 80 (95), 79 (60), 77 (43), 69 (97), 68 (89), 67 (95), 66 (47), 59 (98), 56 (66), 55 (100), 54 (63), 53 (97), 52 (97), 51 (51), 43 (97), 42 (60), 41 (97), 39 (97); mol wt calcd for $C_{16}H_{22}N_2O_4$ 306.1579, found 306.1572.

The spectral data for **11b** were estimated from the mixture of **10b** and **11b** obtained from (*Z*)-3-methyl-2-pentene: NMR ($CDCl_3$) δ 4.84 (br s, 2).

The spectral data for **8** ($R_1 = R_2 = R_3 = CH_3$) follow: NMR ($CDCl_3$) δ 3.80 (several s, 6), 2.4–2.8 (m, 2), 0.9–2.4 (m, 14); IR (neat) 2980, 2250, 1755 cm^{-1}; mol wt calcd for $C_{16}H_{22}N_2O_4$ 306.1579, found 306.1588.

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Registry No. 1, 137-05-3; (*E*)-**10a** (isomer 1), 77257-17-1; (*E*)-**10a** (isomer 2), 77257-18-2; (*Z*)-**10a** (isomer 1), 77257-19-3; (*Z*)-**10a** (isomer 2), 77257-20-6; **10b**, 77257-21-7; **11a** (isomer 1), 77270-01-0; **11a** (isomer 2), 77257-22-8; **11b**, 77257-23-9; **12a**, 77257-24-0; **12b**, 77257-25-1; **12c**, 77287-00-4; **13a**, 77257-26-2; **13b**, 77287-01-5; **13c**, 77287-02-6; methylenecyclohexane, 1192-37-6; 2-methyl-2-butene, 513-35-9; (*Z*)-3-methyl-2-pentene, 922-62-3; (*E*)-3-methyl-2-pentene, 616-12-6; 1-hexene, 592-41-6; Me_2AlCl, 1184-58-3.

Condensations at the 6 Position of the Methyl Ester and the Dimethylamide of 3,5-Dioxohexanoic Acid via 2,4,6-Trianions

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The trianions of methyl 3,5-dioxohexanoate and *N,N*-dimethyl-3,5-dioxohexanamide have been prepared by treatment of the compounds first with NaH to form the monoanions and then with 2 equiv of *sec*-butyllithium. The trianions are highly nucleophilic at the 6 position. Alkylation with benzyl chloride, aldol condensation with benzophenone, and acylation with methyl benzoate gave terminal condensation products but methyl acetate failed to condense with the trianions, proton transfer from the acetyl methyl group occurring instead. Both trianions underwent β-ketoacylation with methyl benzoylacetate but only the diketo ester trianion condensed with methyl acetoacetate. The resulting 1,3,5,7,9-pentacarbonyl compounds underwent cyclization reactions to give aromatic products. Complex aromatic products derived from 1,3,5,7,9,11-hexacarbonyl compounds were obtained from condensations of the diketo ester trianion with 4-methoxy-6-methyl-2-pyrone and of the diketo amide trianion with 4-methoxy-6-phenyl-2-pyrone.

Several classes of 1,3-dicarbonyl compounds have been converted to 2,4-dianions by treatment with 2 equiv of strong bases.[1] In all cases the resulting dianions have been highly nucleophilic and the initial reactions with electro-

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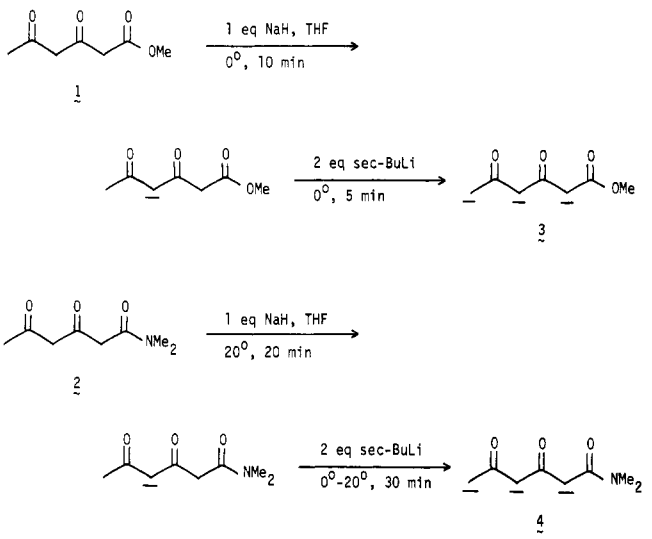
Scheme I

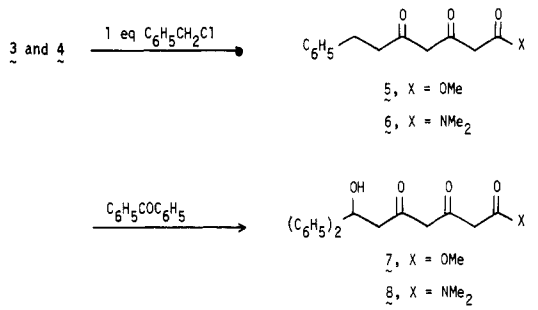


philes have been observed exclusively at the less stable 4 anions. Many examples of the use of these dianions have been reported.[1] Little attention has been given to the corresponding trianions of 1,3,5-tricarbonyl compounds, other than those of triketones,[2] although such intermediates could have substantial synthetic value. Herein we report studies of the trianions of the diketo ester methyl 3,5-dioxohexanoate (1) and the diketo amide *N,N*-dimethyl-3,5-dioxohexanamide (2).

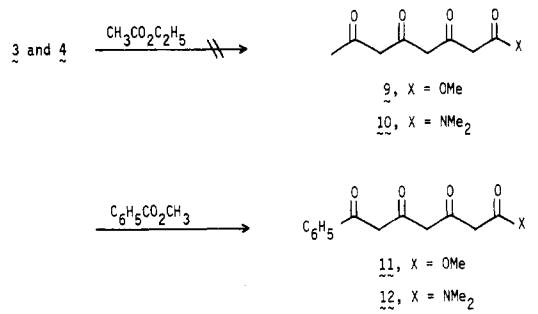
Diketo ester 1 is readily available by methanolysis of dehydroacetic acid.[3] The procedure for conversion of 1 to its trianion (3) involves treatment with 1 equiv of NaH to form the 4 monoanion, followed by treatment with 2 equiv of *sec*-butyllithium (Scheme I). Neither NaH nor *sec*-butyllithium alone is satisfactory for formation of trianion 3. The 2,4-dianion of 1 can be formed by treatment with NaH at elevated temperatures but the trianion is not formed. With alkyllithiums, nucleophilic addition competes with ionization if 1 is not first converted to the mono- or dianion. An earlier communication from this laboratory[4] described formation of the trilithium salt of diketo ester 1 by treatment with 3 equiv of lithium diisopropylamide (LDA).[5] Subsequent investigations have indicated that LDA is not sufficiently basic to drive the formation of trianion 3 to completion. Treatment of LDA-generated 3 with electrophiles has given mixed results because of competition between 3 and the residual LDA.

Diketo amide 2 was prepared in 83% yield by condensation of the dianion of 2,4-pentanedione with methyl *N,N*-dimethylcarbamate (2:1 stoichiometry). This procedure for preparation of 2 is superior to one involving acetylation of the dianion of *N,N*-dimethyl-3-oxobutyramide[1c] because the latter requires chromatography to separate 3 from returned β-keto amide, whereas recovered 2,4-pentanedione can be separated from 3 by distillation. The diketo amide was converted to trianion 4 by treatment with 1 equiv of NaH followed by 2 equiv of *sec*-butyllithium.

The high reactivity of the 6 positions of trianions 3 and 4 was demonstrated by reactions with benzyl chloride. Treatment of the trianions with 1 equiv of the alkyl halide for 1 h at 20 °C gave the 6-benzyl adducts 5 and 6 in yields of 82 and 59%, respectively. ^{1}H NMR spectra showed that alkylation had occurred at the 6 position in both cases; the terminal methyl signals in the starting tricarbonyl compounds were replaced by AA′BB′ multiplets in the products. No products of alkylation at the 2 or 4 positions were detected. Similar condensations with benzophenone gave terminal aldol adducts 7 and 8 in yields of 74 and 73%, respectively, as the only products; the structures of 7 and 8 were supported by ^{1}H NMR spectra.



Acylations of trianions 3 and 4 were investigated. When the trianions were treated with ethyl acetate no evidence could be found for the anticipated acetylation products 9 and 10. Proton abstraction from the acetate methyl group apparently occurs in preference to nucleophilic attack on the carbonyl group. Ultimately, ethyl acetoacetate is formed by acetylation of the resulting enolate anion of ethyl acetate. The basicity of the trianions would appear to pose a serious problem for the use of aliphatic esters as acylating agents. Similar attempts to acylate trianions of 2,4,6-triketones with aliphatic esters have previously met with failure.[6] The condensations of trianions 3 and 4 with nonenolizable esters proceed satisfactorily. Acylations with methyl benzoate gave triketo ester 11 and triketo amide 12 in yields of 59 and 66%, respectively.



The preparation of β-oligoketo acids, in particular 2,4,6-triketo acids and their derivatives, has attracted considerable attention in relation to biomimetic syntheses of aromatic natural products.[7] Previously described methods for the synthesis of esters and amides involve condensations linking C-4 with C-5 or C-1 with C-2. Linkage of C-4 with C-5 is represented by β-ketoacylation of dianions of β-keto esters and amides and has been used successfully for the synthesis of 9,[4] 10,[1c] and 12[1c] but not for triketo ester 11. Ester 11 is not well suited for preparation by β-ketoacylation because it requires condensation

(1) (a) Harris, T. M.; Harris, C. M. *Org. React.* **1969**, *17*, 155. (b) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343. (c) Hubbard, J. S.; Harris, T. M. *Tetrahedron Lett.* **1979**, 4601.

(2) (a) Harris, T. M.; Murphy, G. P.; Poje, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 7733. (b) Harris, T. M.; Carney, R. L. *Ibid.* **1967**, *89*, 6734.

(3) Batelaan, J. G. *Synth. Commun.* **1976**, *6*, 81.

(4) Harris, T. M.; Murray, T. P.; Harris, C. M.; Gumulka, M. *J. Chem. Soc., Chem. Commun.* **1974**, 362.

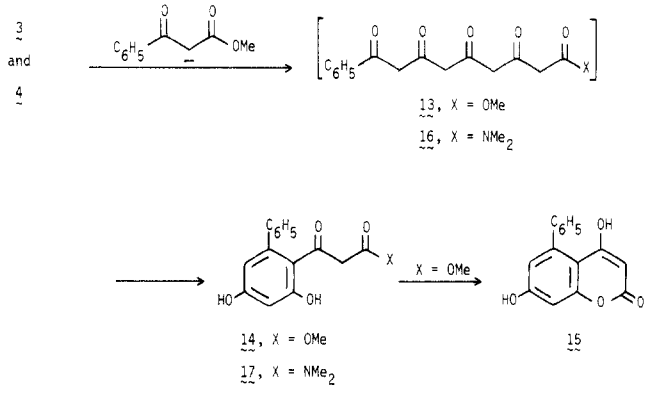
(5) Conjugate additions of trianion 3 with β-nitrostyrenes have also been described: Ehrig, V.; Seebach, D. *Chem. Ber.* **1975**, *108*, 1961.

(6) Murphy, G. P., unpublished observation.

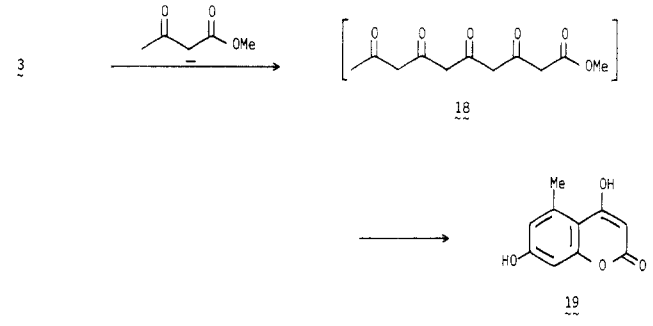
(7) Harris, T. M.; Harris, C. M.; Hindley, K. B. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 217. Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.

between *two different* β-keto esters. Esters **9** and **11** have been prepared by linkage of C-1 with C-2, i.e., carboxylation of trianions of the triketones followed by esterification with CH_2N_2.[2] Triketo amides **10** and **12** should be accessible by acylation of the triketone trianions with methyl *N,N*-dimethylcarbamate, although these condensations have not been reported. We have now performed the synthesis of **10** by this route, obtaining the triketo amide in 72% yield.

β-Ketoacylation was investigated as a route to derivatives of 3,5,7,9-tetraketo acids. Acylation with β-keto esters require preliminary ionization of the acidic 2-methylene groups; only highly reactive nucleophles can be acetylated with these negatively charged electrophiles.[8] Acylation of **3** with methyl benzoylacetate gave tetraketo ester **13** in good yield; however, chromatographic separation from diketo ester **1** proved to be difficult because **13** underwent cyclization on silica gel to give resorcinol **14** and coumarin **15**. A similar condensation of trianion **4** gave amide **17** derived from tetraketo amide **16**. The stability of the

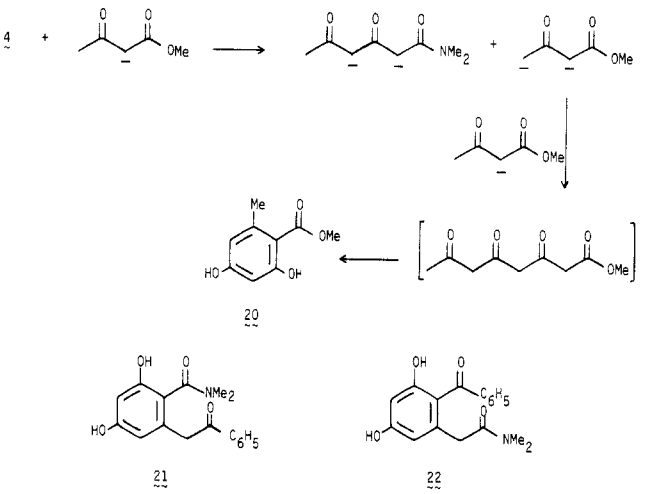


amide group in **17** precluded lactonization to **15**. Condensation of trianion **3** with methyl acetoacetate gave tetraketo ester **18** which cyclized to coumarin **19**. The



reaction of trianion **4** with methyl acetoacetate failed to give tetraketo amide or its cyclization product(s). The reaction yielded methyl orsellinate (**20**) which arose by trianion **4** converting the monoanion of methyl acetoacetate to the dianion which condensed with methyl acetoacetate monoanion to give methyl 3,5,7-trioxooctanoate. Aldol cyclization of the latter during chromatography of the reaction mixture gave **20**.

Compounds **15**,[9] **19**,[10] and **20**[2a] had been reported previously and their structures were established in the present case by comparisons of physical and spectroscopic properties with published data. The structural assignment for amide **17** rests upon distinction from isomeric formulations **21** and **22**, each of which might be formed by aldol cyclization of tetraketo amide **16**. Structure **17** was indicated by the fact that the phenyl protons produced a sharp signal in the ^1H NMR spectrum, consistent with attachment of the phenyl group to another aromatic ring rather than to a carbonyl group which would strongly deshield the protons at positions 2 and 6. In further support of structure **17**, no coupling or nuclear Overhauser effect could be demonstrated between the protons of the methylene group and those of the resorcinol ring.



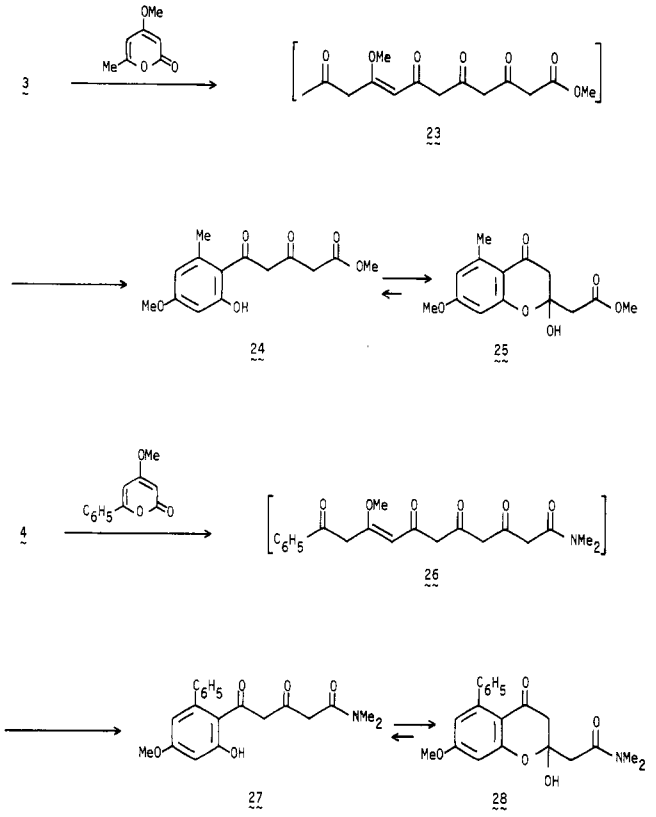
4-Hydroxy-2-pyrones and their derivatives are formal equivalents of 3,5-diketo esters and can in some cases be used to acylate reactive nucleophiles, thus adding a tricarbonyl group.[11] Trianion **3** was treated with 4-methoxy-6-methyl-2-pyrone to give aromatic diketo ester **24** via enol ether **23** of methyl 3,5,7,9,11-pentaoxododecanoate. ^1H NMR revealed that **24** existed primarily as hemiketal **25** in acetone-d_6. Strong nonequivalence between the protons of one of the methylene groups was observed; one alcoholic OH group was present but no enolic ones. Similar treatment of amide trianion **4** with 4-methoxy-6-phenyl-2-pyrone gave aromatic diketo amide **27** via enol ether **26**. Compound **27** existed mainly as an enol form in dimethyl-d_6 sulfoxide but underwent conversion to hemiketal **28** in $CDCl_3$. The shape of the aromatic signals of both **27** and **28** indicated that the phenyl group was attached to an aromatic ring rather than to a carbonyl group, providing additional support for the proposed structures. Neither acylation reaction occurred in high yield but this shortcoming is at least partially offset by the fact that complex hexaketide structures are being assembled in a single step from readily available starting materials.

Diketo ester **1** is more convenient to prepare than diketo amide **2**, is purified more readily, shows better stability during storage, and is easier to maintain in an anhydrous state. Furthermore, the trianion of **1** appears not to be as strongly basic as the trianion of **2** and consequently less prone to side reactions with the electrophiles. These factors dictate that the trianion of **1** should be the reagent of choice in all cases except those in which the target compound contains the amide functionality. Both of these highly nucleophilic species will certainly find a role in synthesis, particularly for the preparation of β-oligocarbonyl compounds needed for biomimetic syntheses of aromatic natural products.

Experimental Section

General Procedures. All organometallic reactions were carried out under nitrogen in oven-dried glassware with solvents that had

(8) Murray, T. P.; Harris, T. M. *J. Am. Chem. Soc.* **1972**, *94*, 8253.
(9) Harris, T. M.; Murphy, G. P. *J. Am. Chem. Soc.* **1971**, *93*, 6708.
(10) Iguchi, S.; Utsugi, N. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1290.
(11) Stockinger, H.; Schmidt, U. *Justus Liebigs Ann. Chem.* **1976**, 1617.



been carefully dried immediately before use. The usual workup procedure involved evaporation of reaction mixtures to dryness, addition of Et_2O and ice, acidification with cold 6 M HCl to pH 3–6, separation of layers, further extraction of the aqueous layer with Et_2O, drying of the combined organic extracts with $MgSO_4$, and evaporation. Column chromatography was carried out either (1) on 60–100-mesh silica gel (Davison Chemical Co.), using a stepwise solvent gradient, or (2) on TLC-grade, silica gel (Merck), using a single solvent mixture. In general, superior results were obtained when the silica gel had been acid washed to remove metallic impurities; after acid treatment, the silica gel was washed with water until the effluent was pH 5.5 and then dried in air. ^1H NMR spectra were recorded on either a JEOL MH-100 or FX-90Q spectrometer, using tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 727 spectrophotometer, using KBr pellets for both solids and liquids. Mass spectra (70 eV) were obtained with an LKB-9000 spectrometer by direct insertion. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Methyl 3,5-dioxohexanoate (1) was prepared by methanolysis of dehydroacetic acid as described by Batelaan.[3]

***N,N*-Dimethyl-3,5-dioxohexanamide (2).** 2,4-Pentanedione (3.99 g, 39.9 mmol) was added to 80 mmol of lithium diisopropylamide (prepared from 8.68 g, 85.9 mmol, of diisopropylamine and 80 mmol of *n*-butyllithium in 100 mL of THF at −78 °C) at −78 °C and the mixture was allowed to warm to 0 °C over 20 min to form a colorless solution of the dianion. Methyl *N,N*-dimethylcarbamate (2.04 g, 19.8 mmol) was added. After stirring for 16 h at ambient temperature, the dark red suspension was concentrated in vacuo; Et_2O and ice were added followed by cold 6 M HCl to lower the pH to 7.0. The ether layer was discarded. The aqueous solution was further acidified to pH 3 and extracted with $CHCl_3$. The organic solution was dried and concentrated. Residual 2,4-pentanedione was separated by distillation (25 °C, 0.2 mm). The remaining material was distilled with a Kugelrohr apparatus to give 2.78 g (82% yield) of **2**, bp ca. 130–140 °C (0.1 mm), as a yellow oil. The ^1H NMR spectrum indicated that **2** existed mainly as the 4-enol tautomer: ^1H NMR ($CDCl_3$) δ 2.12 (s, 6-Me), 3.08 (s, NMe), 2.16 (s, NMe), 3.54 (s, 2-CH_2), 5.84 (s, 4-CH), 15.4 (br s, OH); IR (KBr) 1620, 1700, 2900, 3390 cm^{-1}; mass spectrum, *m/e* (relative intensity) 171 (M^+·, 100%), 129 (41), 114 (31), 87 (74), 86 (49). Anal. Calcd for $C_{18}H_{13}NO_3$: C, 56.13; H, 7.65. Found: C, 56.15; H, 7.25.

Preparation of Trianions 3 and 4. Methyl ester **1** (1.27 g, 8.0 mmol) was added slowly to a vigorously stirred suspension of NaH (0.25 g, 10.4 mmol) in THF (50 mL) at 0 °C. After evolution of H_2 had ceased (5 min), 16 mmol of *sec*-butyllithium (13.3 mL of 1.21 M in hexane) was added at 0 °C. The cherry red suspension of trianion **3** appeared to be formed immediately but was allowed to stand for 10 min before treatment with electrophiles.

For the preparation of trianion **4**, the monoanion was formed by treatment of amide **2** (0.90 g, 5.26 mmol) with NaH (0.50 g, 20.8 mmol) for 1 h at 20 °C. The monoanion was further ionized by treatment with 10.8 mmol of *sec*-butyllithium which was added at −78 °C; the mixture was allowed to warm to ambient temperature during 30 min to give **4** as a dark red suspension.

Alkylation of 3 and 4 with Benzyl Chloride. Trianion **3** (7.54 mmol) was treated with benzyl chloride (0.94 g, 7.34 mmol) in THF for 30 min at 25 °C. Workup included chromatography on silica gel (hexane–EtOAc mixtures) to give 1.57 g (82% yield) of methyl 7-phenyl-3,5-dioxoheptanoate (**5**) as a yellow oil, which the ^1H NMR spectrum indicated was mainly the 4-enol tautomer: ^1H NMR ($CDCl_3$) δ 2.52–3.0 (AA′BB′, m, CH_2CH_2), 3.34 (s, 2-CH_2), 3.77 (s, OCH_3), 5.63 (s, 4-CH), 7.32 (m, C_6H_5), 15.16 (br s, OH); IR (KBr) 1605, 1740, 2969, 3040 cm^{-1}; mass spectrum, *m/e* (relative intensity) 248 (M^+·, 25%), 205 (37), 175 (22), 131 (43), 102 (71), 91 (100). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.49. Found: C, 67.68; H, 6.61.

In the benzylation of **4**, 4 mmol of **4** was treated with 0.52 g (4.1 mmol) of benzyl chloride in THF for 1 h at 20 °C to give 618 mg (59% yield) of *N,N*-dimethyl-7-phenyl-3,5-dioxoheptanamide (**6**) as a yellow oil, which the ^1H NMR spectrum indicated was mainly the 4-enol tautomer: ^1H NMR ($CDCl_3$) δ 2.44–2.90 (AA′BB′ m, CH_2CH_2), 3.0 (m, 6, NMe_2), 3.42 (s, 2-CH_2), 5.58 (s, 4-CH), 7.25 (m, C_6H_5), 14.5 (br s, OH); IR (neat) 1620, 1705, 3340 cm^{-1}; mass spectrum, *m/e* (relative intensity) 261 (M^+·, 67%), 2.8 (100), 129 (38), 114 (61), 91 (46). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33. Found: C, 68.70; H, 7.57.

Aldol Condensation of 3 and 4 with Benzophenone. Trianion **3** (7.91 mmol) in THF was treated with benzophenone (1.43 g, 7.85 mmol) for 1 h at 20 °C. Workup yielded an oil which was chromatographed on TLC silica gel (74:25:1, hexane–EtOAc–MeOH) to give 1.99 g (74% yield) of **7** as a yellow oil, which the ^1H NMR spectrum indicated was mainly the 4-enol tautomer: ^1H NMR ($CDCl_3$) δ 3.22 (s, 2-CH_2), 3.34 (s, 6-CH_2), 3.69 (s, OCH_3), 5.60 (s, 4-CH), 7.2–7.5 (m, alcoholic OH and 2 C_6H_5), 14.2 (br s, enolic OH); IR (KBr) 1610, 1720, 2980, 3000, 3450 cm^{-1}. No parent ion (*m/e* 340) was present in the mass spectrum. The major fragmentation involved retro-aldol cleavage to give fragment ions *m/e* 158 and 182. Anal. Calcd for $C_{20}H_{20}O_8$: C, 70.58; H, 5.92. Found: C, 70.80; H, 6.17.

Trianion **4** (4.1 mmol) was treated with benzophenone (0.72 g, 4.0 mmol) for 45 min at 20 °C. Chromatography on TLC silica gel (1:1, hexane–EtOAc) gave 1.05 g (73% yield) of amide **8** as a yellow oil which existed mainly as the 4-enol tautomer: ^1H NMR ($CDCl_3$) δ 2.96 (s, NMe_2), 3.05 (s, 6-CH_2), 3.32 (s, 2-CH_2), 5.63 (s, 4-CH), 7.2–7.6 (m, alcoholic OH and 2 C_6H_5), 14.0 (br s, enolic OH); IR (KBr) 1625, 1710, 3425 cm^{-1}. The mass spectrum showed no parent ion (*m/e* 353); retro-aldol cleavage yielded *m/e* 171 and 182 fragments. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56. Found: C, 71.17; H, 6.70.

Preparation of Triketo Amide 10 by Acylation of 2,4,6-Heptanetrione with Methyl *N,N*-Dimethylcarbamate. 2,4,6-Heptanetrione (0.78 g, 5.5 mmol) was converted to the trilithium salt by treatment with 16.4 mmol of lithium diisopropylamide (formed from 1.66 g of diisopropylamine and 16.4 mmol of *n*-butyllithium in 50 mL of THF at −78 °C) at −78 °C. The mixture was warmed to 25 °C and after 1 h methyl *N,N*-dimethylcarbamate (0.27 g, 2.62 mmol) was added. After 12 h, the solvent was evaporated. Ether and ice were added followed by cold 6 M HCl to bring the pH to 7.0. The ether layer, which contained 2,4,6-heptanetrione, was discarded. The aqueous layer was acidified to pH 3 and extracted with $CHCl_3$. The extract was dried, concentrated, and chromatographed on acid-washed TLC silica gel (98:2, $CHCl_3$–MeOH) to give 421 mg (72% yield) of amide **10** as a yellow oil. The ^1H NMR spectrum of **10** showed a complex mixture of enol and keto tautomers: IR (KBr) 1620, 1700, 2930, 3300, 3400 cm^{-1}; mass spectrum, *m/e* (relative intensity) 213 (M^+·,

46%), 195 (22), 182 (23), 168 (25), 129 (24), 127 (28), 114 (46), 105 (37), 87 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.40; H, 6.94.

Acylation of 3 and 4 with Methyl Benzoate. Trianion 3 (8.0 mmol) was treated with methyl benzoate (0.54 g, 4.0 mmol) in THF for 1 h at 20 °C. Isolation gave an oil which was chromatographed on silica gel (hexane–EtOAc mixtures) to give 618 mg (59% yield) of ester 11 as a yellow solid, mp 72–74 °C (lit.[12] mp 73–76 °C).

Treatment of trianion 4 (3.11 mmol) with methyl benzoate (0.22 g, 1.6 mmol) in THF for 1 h at 20 °C gave triketo amide 12 in good yield but it could not be completely separated from recovered diketo amide 2 by chromatography on silica gel. Preparative-scale reverse-phase chromatography (3:1, $CHCl_3$–MeOH) on silica gel plates which had been pretreated with octadecyltrichlorosilane gave 286 mg (66% yield) of amide 12 as a yellow oil. The ^1H NMR spectrum indicated a complex mixture of enol–keto tautomers: IR (KBr) 1595, 1705, 2920, 3410 cm^{-1}; mass spectrum, *m/e* (relative intensity) 275 (M^+·, 8%), 230 (10), 211 (9), 191 (14), 161 (14), 149 (17), 147 (18), 129 (85), 121 (29), 105 (100), 87 (54). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22. Found: C, 65.68; H, 6.52.

Condensation of 3 and 4 with Methyl Benzoylacetate. Trianion 3 (8.0 mmol) was treated with 4.0 mmol of the sodium salt of methyl benzoylacetate (prepared by treatment of the ester with excess NaH) in THF for 48 h at 50 °C. Workup yielded an oil which the ^1H NMR spectrum indicated to be approximately an equal mixture of tetraketo ester 13 and diketo ester 1. Complete separation of the two esters on silica gel was not possible because 13 underwent cyclization during the slow elution required for the separation. The cyclization products included resorcinol 14[9] and coumarin 15.[9]

Similar treatment of trianion 4 (6.5 mmol) with the sodium salt of methyl benzoylacetate (3.26 mmol) for 48 h at 45 °C gave pentaketo amide 16 which cyclized during isolation to resorcinol 17. EtOAc was required for extraction of sparingly soluble 17. The crude 17 (263 mg, 27% yield, mp 180–186 °C) was recrystallized from aqueous MeOH to give 186 mg of white crystals: mp 195–197 °C; ^1H NMR (Me_2SO-d_6) δ 2.69 (s, NMe), 2.78 (s, NMe), 3.70 (s, CH_2), 6.24 (d, J = 1 Hz, aromatic CH), 6.47 (d, J = 1 Hz, aromatic CH), 7.40 (s, C_6H_5), 10.10 (br s, OH), 10.85 (br s, OH); IR (KBr) 1600, 3100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 299 (M^+·, 24%), 255 (30), 227 (42), 226 (100), 213 (52), 212 (31). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72. Found: C, 67.91; H, 5.61.

Condensation of 3 with Methyl Acetoacetate. The condensation of trianion 3 (8.0 mmol) with the monosodium salt (4.0 mmol) of methyl acetoacetate (prepared from the ester and NaH) in THF at 60 °C for 44 h gave tetraketo ester 18 which cyclized during workup (EtOAc extraction) to give coumarin 19, isolated as a light yellow solid (190 mg, 25% yield) by chromatography on silica gel (hexane–EtOAc mixtures): mp 270 °C (lit.[10] mp 266–267 °C); ^1H NMR (Me_2SO-d_6) δ 2.64 (s, Me), 5.47 (s, 3-CH), 6.59 (s, aromatic CH's) (lit.[10] ^1H NMR δ 2.61, 5.46, 6.59).

Condensation of 3 with 4-Methoxy-6-methyl-2-pyrone. Trianion 3 (8.5 mmol) was treated with the title pyrone[13] (0.59 g, 4.2 mmol) for 1 h at 20 °C. Workup of the reaction involved EtOAc extraction followed by chromatography of the crude product on silica gel (2:3, EtOAc–hexane) to give a red oil which crystallized in the presence of Et_2O. Recrystallization from $CHCl_3$–hexane gave 91 mg (8% yield) of hemiketal 25: mp 137 °C; ^1H NMR (acetone-d_6) δ 2.54 (s, Me), 2.73 (d, J = 16 Hz, one proton of diastereotopic CH_2), 2.81 (s, CH_2), 3.15 (d, J = 16 Hz, one proton of diastereotopic CH_2), 3.67 (s, OMe), 3.76 (s, OMe), 5.96 (br s, OH), 6.21 (d, J = 1 Hz, aromatic CH), 6.31 (d, J = 1 Hz, aromatic CH); IR (KBr) 1600, 1640, 1730, 3250 cm^{-1}; mass spectrum, *m/e* (relative intensity) 280 (M^+·, 27%), 262 (24), 207 (52), 165 (100), 164 (38). Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 60.22; H, 5.92.

Condensation of 4 with 4-Methoxy-6-phenyl-2-pyrone. Trianion 4 (3.7 mmol) was treated with the title pyrone[13] (0.37 g, 1.8 mmol) in THF for 80 min at 20 °C. Isolation, which included extraction with EtOAc and trituration with $CHCl_3$, yielded 221 mg (35% yield) of 28. Recrystallization from EtOAc gave white solid: mp 180–184 °C; ^1H NMR (Me_2SO-d_6) δ 2.96 (s, NMe), 3.04 (s, CH_2), 3.14 (s, NMe), 3.32 (s, CH_2), 3.85 (s, OMe), 6.43 (d, J = 1 Hz, aromatic CH), 6.56 (d, J = 1 Hz, aromatic CH), 7.42 (m, C_6H_5), 7.81 (s, OH); IR (KBr) 1585, 1600, 1680, 2940, 3200, 3450 cm^{-1}; mass spectrum, *m/e* (relative intensity) 355 (M^+·, 23%), 337 (36), 292 (74), 268 (81), 266 (52), 240 (100), 228 (65), 227 (91), 226 (35), 139 (28). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96. Found: C, 67.52; H, 5.86.

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(12) Harris, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5686.

(13) Bu'Lock, J. D.; Smith, H. G. *J. Chem. Soc.* **1960**, 502.

Synthesis of Substituted Pyrroles by Intramolecular Condensation of a Wittig Reagent with the Carbonyl Group of a Tertiary Amide

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1,2,5-Trisubstituted pyrroles are obtained in 50–100% yields by addition of the conjugate bases of open-chain analogues of Reissert compounds to the vinyltriphenylphosphonium cation, with subsequent cyclization by an intramolecular Wittig reaction and base-catalyzed elimination of hydrogen cyanide.

Syntheses of 2,3-dihydrofurans in 56–93% yields by intramolecular Wittig reactions involving the carbonyl group of esters have been reported.[1] Also, several examples of intramolecular Wittig reactions between esters and stabilized phosphoranes have been reported.[2-6] With the exception of formate esters, all of the latter esters contained strongly electron-withdrawing groups adjacent to

(1) Dauben, W. G.; Hart, D. J. *Tetrahedron Lett.* **1975**, 4353–4356.

(2) Grell, S.; Machleidt, H. *Justus Liebigs Ann. Chem.* **1966**, *693*, 134–157.

(3) Bestmann, H. J.; Rostock, K.; Dornauer, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 308.

0022-3263/81/1946-2570$01.25/0