Synthesis of α-Keto Esters and Amides via Oxidative Cleavage of Cyanoketophosphoranes by Dimethyldioxirane

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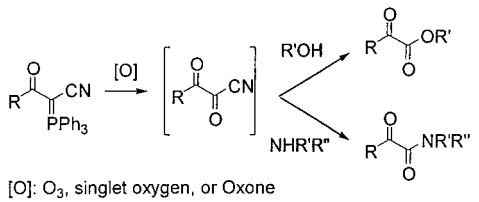
Introduction

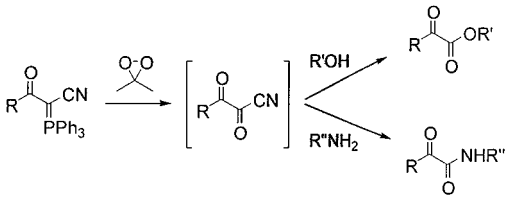
α-Keto esters and amides have been recognized as important functional moieties for inhibitors of hydrolytic enzymes such as serine and cysteine proteases.[1] The inhibitory activities can be attributed to the facile formation of stable tetrahedral adducts between the electrophilic α-keto groups and nucleophilic residues at the enzyme active sites. Development of efficient synthetic methods for these α-keto esters and amides is thus of great interest.[2] Wasserman and co-workers devised an efficient method for synthesizing α-keto esters and amides via oxidative cleavage of C=P double bonds followed by trapping with alcohols and amines, respectively (Scheme 1).[3] This method has been employed in the synthesis of a variety of enzyme inhibitors such as poststatin, eurystatin A, YM-47141, and YM-47142.[4] Ozone is generally employed as the oxidant for the cleavage reactions.[5] However, for substrates bearing sensitive functionalties, milder and more selective oxidants have to be used.[6]

Dioxiranes,[7] a new class of versatile oxidants, are known to cleave C=N[8] and C=P[9] double bonds under mild reaction conditions. Indeed, Wasserman and co-workers reported that dimethyldioxirane can substitute for ozone in the cleavage reactions of phosphorus ylides to afford vicinal tricarbonyl compounds while sensitive functional groups remained intact.[9b,10] In this paper, we extend this efficient method to the synthesis of α-keto esters and amides via dioxirane-mediated oxidative cleavage of cyanoketophosphoranes and subsequent trapping with nucleophiles (Scheme 2).[11]

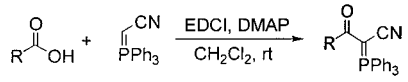
Scheme 1



Scheme 2



Scheme 3



Results and Discussion

According to the procedure described by Wasserman and co-workers,[3a] cyanoketophosphoranes **1**−**12** were readily prepared by coupling of the corresponding carboxylic acids and (cyanomethylene)phosphorane in the presence of EDCI (Scheme 3).[12]

α-Keto esters and amides were prepared by using two slightly different protocols. For the preparation of α-keto esters **1a**−**12a** (Table 1, entries 1−12), dimethyldioxirane[13] (2 equiv, 0.04−0.06 M in acetone) was added to solutions of cyanoketophosphoranes **1**−**12** in MeOH. For the preparation of α-keto amides **13a** and **14a** (Table 1,

(1) (a) Otto, H.-H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133. (b) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.

(2) (a) Wipf, P.; Kim, H.-Y. *Tetrahedron Lett.* **1992**, *33*, 4275. (b) Wipf, P.; Kim, H.-Y. *J. Org. Chem.* **1993**, *58*, 5592. (c) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190. For reviews on vicinal polycarbonyl compounds, see: (d) Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177. (e) Rubin, M. B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121.

(3) (a) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364. (b) Wasserman, H. H.; Wang, J. *J. Org. Chem.* **1998**, *63*, 5581.

(4) (a) Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. *J. Am. Chem. Soc.* **1996**, *118*, 5519. (b) Wasserman, H. H.; Petersen, A. K. *Tetrahedron Lett.* **1997**, *38*, 953. (c) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972. (d) Wasserman, H. H.; Chen, J.-H.; Xia, M. *J. Am. Chem. Soc.* **1999**, *121*, 1401. (e) Wasserman, H. H.; Xia, M.; Petersen, A. K.; Jorgensen, M. R.; Curtis, E. A. *Tetrahedron Lett.* **1999**, *40*, 6163. (f) Paris, M.; Pothion, C.; Michalak, C.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **1998**, *39*, 6889. (g) Fretz, H. *Tetrahedron Lett.* **1996**, *37*, 8475.

(5) Singlet oxygen is also effective in the cleavage reactions. See: (a) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; Vanduzer, J.; Lombarbo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371. (b) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785.

(6) For the use of Oxone in the cleavage reactions, see: (a) Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 5205. (b) Wasserman, H. H.; Ennis, D. S.; Power, P. L.; Ross, M. J.; Gomes, B. *J. Org. Chem.* **1993**, *58*, 4785. (c) ref 4a.

(7) For excellent reviews on dioxirane chemistry, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich. CT, 1990; Vol. 2, p 1. (d) Adam, W.; Hadjiarapoglou, L. P. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1993; Vol. 164, p 45.

(8) For the cleavage of C=N double bonds to carbonyls, see: (a) Altamura, A.; Curci, R.; Edwards, J. O. *J. Org. Chem.* **1993**, *58*, 7289. (b) Saba, A. *Synth. Commun.* **1994**, *24*, 695. (c) Hamilton, R.; Mckervey, M. A.; Rafferty, M. D.; Walker, B. J. *J. Chem. Soc., Chem. Commun.* **1994**, 37.

(9) For the cleavage of C=P double bonds, see: (a) ref 7d; (b) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. *J. Org. Chem.* **1995**, *60*, 8231.

(10) For the oxidation of α-bromo-*β*-dicarbonyls to vicinal tricarbonyls using dimethyldioxirane and base, see: Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7735.

(11) Wasserman and co-workers mentioned one example in which dimethyldioxirane was used for the cleavage of an aliphatic cyanoketophosphorane in MeOH to furnish the α-keto methyl ester. See: ref 9b.

(12) Detailed procedures for the preparation of cyanoketophosphoranes **1**−**12** are available in the Supporting Information.

(13) For the preparation of isolated dimethyldioxirane, see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (c) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227.

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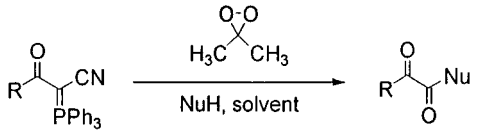
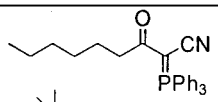
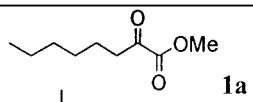
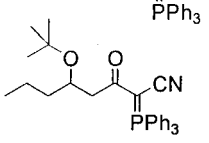
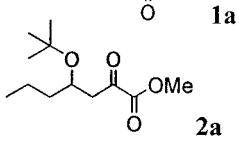
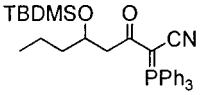
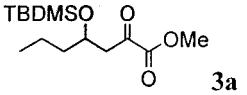
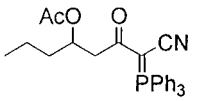
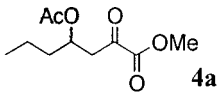
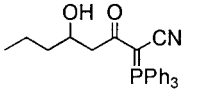
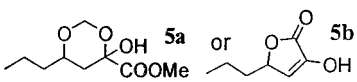
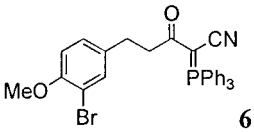
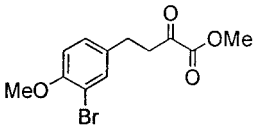
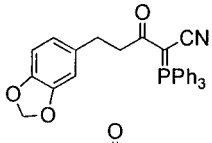
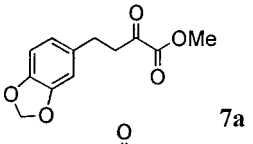
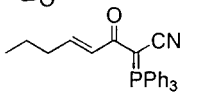
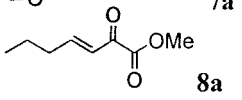
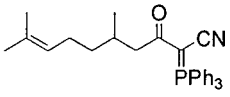
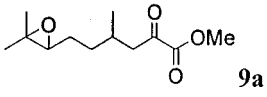
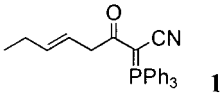
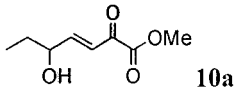
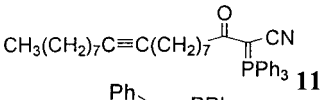
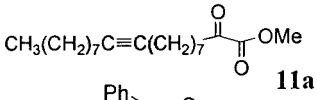
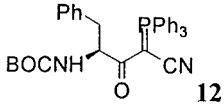
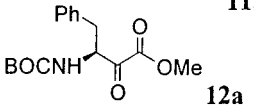
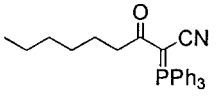
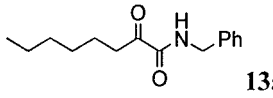
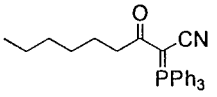
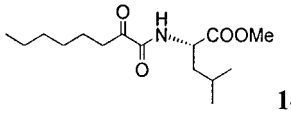
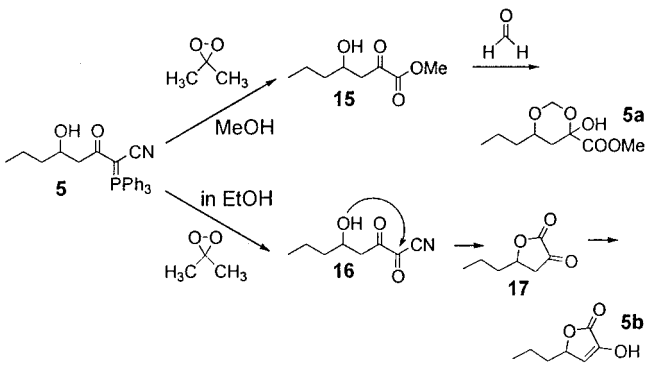
Table 1. Oxidative Cleavage of Cyanoketophosphoranes by Dimethyldioxirane[a]



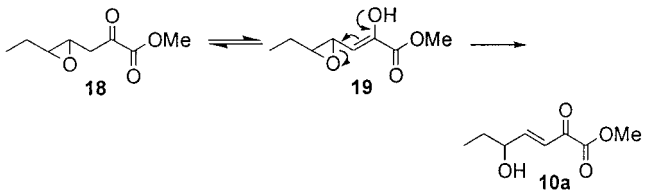
entry	substrate	product	isolated yield (%)[b]
1	 **1**	 **1a**	82
2	 **2**	 **2a**	89
3	 **3**	 **3a**	88
4[c]	 **4**	 **4a**	82
5[d]	 **5**	 **5a** or **5b**	**5a** 32 **5b** 37
6	 **6**	 **6a**	86
7[e]	 **7**	 **7a**	64
8	 **8**	 **8a**	85
9[f]	 **9**	 **9a**	79
10	 **10**	 **10a**	56
11[g]	 **11**	 **11a**	87
12	 **12**	 **12a**	62
13[h]	 **1**	 **13a**	81
14[i]	 **1**	 **14a**	72

[a] Unless otherwise indicated, all reactions were carried out with cyanoketophosphoranes (0.1−0.3 mmol) in MeOH (5 mL) and a solution of dimethyldioxirane (2 equiv) in acetone (ca. 0.04−0.06 M) at room temperature. [b] Isolated yield after flash column chromatography.[c] **4a** was found to be contaminated with a trace amount of **8a** coming from elimination of the acetate moiety. [d] **5b** was obtained when the reaction was conducted in EtOH (5 mL). [e] −78 °C. [f] Reaction was performed at 0 °C with 2.4 equiv of dimethyldioxirane. [g] 0 °C. [h] Reaction was performed in CH_2Cl_2 (5 mL) at −78 °C with benzylamine (1 equiv) in CH_2Cl_2 (2 mL) as the nucleophile. [i] Reaction was performed in CH_2Cl_2 (5 mL) at −78 °C with L-leucine methyl ester (1 equiv) in CH_2Cl_2 (2 mL) as the nucleophile.

Scheme 4



Scheme 5



entries 13 and 14), 1 equiv of the corresponding amine in CH_2Cl_2 was added after the oxidative cleavage reaction was complete in CH_2Cl_2 at −78 °C as judged by TLC (within 5 min).

As illustrated in Table 1, unsubstituted, *tert*-butyloxy-, silyloxy-, and acetoxy-substituted cyanoketophosphoranes **1**−**4** afforded the corresponding α-keto methyl esters **1a**−**4a**[14] in 82−89% yields (entries 1−4). However, for oxidative cleavage of unprotected *β*-hydroxy cyanoketophosphorane **5**, a cyclic acetal **5a** instead of the anticipated α-keto ester was formed in 32% yield (entry 5). This may be due to the fact that there was a trace amount of formaldehyde present in methanol. When the expected α-keto ester **15** was formed, the *γ*-hydroxyl group attacked formaldehyde to provide **5a** as the final product (Scheme 4). In contrast, when the reaction was carried out in EtOH, a five-membered ring lactone **5b** was isolated in 37% yield (entry 5). It is likely that the nucleophilic addition of ethanol to the intermediate α,*β*-diketonitrile **16** was slower than that of methanol (Scheme 4). Consequently, the hydroxyl group of **16** immediately attacked the carbonyl group adjacent to the nitrile group intramolecularly to give the stable five-membered ring α-ketolactone **17**, which tautomerized to the final product **5b**.

Cyanoketophoshporanes **6** and **7** with electron rich aryl rings underwent smooth cleavage to provide **6a** and **7a** in 86 and 64% yield, respectively (entries 6 and 7). While cyanoketophoshorane **8** gave **8a** in 85% yield with the conjugated double bond remained intact (entry 8), for cyanoketophosphorane **9** with an isolated trisubstituted double bond, the one-pot cleavage and epoxidation of **9** furnished epoxy keto ester **9a** in 79% yield (entry 9). More interestingly, when compound **10** with an *γ*−*δ* double bond was subjected to the reaction conditions, keto ester **10a** bearing an allylic alcohol moiety was obtained in 56% yield after silica gel chromatography (entry 10). Apparently, compound **10a** came from the rearrangement of epoxy keto ester **18** via enol intermediate **19** (Scheme 5). As shown in entry 11, cyanoketophoshorane **11** gave **11a** in 87% yield with the triple bond remaining intact. For cyanoketophosphorane **12** bearing an α-substituent, the reaction rate was slower, and keto ester **12a** was formed in 62% yield in 20 min (entry 12).

α-Keto amides **13a** and **14a** were obtained in 81 and 72% yields by oxidative cleavage of cyanoketophosphorane **1** at −78 °C and subsequent trapping with benzylamine and L-leucine methyl ester, respectively (entries 13 and 14). However, the sterically bulky substrate **12** could not be cleaved at −78 °C even after 3 h. When the cleavage reaction was carried out at room temperature, the starting material disappeared in 20 min, and subsequent treatment of benzylamine failed to furnish the desired keto amide. Presumably, the intermediate α,*β*-diketonitrile generated after the addition of dimethyldioxirane quickly decomposed at room temperature even before benzylamine was added.

This protocol for the preparation of α-keto esters and amides via oxidative cleavage of cyanoketophosphoranes utilizes isolated dimethyldioxirane under mild and neutral conditions. It requires short reaction time (usually less than 5 min) and simple workup procedure. Future work will be directed at exploring the potential of this method in other synthetic applications.

Experimental Section

General Methods. All reactions were performed in oven-dried apparatus. Dichloromethane was distilled over calcium hydride. Flash column chromatography was performed using the indicated solvent system on E. Merck silica gel 60 (230−400 mesh ASTM). Dimethyldioxirane was prepared according to the literature procedure.[13]

General Procedure for Oxidative Cleavage of Cyanoketophosphoranes 1−12 (Table 1, entries 1−12). To a solution of **1** (0.10 g, 0.24 mmol) in MeOH (5 mL) was added a solution of dimethyldioxirane in acetone (0.04 M, 12 mL, 0.48 mmol) at room temperature. After stirring for 5 min, TLC analysis indicated the disappearance of starting materials. The reaction mixture was concentrated, and the crude residue was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford **1a**[15] (0.034 g, 82% yield) as a colorless oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f = 0.55$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.84 (t, J = 7.3 Hz, 2H), 1.63 (m, 2H), 1.30 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 194.77, 161.98, 53.28, 39.71, 31.84, 28.98, 23.28, 22.82, 14.38; IR (CH_2Cl_2) 1732 cm^{-1}; EIMS (20 eV) *m*/*z* 172 (M^+, 2), 113 (100), 85 (26); HRMS (EI) for $C_9H_{16}O_3$ (M^+), calcd 172.1099, found 172.1097.

Oxidative Cleavage of Cyanoketophosphorane 1 to α-Keto Amide 13a (Table 1, entry 13). To a solution of **1** (0.10 g, 0.24 mmol) in CH_2Cl_2 (5 mL) was added a solution of dimethyldioxirane in acetone (0.04 M, 12 mL, 0.48 mmol) at −78 °C. After stirring for 5 min, TLC analysis indicated the disappearance of starting materials. A solution of benzylamine (26 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture. After stirring for 10 min, the solvents were evaporated off under reduced pressure. The crude residue was subjected to flash column chromatography (5% EtOAc in *n*-hexane) to provide **13a** (0.048 g, 81% yield) as a colorless oil. Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.76$; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28−7.44 (m, 5H), 4.46 (d, J = 6.1 Hz, 2H), 2.94 (t, J = 7.3 Hz, 3H), 1.38−1.66 (m, 2H), 1.27−1.34 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 199.23, 160.06, 137.06, 128.84, 127.89, 127.86, 43.41, 36.86, 31.51, 28.74, 23.18, 22.46, 14.01; IR (CH_2Cl_2) 3413, 1719, 1687 cm^{-1}; EIMS (20 eV) *m*/*z* 247 (M^+, 42), 113 (100); HRMS (EI) for $C_{15}H_{21}NO_2$ (M^+), calcd 247.1572, found 247.1569.

(14) It was found that **4a** was prone to elimination of the acetoxy moiety to give **8a** during the purification by column chromatography. Thus, the reaction mixture was concentrated under reduced pressure after the disappearance of starting material **4**, and the residue was diluted with 50 mL of 20% EtOAc in *n*-hexane and filtered through a short pad of silica gel to provide **4a**.

(15) Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.

Oxidative Cleavage of Cyanoketophosphorane 1 to α-Keto Amide 14a (Table 1, entry 14). A solution of L-leucine methyl ester in CH_2Cl_2 was prepared by treating L-leucine methyl ester hydrochloride salt (44 mg, 0.24 mmol), K_2CO_3 (0.1 g, 0.72 mmol), and two drops of H_2O in CH_2Cl_2 (2 mL). After stirring for 10 min, the solution was dried over anhydrous Na_2SO_4, filtered, and used for the next step. To a solution of **1** (0.10 g, 0.24 mmol) in CH_2Cl_2 (5 mL) was added a solution of dimethyldioxirane in acetone (0.04 M, 12 mL, 0.48 mmol) at −78 °C. After stirring for 5 min, TLC analysis indicated the disappearance of starting materials. The solution of L-leucine methyl ester in CH_2Cl_2 was added to the reaction mixture. After stirring for 10 min, the solvents were evaporated off under reduced pressure. The crude residue was subjected to flash column chromatography (20% EtOAc in *n*-hexane) to provide **14a** (0.049 g, 72% yield) as a colorless oil. Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.71$; $[\alpha]^{20}_D = -10.7°$ (*c* 0.42, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J = 6.4$ Hz, 1H), 4.56−4.60 (m, 1H), 3.75 (s, 3H), 2.90 (t, $J = 7.0$ Hz, 2H), 1.68−1.74 (m, 1H), 1.58−1.66 (m, 3H), 1.29−1.34 (m, 7H), 0.95 (d, $J = 6.2$ Hz, 6H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 198.58, 172.39, 159.83, 52.48, 50.72, 41.42, 36.77, 31.51, 28.72, 24.86, 23.14, 22.77, 22.46, 21.79, 14.01; IR (CH_2Cl_2) 3401, 1745, 1689 cm^{-1}; EIMS (20 eV) *m*/*z* 285 (M^+, 3), 229 (26), 172 (22), 144 (100); HRMS (EI) for $C_{15}H_{27}NO_4$ (M^+), calcd 285.1940, found 285.1923.

Methyl 4-*tert*-Butoxy-2-oxoheptanoate (2a). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.5$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (quintet, $J = 5.9$ Hz, 1H), 3.87 (s, 3H), 3.00 (dd, $J = 15.4$, 6.4 Hz, 1H), 2.95 (dd, $J = 15.3$, 5.6 Hz, 1H), 1.29−1.51 (m, 4H), 1.16 (s, 9H), 0.91 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 193.72, 161.71, 73.98, 67.89, 52.81, 46.14, 39.28, 28.31, 18.60, 14.07; IR (KBr) 1731 cm^{-1}; MS (ESI) *m*/*z* 231 ($M^+ + 1$, 10), 157 (16); HRMS (EI) for $C_8H_{13}O_3$ ($M^+ - t$-BuO), calcd 157.0865, found 157.0865.

Methyl 4-*tert*-Butyldimethylsilyloxy-2-oxoheptanoate (3a). Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.6$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (quintet, $J = 5.5$ Hz, 1H), 3.80 (s, 3H), 2.97 (dd, $J = 15.5$, 7.1 Hz, 1H), 2.85 (dd, $J = 15.5$, 5.1 Hz, 1H), 1.20−1.47 (m, 4H), 0.96 (t, $J = 7.0$ Hz, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 193.18, 161.43, 68.65, 52.93, 46.44, 39.97, 25.75, 18.20, 17.95, 14.12, −4.52, −4.86; IR (KBr) 1732 cm^{-1}; CIMS *m*/*z* 289 ($M^+ + 1$, 17), 231 (8), 201 (26), 187 (100), 159 (53); HRMS (EI) for $C_{10}H_{19}O_4Si$ ($M^+ - t$-Bu), calcd 231.1053, found 231.1058.

Methyl 4-Acetoxy-2-oxoheptanoate (4a). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.5$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20−5.30 (m, 1H), 3.88 (s, 3H), 3.11 (dd, $J = 16.3$, 4.3 Hz, 1H), 2.98 (dd, $J = 16.3$, 8.0 Hz, 1H), 2.01 (s, 3H), 1.24−1.69 (m, 4H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 190.80, 170.88, 160.96, 69.93, 53.12, 44.16, 36.35, 20.96, 18.43, 13.75; IR (CH_2Cl_2) 1735 cm^{-1}; CIMS *m*/*z* 217 ($M^+ + 1$, 12), 129 (18); HRMS (EI) for $C_7H_{13}O_2$ ($M^+ -$ COCOOMe), calcd 129.0916, found 129.0927.

Methyl 4-Hydroxy-6-propyl-[1,3]dioxane-4-carboxylate (5a). Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.23$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (d, $J = 6$ Hz, 1H), 4.89 (d, $J = 6$ Hz, 1H), 3.86−3.96 (m, 1H), 3.85 (s, 3H), 3.82 (br s, 1H), 2.12 (t, $J = 12$ Hz, 2H), 1.26−1.64 (m, 5H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.48, $CDCl_3$) δ 170.11, 93.27, 87.40, 71.91, 53.33, 37.74, 36.45, 17.95, 13.91; IR (CH_2Cl_2) 3501, 1763 cm^{-1}; EIMS (20 eV) *m*/*z* 204 (M^+, 6); HRMS (EI) for $C_9H_{16}O_5$ (M^+), calcd 204.0998, found 204.0986.

3-Hydroxy-5-propyl-5*H*-furan-2-one (5b). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.3$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (br s, 1H), 6.22 (d, $J = 1.9$ Hz, 1H), 4.96 (m 1H), 1.30−1.80 (m, 4H), 0.97 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 170.36, 142.03, 119.06, 79.57, 36.20, 18.22, 13.81; IR (CH_2Cl_2) 3502, 1763 cm^{-1}; EIMS (20 eV) *m*/*z* 142 (M^+, 11), 125 (16); HRMS (EI) for $C_7H_{10}O_3$ (M^+), calcd 142.0630, found 142.0639.

Methyl 4-(3-Bromo-4-methoxyphenyl)-2-oxobutyrate (6a).[16] Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.36$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 2.0$ Hz, 1H), 7.11 (dd, $J = 8.4$, 2.0 Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.15 (t, $J = 7.4$ Hz, 2H), 2.88 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 192.94, 161.14, 154.45, 133.62, 133.15, 128.44, 111.99, 111.57, 56.28, 53.05, 40.95, 27.66; IR (CH_2Cl_2) 1734 cm^{-1}; EIMS (20 eV) *m*/*z* 302 (M^+, 47), 300 (M^+, 48), 284 (12), 282 (12), 243 (23), 241 (26), 201 (95), 199 (100); HRMS (EI) for $C_{12}H_{13}O_4Br$ (M^+), calcd 299.9997, found 299.9985.

Methyl 4-Benzo[1,3]dioxol-5-yl-2-oxobutyrate (7a). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.56$; as a white solid; mp 51−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63−6.74 (m, 3H), 5.92 (s, 2H), 3.86 (s, 3H), 3.14 (t, $J = 7.4$ Hz, 2H), 2.88 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 193.15, 161.23, 147.71, 146.05, 133.78, 121.20, 108.87, 108.30, 100.89, 53.01, 41.26, 28.70; IR (CH_2Cl_2) 1732 cm^{-1}; EIMS (20 eV) *m*/*z* 236 (M^+, 30), 177 (13), 135 (100); HRMS (EI) for $C_{12}H_{12}O_5$ (M^+), calcd 236.0685, found 236.0682.

Methyl 2-Oxohept-3-enoate (8a). Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f = 0.5$; as a syrup; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.21 (dt, $J = 16.0$, 7.0 Hz, 1H), 6.66 (dt, $J = 16.0$, 2.0 Hz, 1H), 3.89 (s, 3H), 2.30 (ddd, $J = 14.5$, 7.5, 2.0 Hz, 2H), 1.55 (sextet, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 183.01, 162.78, 155.21, 125.20, 52.87, 35.10, 21.06, 13.71; IR (CH_2Cl_2) 1737 cm^{-1}; EIMS (20 eV) *m*/*z* 156 (M^+, 1), 113 (13); HRMS (EI) for $C_8H_{12}O_3$ (M^+), calcd 156.0786, found 156.0765.

Methyl 6-(3,3-Dimethyl-oxiran-2-yl)-4-methyl-2-oxohexanoate (9a). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.66$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.86 (ddd, $J = 17.0$, 6.0, 3.5 Hz, 1H), 2.66−2.74 (m, 2H), 2.12 (septet, $J = 6.6$ Hz, 1H), 1.34−1.63 (m, 4H), 1.31 (s, 3H), 1.27 (d, $J = 2.0$ Hz, 3H), 0.97 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 193.82, 161.62, 64.20, 64.16, 58.35, 58.23, 52.95, 46.26, 46.20, 33.35, 28.61, 28.59, 26.37, 26.34, 24.86, 19.63, 19.60, 18.70, 18.65; IR (KBr) 1731 cm^{-1}; EIMS (20 eV) *m*/*z* 228 (M^+, 1), 211 (13), 169 (26), 123 (100); HRMS (EI) for $C_{12}H_{20}O_4$ (M^+), calcd 228.1362, found 228.1357.

Methyl 5-Hydroxy-2-oxohept-3-enoate (10a). Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.8$; as a syrup; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, $J = 16.0$, 4.5 Hz, 1H), 6.91 (dd, $J = 16.0$, 2.0 Hz, 1H), 4.35−4.39 (m, 1H), 3.90 (s, 3H), 1.61−1.74 (m, 2H), 0.10 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125.78 MHz, $CDCl_3$) δ 182.87, 162.37, 154.94, 123.04, 72.50, 52.96, 29.44, 9.47; IR (KBr) 3473, 1737 cm^{-1}; EIMS (20 eV) *m*/*z* 113 ($M^+ -$ COOMe, 100); HRMS (EI) for $C_6H_9O_2$ ($M^+ -$ COOMe), calcd 113.0602, found 113.0589.

Methyl 2-Oxononadec-10-ynoate (11a). Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.6$; as a syrup; ^{1}H NMR (300 MHz, $CDCl_3$) 3.87 (s, 3H), 2.84 (t, $J = 7.2$ Hz, 2H), 2.11−2.16 (m, 4H), 1.27−1.61 (m, 22H), 0.86−0.89 (m, 3H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 194.24, 161.55, 80.32, 79.98, 52.83, 39.24, 31.81, 29.19, 29.12, 29.09, 28.99, 28.84, 28.79, 28.77, 28.53, 22.85, 22.62, 18.71, 18.66, 14.06; IR (CH_2Cl_2) 1733 cm^{-1}; EIMS (20 eV) *m*/*z* 322 (M^+, 7), 263 (26); HRMS (EI) for $C_{20}H_{34}O_3$ (M^+), calcd 322.2508, found 322.2512.

12a.[3a] Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.36$; as a syrup; $[\alpha]^{20}_D = +24.5°$ (*c* 0.92 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.31 (m, 5H), 5.12−5.20 (m, 1H), 5.02−5.08 (m, 1H), 3.85 (s, 3H), 3.01−3.24 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 192.07, 160.63, 154.78, 135.01, 129.14, 128.50, 127.02, 80.25, 57.71, 53.00, 37.09, 28.15; IR (CH_2Cl_2) 3430, 1756, 1720 cm^{-1}; MS (ESI) *m*/*z* 307 (M^+, 7); HRMS (EI) for $C_{13}H_{18}NO_2$ ($M^+ -$ COCOOMe), calcd 220.1337, found 220.1331.

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Supporting Information Available: Experimental details for preparation of cyanoketophosphoranes **1**−**12**; ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Yang, D.; Wong, M.-K.; Yan, Z. *J. Org. Chem.* **2000**, *65*, 4179.

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