The Intramolecular Wadsworth–Emmons Condensation of γ-(Acyloxy)-β-ketophosphonates. A New Route to 3(2*H*)-Furanones

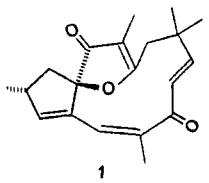
Paul Sampson, Vassilios Roussis, Gary J. Drtina, Frederick L. Koerwitz, and David F. Wiemer*†

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

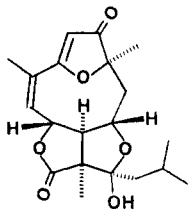
Received September 16, 1985

A series of γ-(acyloxy)-β-ketophosphonates has been synthesized, either from the corresponding α-iodo keto ester by an Arbuzov reaction or by acylation of an alkylphosphonate anion. When treated with potassium carbonate in DMF, these γ-(acyloxy)-β-ketophosphonates undergo an intramolecular Wadsworth–Emmons-type condensation to afford 3(2*H*)-furanones, providing a new route to this heterocyclic system.

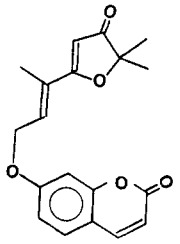
In recent years the number of natural products found to contain the 3(2*H*)-furanone moeiety has grown dramatically, and interest in methods for formation of this system has increased accordingly. Among the natural products that might be viewed as derivatives of this system are jatrophone (**1**),[1] eremantholide A (**2**),[2] geiparvarin (**3**),[3] and budlein A (**4**).[4]



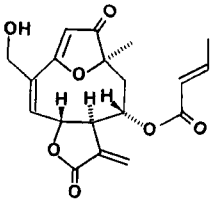
1



2

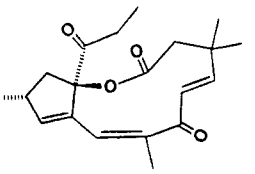


3



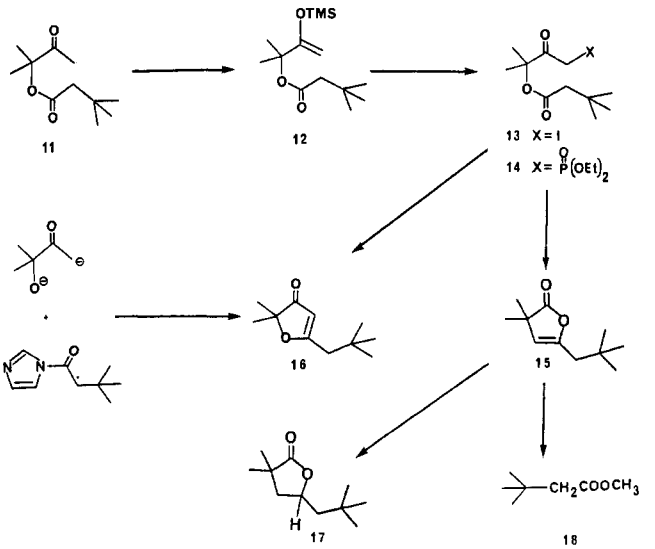
4

Conceptually, the intramolecular condensation of an an α-acyloxy ketone (**5**, Scheme I) appears to be the most straightforward route to the 3(2*H*)-furanone system. However, if the ester substituent has two or more α hydrogens, a reaction sequence involving equilibrium formation of the ester enolate, condensation with the ketone carbonyl, and elimination of water upon acidic workup results in formation of the isomeric 2(5*H*)-furanone system (**6**).[5,6] A clever alternative to this strategy involves the cyclization of a 1,3-diketone such as compound **8**, prepared by acylation of the dianion of α-hydroxy ketone **7** or, in better yield, by aldol condensation of an aldehyde with the dianion of compound **7**, followed by oxidation of the aldol.[6] With this latter approach, cyclization often occurs immediately upon oxidation, and the 3(2*H*)-furanones **9** are obtained in good yield provided that the aldehyde component is not readily enolized. However, our approach to the total synthesis of (+)-jatrophone[7] required formation of the 3(2*H*)-furanone ring from a lactone intermediate such as compound **10**, and neither this dianion approach nor other recent methods for furanone formation[8] appeared suitable to our needs. Accordingly, we have explored a new approach to the 3(2*H*)-furanone system which utilizes a Wadsworth–Emmons-type reaction for the key ring formation.



10

As our first model compound, we chose the ketophosphonate **14**. This compound is prepared in a straightforward manner, beginning with the acylation of 3-hydroxy-3-methylbutanone (**7**) by *tert*-butylacetyl chloride. Treatment of the resulting keto ester **11** with 1,8-diazabicyclo[5.4.0]undecene and chlorotrimethylsilane results in selective formation of the silyl enol ether **12**, with no trace of silylation at the ester carbonyl group or condensation products. This is the key step in the sequence,



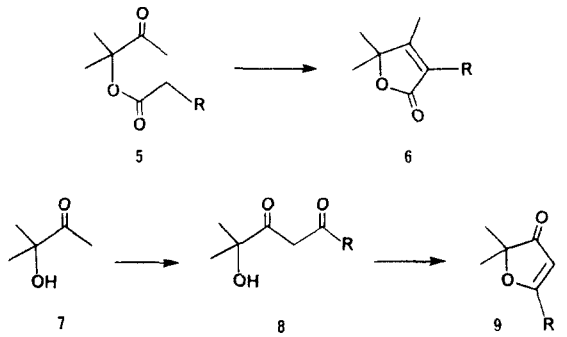
for it allows subsequent functionalization α to the ketone without competing reactions α to the ester. When treated with iodine and silver acetate, this enol ether affords the α-iodo ketone **13**, and a subsequent Arbuzov reaction[9] with

† Fellow of the Alfred P. Sloan Foundation, 1985–1987.

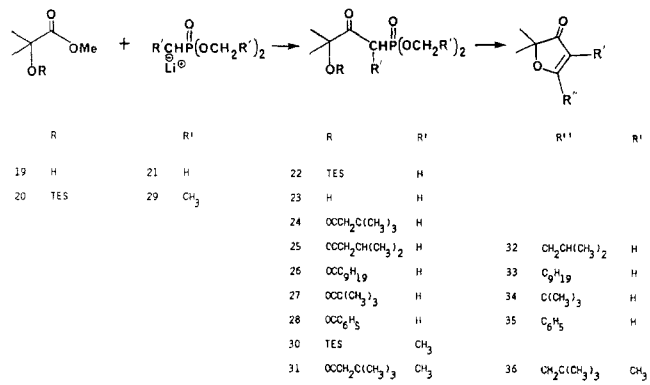
(1) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 2295.
(2) LeQuesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1572.
(3) Lahey, F. N.; MacLeod, J. K. *Aust. J. Chem.* **1967**, *20*, 1943. Carman, R. M.; Lahey, F. N.; MacLeod, J. K. *Ibid.* **1967**, *20*, 1957.
(4) de Vivar, A. R.; Guerrero, C.; Diaz, E.; Ortega, A. *Tetrahedron* **1970**, *26*, 1657.
(5) Lehmann, H. G. *Angew Chem., Int. Ed. Engl.* **1965**, *4*, 783.
(6) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
(7) For a preliminary account of this work, cf.: Drtina, G. J.; Sampson, P.; Wiemer, D. F. *Tetrahedron Lett.* **1984**, *25*, 4467.
(8) Jackson, R. F. W.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, *535*. Saimoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3078. Saimoto, H.; Shinoda, M.; Matsubara, S.; Oshima, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3088.

0022-3263/86/1951-2525$01.50/0

Scheme I



Scheme II



triethyl phosphite gives the desired phosphonate **14**.

Our first attempt to convert phosphonate **14** into the desired 3(2*H*)-furanone **16** involved treatment with sodium hydride in dimethoxyethane, conditions analogous to those used in previous Wadsworth–Emmons reactions involving esters.[10] This reaction gave a single major product, but, much to our surprise, upon comparison with an authentic sample of the 3(2*H*)-furanone **16** (prepared from the dianion of α-hydroxybutanone[6]), the two products were *not* identical. The most revealing differences were in the ^{13}C NMR spectra. The spectrum of the authentic sample contained predictable resonances for the ketonic, olefinic, and carbinol carbons (at δ 207.4, 190.2, 103.2, and 88.6), while the spectrum of our reaction product contained signals corresponding to ester carbonyl and olefinic carbons (at δ 182.9, 152.6, and 113.4) and no resonance indicative of a carbinol carbon (cf. Experimental Section). Furthermore, the IR spectrum of this reaction product had a carbonyl absorption at 1817 cm^{-1}, typical of an enol lactone.[11] On the basis of its spectral data, we assigned the structure of the isomeric 2(3*H*)-furanone **15** to our reaction product. Because a mechanism for this transformation was not readily apparent, we confirmed this assignment by degradative experiments. Catalytic hydrogenation of compound **15** resulted in formation of the lactone **17**, and, after ozonolysis of compound **15**, reductive workup, and esterification with diazomethane, we obtained methyl *tert*-butyl acetate. These degradative studies confirm the assignment of the 2(3*H*)-furanone structure to this reaction product. Our further investigation of the interesting skeletal rearrangement which affords 2(3*H*)-furanones (e.g., compound **15**) from the γ-(acyloxy)-β-ketophosphonates will be reported in due course.

To pursue formation of the desired 3(2*H*)-furanone **16** from the phosphonate **14**, we explored the use of various combinations of base and solvent. The use of potassium bases and a polar medium has been recommended[12] for Wadsworth–Emmons reactions, and indeed these factors affect the product ratio in this case as well. Upon treatment of phosphonate **14** with potassium carbonate and dicyclohexyl-18-crown-6 in refluxing toluene, the 3(2*H*)-isomer **16** becomes a major product (27% isolated yield after column chromatography vs. 35% yield for the 2(3*H*)-isomer **15**). Treatment of phosphonate **14** with K_2CO_3 in DMF at 110 °C gives the 3(2*H*)-isomer **16** as the only detectable product (47% isolated yield). Cesium carbonate in DMF also yields only the 3(2*H*)-isomer.

Before concluding that this approach to the synthesis of 3(2*H*)-furanones would be viable and general, it appeared prudent to prepare and test at least a short series of γ-(acyloxy)-β-ketophosphonates. We first sought a more flexible route to this class of compounds, and developed the synthetic sequence shown in Scheme II. After protection of methyl 2-hydroxyisobutyrate (**19**) as its triethylsilyl (TES) ether **20**, reaction with the anion of dimethyl methylphosphonate (**21**) results in acylation to afford the β-ketophosphonate **22**. The silyl protecting group can be readily cleaved by treatment with fluoride ion, yielding the alcohol **23**, and esterification with *tert*-butylacetyl chloride then affords the phosphonate **24**. However, with more hindered acid chlorides, acylation at the carbonyl oxygen of compound **23** becomes a competitive reaction. To avoid this potential problem, the silyl ether **22** can be converted directly to its analogous ester derivatives by reaction with an acid chloride in the presence of a Lewis acid catalyst ($FeCl_3$).[13] By this latter sequence we prepared the valerate (**25**), decanoate (**26**), trimethylacetate (**27**), and benzoate (**28**) esters. By reaction of compound **20** with the anion of diethyl ethylphosphonate **29**, we prepared the homologous phosphonate **30**, which was, in turn, converted to its *tert*-butylacetyl ester **31** by reaction with the corresponding acid chloride.

Upon treatment with potassium carbonate in DMF, each of these γ-(acyloxy)-β-ketophosphonates was converted to the expected 3(2*H*)-furanones (compounds **32–36**). Yields for this final step are generally good, typically about 70%. The synthesis of bullatenone (**35**), a natural product isolated from the blistered-leaf myrtle *Myrtus bullata*,[14] allows comparisons of this methodology with other approaches to this furanone system.[6,7,14]

These studies have shown that this intramolecular variation of the Wadsworth–Emmons reaction is a reliable method for formation of the 3(2*H*)-furanone ring system. While the reaction is sensitive to the choice of solvent and base, with an unusual rearrangement intervening under certain reaction conditions, we have shown that aliphatic and aromatic esters undergo this condensation smoothly upon treatment with potassium carbonate and DMF. This work provides a useful new route to the 3(2*H*)-furanone system because the synthetic sequence from an α-hydroxy ester is only four steps, the starting hydroxy esters are readily available in some variety, and the overall yields for the sequence are high (ca. 40–50%).

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Flash column chromatography was done on Merck grade 60 silica gel, 230–400 mesh. The ^1H NMR and broadband decoupled ^{13}C NMR spectra were

(9) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.
(10) Duggan, A. J.; Adams, M. A.; Byrnes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323.
(11) Bellamy, L. J. *Infrared Spectra of Complex Molecules*, 3rd ed.; Chapman and Hall: London, 1975; Vol. 1, p 213.
(12) Aristoff, P. A. *Synth. Commun.* **1983**, *13*, 145.
(13) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.
(14) Parker, W.; Raphael, R. A.; Wilkinson, D. I. *J. Chem. Soc.* **1958**, 3871.

recorded on either a JEOL FX-90Q or a Brucker WM 360 spectrometer, with deuterochloroform as the solvent. The ^1H chemical shifts are reported in parts per million downfield from internal $(CH_3)_4Si$. The ^{13}C chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$ but with the deuterochloroform resonance as the internal standard (77.0). Low-resolution mass spectra were recorded with a Hewlett-Packard 5985B instrument; only selected ions are reported here. Electron impact (EI) spectra were obtained at 70 eV; ion abundances are reported as percentages of the most abundant ion. Chemical ionization (CI) spectra were obtained with methane as the reagent gas. High-resolution mass spectra were recorded on an AEI MS-902 instrument at Cornell University, Mass Spectrometry Laboratories, or on a Kratos MS-50 instrument at the Midwest Center for Mass Spectrometry. Microanalyses were conducted by Galbraith Laboratories, Knoxville, Tn.

3-(*tert*-Butylacetoxy)-3-methylbutanone (11). After the dropwise addition of *tert*-butylacetyl chloride (23 mL, 0.17 mol) to a pyridine solution (250 mL) of 3-hydroxy-3-methyl-2-butanone (15.3 g, 0.15 mol) at 0 °C, the reaction mixture was stirred overnight at room temperature. The resulting mixture was then filtered, and the filtrate was diluted with water (to allow removal of pyridine as its azeotrope) and then was concentrated in vacuo. The residue was poured into Et_2O (1 L), extracted sequentially with 2 M HCl, 1 M $NaHCO_3$, and brine, and then dried. Solvent evaporation and distillation gave pure keto ester **11** (18.7 g, 62%): bp 43–44 °C (0.15 mmHg); ^1H NMR δ 2.22 (2, s, RCH_2CO_2R), 2.12 (3, s, $CH_3C{=}O$), 1.46 (6, s, $R_2C(CH_3)_2$), 1.05 (9, s, $RC(CH_3)_3$); ^{13}C NMR δ 205.2, 170.6, 82.5, 47.0, 30.2, 28.9, 22.9, 22.7; EIMS, m/z (relative intensity) 200 (M^+, 0.3), 185 (1), 157 (19), 144 (4), 100 (7), 99 (100), 85 (49), 83 (13), 71 (18), 57 (64); HRMS, calcd m/z for $C_{11}H_{20}O_3$ 200.1412, found 200.1411.

3-(*tert*-Butylacetoxy)-3-methyl-2-(trimethylsiloxy)-1-butene (12). 1,8-Diazabicyclo[5.4.0]undecene (2.2 mL, 14.7 mmol) and Me_3SiCl (1.7 mL, 13.4 mmol)[15] were added to a solution of keto ester **11** (2.06 g, 10.3 mmol) in anhydrous CH_2Cl_2 (25 mL), and the resulting mixture was heated at reflux overnight. After concentration in vacuo, dilution with hexane, and filtration, the filtrate was concentrated to give essentially pure silyl enol ether **12** (2.45 g, 87%): ^1H NMR δ 4.23 and 4.00 (1, 1, s, s, $R_2C{=}CH_2$), 2.06 (2, s, RCH_2CO_2R), 1.46 (6, s, $R_2C(CH_3)_2$), 0.97 (9, s, $RC(CH_3)_3$), 0.16 (9, s, $ROSi(CH_3)_3$); ^{13}C NMR δ 170.4, 160.1, 87.1, 80.1, 48.6, 30.5, 29.5, 25.2, –0.1; EIMS, m/z (relative intensity) 272 (M^+, 1), 158 (5), 157 (28), 156 (20), 143 (11), 142 (13), 141 (100), 127 (7), 117 (12), 99 (18), 91 (20), 83 (8), 75 (41), 73 (27).

3-(*tert*-Butylacetoxy)-1-iodo-3-methylbutanone (13). According to the procedure of Rubottom and Mott,[16] iodine (1.07 g, 4.2 mmol) and AgOAc (0.71 g, 4.3 mmol) were placed in anhydrous CH_2Cl_2 (30 mL) and, after stirring for 20 min at room temperature, the silyl enol ether **12** (1.17 g, 4.3 mmol) was added to the red slurry. After 30 min, the mixture was filtered, the yellow precipitate was rinsed with methylene chloride (30 mL), and triethylammonium fluoride (1.06 g, 8.8 mmol) was added to the filtrate. After 30 min, the red solution was washed with 5% aqueous sodium thiosulfate (50 mL), water (2 × 50 mL), and brine (50 mL) and then dried (Na_2SO_4). Concentration in vacuo gave a yellow oil (1.07 g) which was distilled to give pure iodo ketone **14** (0.74 g, 53%): bp 98 °C (0.6 mmHg); ^1H NMR δ 4.02 (2, s, $IH_2CC{=}O$), 2.22 (2, s, RCH_2CO_2R), 1.59 (6, s, $R_2C(CH_3)_2$), 1.04 (9, s, $RC(CH_3)_3$); ^{13}C NMR δ 201.4, 171.8, 82.2, 47.3, 30.8, 29.5, 24.5, 0.8; EIMS m/z (relative intensity) 270 ($M^+ - C_4H_8$, 2), 211 (39), 183 (5), 169 (15), 157 (60), 141 (16), 99 (100), 71 (9), 57(15); HRMS, calcd m/z for $C_7H_{11}IO_3$ 269.9750, found 269.9755 ($M^+ - C_4H_8$).

Diethyl [3-(*tert*-Butylacetoxy)-3-methyl-2-oxobutyl]-phosphonate (14). Triethyl phosphite (1.0 mL, 5.8 mmol) was added to a solution of the γ-iodo keto ester **13** in anhydrous toluene (3 mL), and heated to near reflux. After 75 min of slow distillation (when complete reaction was indicated by GC), the mixture was concentrated in vacuo (0.5 mmHg) leaving phosphonate **14** (0.74 g, 78%): ^1H NMR δ 4.16 (4, d of q, J = 7.3 Hz, J_{HP} = 7.3 Hz, $P(OCH_2CH_3)_2$), 3.16 (2, d, J_{HP} = 21 Hz, $RCH_2P(O)OR_2$), 2.21 (2, s, RCH_2CO_2R), 1.52 (6, s, $R_2C(CH_3)_2$), 1.33 (6, t, J = 7.3 Hz, $P(OCH_2CH_3)_2$), 1.04 (9, s, $RC(CH_3)_3$); ^{13}C NMR δ 199.9 (d, J = 7.3 Hz), 171.3, 82.9 (d, J = 2.9 Hz), 62.0 (d, J = 7.3 Hz), 47.1, 34.9 (d, J = 134.6 Hz), 30.5, 29.14, 22.7, 15.9 (d, J = 5.9 Hz); ^{31}P NMR 20.4; EIMS, m/z (relative intensity) 321 ($M^+ - CH_3$, 1), 250 (14), 239 (7), 221 (8), 211 (9), 194 (13), 179 (24), 165 (10), 157 (16), 152 (100), 125 (26), 109 (9), 99 (37); CIMS 337 ($M^+ + 1$, 100); HRMS, calcd m/z for $C_{15}H_{29}O_6P$ 336.1702, found 336.1700.

3,3-Dimethyl-5-(2,2-dimethylpropyl)-2(3*H*)-furanone (15). Phosphonate **14** (249 mg, 0.74 mmol) in anhydrous dimethoxyethane (DME, 1 mL) was added via syringe to a stirred suspension of sodium hydride (39 mg, 0.82 mmol; 50% dispersion in oil washed with three 0.5-mL portions of DME) in the same solvent (4 mL). The mixture, which soon became a thick slush, was stirred at room temperature for 45 min and then heated at 85 °C overnight. Substantial conversion (59%) to a product was indicated by GC. The reaction mixture was diluted with hexane, then washed with 1 M NaOH, water, and brine, and dried (Na_2SO_4). Solvent evaporation gave 99 mg of an oil, which was purified by preparative GC to yield the 2(3*H*)-furanone **15** as needlelike crystals: mp 56 °C; GC–FTIR 2967 (s), 1817 (s, lactone C=O),[11] 1666 (w), 1474 (w), 1242 (m), 1069 (s), 941 (s) cm^{-1}; ^1H NMR δ 5.15 (1, s, $R_2C{=}CHR$), 2.12 (2, s, RCH_2CR_3), 1.30 (6, s, $R_2C(CH_3)_2$), 0.98 (9, s, $RC(CH_3)_3$); ^{13}C NMR δ 182.9, 152.6, 113.4, 44.4, 42.0, 30.9, 29.7 (3), 24.5 (2); EIMS, m/z (relative intensity) 182 (M^+, 16), 154 (6), 139 (10), 126 (78), 111 (100), 83 (79), 57 (40), 55 (18); HRMS, calcd m/z for $C_{11}H_{18}O_2$ 182.1307, found 182.1302.

Hydrogenation of 3,3-Dimethyl-5-(2,2-dimethylpropyl)-2-(3*H*)-furanone (15). The title compound (2.0 mg) was hydrogenated in methanol (0.3 mL) over 10% Pd/C (5.0 mg) at 30 psi for 2 h, when no starting material could be detected (GC). After removal of most of the catalyst by filtration through a small cotton plug, short-path distillation afforded a solution containing the lactone **17** as the only major product: ^1H NMR δ 4.00 (1, quintet, J = 6.1 Hz, lactonic H), 1.4–1.8 (4, m), 1.26 (6, s, $R_2C(CH_3)_2$), 0.99 (9, s, $RC(CH_3)_3$); EIMS (70 eV) m/z (relative intensity) 169 ($M^+ - CH_3$, 4), 140 (7), 128 (13), 113 ($M^+ - C_5H_{11}$, 100), 85 (77), 84 (56), 83 (53), 69 (25), 57 (83); HRMS calcd m/z for $C_{10}H_{17}O_2$ 169.1229, found 169.1227.

Ozonolysis of 3,3-Dimethyl-5-(2,2-dimethylpropyl)-2-(3*H*)-furanone (15). A stream of oxygen containing ozone was bubbled through a solution of the title compound (3.6 mg) in anhydrous CH_2Cl_2 (1 mL) at –78 °C for 5 min. After standing for 3 min, the excess ozone was removed by means of an argon stream, the solution was allowed to warm to room temperature, and then was hydrogenated at 35 psi for 1 h (10% Pd/C catalyst). Methylation with ethereal diazomethane gave methyl *tert*-butylacetate as the only isolated product, identified by GC and GC/MS comparisons with an authentic sample.

Authentic 2,2-Dimethyl-5-(2,2-dimethylpropyl)-3(2*H*)-furanone (16). According to the procedure of Smith et al.,[6] 3-methyl-3-hydroxybutanone (**7**, 680 μL, 6.46 mmol) was added dropwise over a 5-min period to a solution of lithium diisopropylamide (LDA, 15.58 mmol; generated from 2.6 mL of diisopropylamine and 9.8 mL of 1.59 M *n*-butyllithium (*n*-BuLi)) in 25 mL of tetrahydrofuran (THF) kept at –78 °C. After 30 min, *N*-*tert*-butylacetylimidazole[17] (1.39 g, 8.38 mmol) in tetrahydrofuran (8 mL) was added dropwise, and the resulting mixture was stirred for 1.5 h. After warming to room temperature, the reaction mixture was poured into 2 M HCl (140 mL) and extracted with Et_2O (2 × 100 mL). The ethereal solution was washed with water (2 × 50 mL) and brine (3 × 50 mL) and dried (Na_2SO_4). Concentration in vacuo gave 1.31 g of an oil consisting of a mixture of products. Preparative GC gave pure 3(2*H*)-furanone **16**: ^1H NMR δ 5.34 (1, s, $R_2C{=}CHR$), 2.37 (2, s, RCH_2CR_3), 1.38 (6, s, $R_2C(CH_3)_2$), 1.02 (9, s, $RC(CH_3)_3$); ^{13}C NMR δ 207.4, 190.2, 103.2, 88.6, 44.6, 31.8, 29.7, 22.9; EIMS, m/z (relative intensity) 182 (M^+, 34), 139 (15), 126 (100), 111 (68), 98 (19), 83 (18), 81 (33), 68 (35), 57 (79); HRMS, calcd for $C_{11}H_{18}O_2$ 182.1302, found 182.1304.

2,2-Dimethyl-5-(2,2-dimethylpropyl)-3(2*H*)-furanone (16) via Wadsworth–Emmons Condensation. A mixture of (acyloxy)ketophosphonate **14** (221.6 mg, 0.66 mmol) and anhyd-

(15) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229.
(16) Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731.
(17) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351.

Table I. Spectral Data for β-Ketophosphonates and 3(2*H*)-Furanones

compd	yield, %	^{1}H and ^{13}C NMR data, ppm	MS data, *m/z* (rel intensity)
22	86	3.79 (6, d, J_{HP} = 11.4 Hz), 3.39 (2, d, J_{HP} = 20.9 Hz), 1.36 (6, s), 0.97 (9, t, J = 6.6 Hz), 0.68 (6, t, J = 7.0 Hz); 206.9 (d, J = 6.4 Hz), 80.0 (d, J = 3.0 Hz), 52.8 (d, J = 6.0 Hz), 33.8 (d, J = 137.9 Hz), 26.8, 6.98, 6.54	324 (M^+ – CH_3, 0.5), 295 (53) 238 (19), 210 (15), 193 (M^+ – OTES, 0.7), 173 (100), 151 (30), 115 (82), 87 (52), 75 (18), 59 (26); calcd for $C_{13}H_{29}O_6PSi$ 295.1126 (M^+ – OEt); found 295.1128[a]
23	66	5.63 (1, s), 3.73 (6, d, J_{HP} = 11 Hz), 3.34 (2, d, J_{HP} = 22.7), 1.28 (6, s)	195 (M^+ – CH_3, 2), 193 (M^+ – 17, 0.5), 124 (100), 109 (11), 94 (39), 79 (14); calcd for $C_7H_{14}O_5P$ 209.0586, (M^+ – 1) found 209.0577
24	80	3.79 (6, d, J_{HP} = 11 Hz), 3.17 (2, d, J_{HP} = 21.2 Hz), 2.21 (2, s), 1.51 (6, s), 1.04 (9, s)	309 (M^+ – CH_3, 4), 277 (3), 252 (7), 222 (80), 211 (61), 193 (90), 166 (59), 151 (100), 124 (54), 109 (95), 99 (14), 57 (23); calcd for $C_{13}H_{24}O_6P$ 307.1304, (M^+ – 1) found 307.1311
25	69	3.80 (6, d, J_{HP} = 11.3 Hz), 3.16 (2, d, J_{HP} = 21.2 Hz), 2.21 (2, d, J = 7 Hz), 2.10 (1, m), 1.51 (6, s), 0.97 (6, d, J = 7 Hz)	208 (M^+ – 86, 3), 193 (5), 161 (4), 151 (23), 124 (100), 109 (10), 95 (14), 85 (16), 57 (8), 41 (3)[a]
26	94	3.79 (6, d, J_{HP} = 11.3 Hz), 3.14 (2, d, J_{HP} = 21.2 Hz), 2.32 (2, t, J = 7.3 Hz), 1.50 (6, s), 1.27 (16, br) 0.87 (3, br)	278 (M^+ – 86, 0.3), 211 (5), 193 (7), 155 (8), 151 (24), 127 (2), 124 (100), 109 (10), 94 (12); calcd for $C_{17}H_{34}O_6P$ 365.2093 (M^+ + 1, CI) found 365.2093
27	96	3.79 (6, d, J_{HP} = 11.4 Hz), 3.11 (2, d, J_{HP} = 21.2 Hz), 1.49 (6, s), 1.21 (9, s)	263 (M^+ – OCH_3, 0.2), 208 (12), 161 (7), 151 (26), 124 (100), 109 (15), 94 (15), 85 (13), 57 (31), 41 (7); calcd for $C_3H_9O_3P$ 124.0287, found 124.0290[a]
28	72	7.94–7.44 (5), 3.80 (6, d, J_{HP} = 11 Hz), 3.22 (2, d, J_{HP} = 21.3 Hz), 1.65 (6, s)	314 (M^+, 0.2), 283 (0.6), 228 (100), 161 (5), 151 (49), 119 (10), 109 (37), 105 (83), 77 (39), 51 (8); calcd for $C_{14}H_{20}O_6P$ 315.0992; (M^+ + 1, CI) found 315.1002
30	62	4.21–4.10 (4, m), 3.47 (1, q, J = 7.0 Hz), 1.41 (3, s), 1.35 (3, s), 1.33 (6, t, J = 7.1 Hz), 1.20 (3, t, J_{HP} = 7 Hz, J_{HH} = 7 Hz), 0.99 (9, t, J = 7 Hz), 0.67 (6, q, J = 7 Hz)	351 (M^+ – CH_3, 0.5), 337 (47), 280 (50), 263 (22), 252 (44), 173 (61), 137 (61), 109 (100), 87 (76), 59 (23); calcd for $C_{16}H_{36}O_5PSi$ 367.2060, found 367.2071
31	80	4.17–4.05 (4, m), 3.72 (1, dq, J_{HP} = 21.4 Hz, J = 7.0 Hz), 2.17 (2, dd, J_{HP} = 15.3 Hz, J = 13.2 Hz), 1.70 (3, s), 1.54 (3, s), 1.42 (3, dd, J_{HP} = 17.7 Hz, J = 7.0 Hz), 1.33 (6, q, J = 6.9 Hz), 1.03 (9, s)	335 (M^+ – CH_3, 0.3), 305 (0.4), 294 (0.2), 264 (9), 235 (7), 193 (13), 166 (100), 139 (11), 109 (12), 57 (11); calcd for $C_{16}H_{32}O_6P$ 351.1928, (M^+ + 1, CI) found 351.1929[a]
32	71	5.35 (1, s), 2.37 (2, d, J = 7.2 Hz), 2.07 (1, m), 1.37 (6, s), 0.99 (6, d, J = 7 Hz); 207.3, 190.8, 101.9, 88.4, 39.8, 26.7, 22.9, 22.3	168 (M^+, 32), 153 (1), 126 (26), 111 (17), 98 (19), 95 (24), 81 (7), 68 (100), 59 (24), 43 (36); calcd for $C_{10}H_{16}O_2$ 168.1151, found 168.1151
33	67	5.33 (1, s), 2.47 (2, t, J = 7.4 Hz), 1.36 (6, s), 1.28 (14, br s), 0.87 (3, t, J = 5.8 Hz); 207.3, 191.9, 100.9, 88.4, 31.8, 30.8, 29.4, 29.2 (2), 29.0, 26.1, 22.9 (2), 22.6, 14.1	238 (M^+, 6), 195 (4), 181 (3), 152 (40), 139 (67), 111 (21), 98 (100), 82 (62), 69 (51), 55 (34), 41 (69); calcd for $C_{15}H_{26}O_2$ 238.1934, found 238.1935
34[6]	65	5.33 (1, s), 1.36 (6, s), 1.24 (9, s); 208.0, 198.9, 98.0, 88.4, 34.5, 27.4, 22.8	168 (M^+, 54), 153 (4), 127 (3), 111 (18), 109 (32), 95 (100), 82 (9), 67 (62), 57 (5), 41 (10)
35[14]	89	7.88–7.51 (5), 5.95 (1, s), 1.48 (6, s); 206.8, 183.3, 132.5, 129.1, 128.7, 127.1, 98.5, 88.9, 23.1	188 (M^+, 18), 173 (0.6), 145 (1), 130 (2), 105 (2), 102 (100), 77 (6), 69 (3), 51 (4)
36	66	2.39 (2, s), 1.66 (3, s), 1.35 (6, s), 1.03 (9, s); 207.8, 185.0, 109.7, 86.1, 42.3, 33.0, 30.1, 29.7, 23.1	196 (M^+, 0.4), 181 (3), 153 (5), 140 (53), 125 (95), 95 (18), 83 (7), 69 (5), 57 (100), 41 (30); calcd for $C_{12}H_{20}O_2$ 196.1458, found 196.1459

[a] Satisfactory (±0.4%) combustion analyses were obtained.

rous potassium carbonate (175 mg, 1.27 mmol) in anhydrous dimethylformamide (DMF, 110 mL) was heated at 115 °C for 10 h. On cooling, the yellow solution was poured into water (500 mL) and extracted with pentane (3 × 250 mL), and the combined pentane extracts were washed with water (3 × 250 mL) and brine (250 mL) and dried ($MgSO_4$) overnight. Removal of the solvent in vacuo left a pale yellow oil (84 mg, 70%), identified as compound **16** by comparison with an authentic sample prepared as described above.

Methyl 2-Methyl-2-(triethylsiloxy)propanoate (20). After adding methyl 2-hydroxyisobutyrate (4.22 g, 40 mmol) dropwise to a pyridine solution (20 mL) of triethylchlorosilane (TESCl, 4.0 g, 34.78 mmol), the reaction mixture was stirred overnight at 60 °C and then filtered. The filtrate was diluted with Et_2O (50 mL), washed several times with 2 M aqueous nickel chloride (to allow removal of pyridine as its nickel complex) and brine, and then dried ($MgSO_4$). Concentration in vacuo gave pure silyl ether **20** (7.34 g, 91%): ^{1}H NMR δ 3.69 (3, s, RCO_2CH_3), 1.43 (6, s, $R_2C(CH_3)_2$), 0.95 (9, t, J = 6.1 Hz, $Si(CH_2CH_3)_3$), 0.64 (6, t, J = 7.1 Hz, $Si(CH_2CH_3)_3$); EIMS, *m/z* (relative intensity) 217 (M^+ – CH_3, 0.3), 203 (39), 175 (47), 173 (23), 117 (100), 115 (21), 89 (32), 75 (11), 59 (21); HRMS, calcd *m/z* for $C_9H_{19}O_3Si$ (M^+ – Et) 203.1103, found 203.1101.

Dimethyl [3-Methyl-3-(triethylsiloxy)-2-oxobutyl]phosphonate (22). Dimethyl methylphosphonate (**21**, 9.5 mL, 87 mmol) was added dropwise to a stirred solution of *n*-BuLi (90 mmol) and diisopropylamine (6.5 mL, 46 mmol) in anhydrous THF (100 mL) at −78 °C and the resulting solution stirred for 1 h. This solution was then transferred via stainless steel canula to a solution of the silyl ether **20** (5 g, 21.6 mmol) in THF (25 mL). Stirring at −78 °C was continued for 2 h, and then the solution was allowed to warm slowly to room temperature. Concentration in vacuo, followed by flash chromatography (50% EtOAc, 50% hexane) afforded pure compound **22** (6.0 g, 86%). (For spectral data, see Table I.)

Dimethyl (3-Hydroxy-3-methyl-2-oxobutyl)phosphonate (23). The siloxyphosphonate **22** (4.89 g, 15 mmol) was dissolved in acetonitrile (20 mL) containing 40% aqueous HF (1 mL),[18] and the reaction was stirred at room temperature. When deprotection was complete (as monitored by TLC), water (10 mL) and $CHCl_3$ (10 mL) were added. After separation of the layers, the aqueous layer was extracted several times with $CHCl_3$, and the combined organic extracts were dried. Concentration in vacuo afforded phosphonate **23** (2.08 g, 66%) as a colorless oil. (For spectral data, see Table I.)

Dimethyl [3-(*tert*-Butylacetoxy)-3-methyl-2-oxobutyl]phosphonate (24) from Alcohol 23. After adding *tert*-butylacetyl chloride (1.7 g, 12.08 mmol) dropwise to a solution of the hydroxyphosphonate **23** (1 g, 4.7 mmol) in anhydrous Et_2O (15 mL) and pyridine (5 mL), the reaction mixture was heated at reflux overnight. The resulting mixture was then filtered, and the filtrate was diluted with Et_2O (50 mL), washed several times with 2 M nickel chloride and brine, and then dried ($MgSO_4$). Concentration in vacuo and purification by flash chromatography (60% EtOAc, 40% hexane) gave compound **24** (1.17 g, 80%) as a colorless oil. (For spectral data, see Table I.)

(18) Newton, R. F.; Reynolds, D. P.; Finch, M. A.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

Dimethyl [3-(*tert*-Butylacetoxy)-3-methyl-2-oxobutyl]-phosphonate (24). (General Procedure for Preparation of (Acyloxy)ketophosphonates from Siloxyketophosphonates.)[13] *tert*-Butylacetyl chloride (0.45 g, 3.7 mmol) was added dropwise to a stirred solution of siloxyphosphonate **22** (1 g, 3.08 mmol) and $FeCl_3$ (0.08 g, 5 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and then allowed to warm slowly to room temperature. After being stirred overnight, the resulting mixture was diluted with $CHCl_3$ (50 mL), washed with 1 M HCl (3 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL), and brine (30 mL), and then dried over $MgSO_4$. After concentration in vacuo, purification by flash chromatography (50% EtOAc, 50% hexane) afforded compound **24** (775 mg, 80%), identical with the material prepared above on the basis of TLC, GC, NMR, and MS comparisons.

2,2-Dimethyl-5-(1,1-dimethylethyl)-3(2*H*)-furanone (34).[6] **(General Procedure for Condensation Reaction.)** The (trimethylacetoxy)phosphonate **27** (260 mg, 0.885 mmol) in anhydrous DMF (5 mL) was added via syringe to a stirred suspension of potassium carbonate (175 mg, 1.25 mmol) in anhydrous DMF (15 mL). The mixture was stirred at room temperature for 1 h and then heated at 110 °C overnight. Quantitative conversion to the product was indicated by GC. The reaction mixture was diluted with 100 mL of water and extracted with pentane (3 × 25 mL). The organic layer was washed with water (50 mL) and brine (25 mL) and then dried ($MgSO_4$). Concentration in vacuo, followed by purification by flash chromatography (80% pentane, 20% Et_2O), afforded compound **34**[6] (98 mg, 65%) as needlelike crystals: mp 50–52 °C. (For spectral data, see Table I.)

Diethyl [3-(Triethylsiloxy)-1,3-dimethyl-2-oxobutyl]-phosphonate (30). A solution of LDA (56.8 mmol, generated from 7.95 mL of diisopropylamine and 35.4 mL of 1.60 M *n*-BuLi in 45 mL of anhydrous THF) was stirred at 0 °C for 10 min and then cooled to −78 °C. Diethyl ethylphosphonate (8.58 g, 51.70 mmol) was added, and the resulting solution was stirred at −78 °C for 1 h. The solution was then transferred via stainless steel canula to a solution of the silylated methyl ester **20** (3.0 g, 12.90 mmol) in THF (8 mL). After being stirred at −78 °C for 2 h, the solution was allowed to warm to room temperature. Following concentration in vacuo, and purification by flash chromatography (75% EtOAc, 25% hexane), compound **30** (2.94 g, 62.4%) was obtained as a colorless oil. (For spectral data, see Table I.)

Acknowledgment. We thank Mr. Timothy Smith for his assistance with the preparation of various synthetic intermediates. We gratefully acknowledge the financial support of the Alfred P. Sloan Foundation and the National Institutes of Health (CA-33743) for this project, and thank the National Science Foundation for an instrumentation award (CHE 82-01836) for the 360 MHz NMR spectrometer.

Registry No. **7**, 115-22-0; **11**, 93827-97-5; **12**, 93827-98-6; **12** (silyl ether), 102307-25-5; **13**, 93827-99-7; **14**, 93828-00-3; **15**, 93828-01-4; **16**, 93828-02-5; **17**, 102307-26-6; **18**, 10250-48-3; **19**, 2110-78-3; **20**, 102307-27-7; **21**, 756-79-6; **22**, 102307-28-8; **23**, 65378-72-5; **24**, 102307-29-9; **25**, 102307-31-3; **26**, 102307-32-4; **27**, 102307-33-5; **28**, 102307-34-6; **30**, 102307-30-2; **31**, 102307-35-7; **32**, 94815-47-1; **33**, 102307-36-8; **34**, 76777-48-5; **35**, 493-71-0; **36**, 102307-37-9; $(CH_3)_3CCH_2COCl$, 7065-46-5; $(CH_3)_2CHCH_2COCl$, 108-12-3; $C_9H_{19}COCl$, 112-13-0; $(CH_3)CCOCl$, 3282-30-2; C_6H_5COCl, 98-88-4; *N*-(*tert*-butylacetyl)imidazole, 4122-55-8.

Liquid-Crystalline Solvents as Mechanistic Probes. 17. Influence of Cholesteric and Smectic Mesophase Order on the Isomerization of Some *N,N'*-Diacylindigos[1]

Srinivasan Ganapathy, Richard G. Zimmermann, and Richard G. Weiss*

Department of Chemistry, Georgetown University, Washington, D.C. 20057

Received October 17, 1985

The rates and activation parameters for cis → trans thermal isomerization of four *N,N'*-diacylindigos have been compared in isotropic and liquid-crystalline phases. The results indicate that cholesteric solvent order has no perceptable influence on the isomerization of *N,N'*-diacetylindigo. The shape changes attendant upon isomerization of *N,N'*-diacylindigos are inhibited by smectic phase order when the acyl chains are incorporated into smectic layers: the indigoid portion of the molecule, per se, does not sense on a microscopic level the macroscopic order of the smectic phase. Thus, the activation parameters for isomerization of *cis*-*N*-acetyl-*N'*-stearoylindigo and *cis*-*N,N'*-distearoylindigo in the isotropic phase of *n*-butyl stearate (BS) are within experimental error of each other and are similar to the values obtained when benzene is solvent; in the smectic B phase of BS, the activation enthalpy and activation entropy of *N,N'*-distearoylindigo are, respectively, 7 kcal/mol larger and 18 eu more positive than the values of *N*-acetyl-*N'*-stearoylindigo.

Previously, we and others have used the microscopic ordering of thermotropic liquid-crystalline phases to investigate conformational[2-4] and configurational[5-12] changes in solutes. Only in some cases do mesophases influence the dynamics of guest molecule reactions. Examples of reactions requiring virtually no shape changes *or* very large shape changes to transform the reactants into products have been shown insensitive to solvent order. The factors

(1) For part 16, see: Zimmermann, R. G.; Jameson, G. B.; Weiss, R. G.; Demailly, G. *Mol. Cryst. Liq. Cryst.* **1985**, *1*, 183.
(2) Cassis, E. G., Jr.; Weiss, R. G. *Photochem. Photobiol.* **1982**, *35*, 439.
(3) (a) Anderson, V. C.; Craig, B. B.; Weiss, R. G. *J. Phys. Chem.* **1982**, *86*, 4642; (b) *Mol. Cryst. Liq. Cryst.* **1983**, *97*, 351. (c) Anderson, V. C.; Weiss, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 6628.
(4) Fung, B. M.; Sigh, R. V.; Alcock, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 7301, and references cited therein.
(5) Otruba, J. P., III; Weiss, R. G. *Mol. Cryst. Liq. Cryst.* **1982**, *80*, 165.
(6) Ortuba, J. P., III; Weiss, R. G. *J. Org. Chem.* **1983**, *48*, 3448.
(7) Ganapathy, S.; Weiss, R. G. In *Organic Phototransformations in Non-Homogeneous Media*; Fox, M. A., Ed.; American Chemical Society: Washington, DC, 1984; p 147.
(8) Leigh, W. J.; Frendo, D. T.; Klawunn, P. J. *Can. J. Chem.* **1985**, *63*, 2131.
(9) (a) Bacon, W. E.; Brown, G. H. *Mol. Cryst. Liq. Cryst.* **1971**, *12*, 229. (b) Dewar, M. J. S.; Nahlovsky, B. D. *J. Am. Chem. Soc.* **1974**, *96*, 460.
(10) (a) Saeva, F. D.; Sharpe, P. E.; Olin, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 204. (b) Eskenazi, C.; Nicoud, J. F.; Kagan, H. B. *J. Org. Chem.* **1979**, *44*, 995. (c) Dondoni, A.; Medici, A.; Colonna, S.; Gottarelli, G.; Samori, B. *Mol. Cryst. Liq. Cryst.* **1979**, *55*, 47.
(11) Bacon, W. E.; Kuo, J.-L.; Brown, G. H. *Mol. Cryst. Liq. Cryst.* **1979**, *56*, 13.
(12) (a) Solladie, G.; Zimmermann, R. G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 348. (b) Ruxer, J. M.; Solladie, G. *Mol. Cryst. Liq. Cryst.* **1978**, *41*, 109.

0022-3263/86/1951-2529$01.50/0