Phospha-Michael Addition to In Situ Prepared 5-Arylmethylidene Meldrum's Acids

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Abstract: Knoevenagel condensation reaction of an aldehyde and Meldrum's acid produces a 5-arylmethylidene Meldrum's acid, which undergoes Michael addition of a trialkyl phosphite under solvent-free conditions to afford the title compounds in good yields.

Key words: trialkyl phosphites, aldehydes, Meldrum's acid, 2-[(dialkoxyphosphoryl)arylmethyl]malonates, phospha-Michael addition

Phosphonates have received considerable attention because of their chemical and biological importance.[1] These compounds act as enzyme inhibitors in a variety of processes because of their structural analogy that refer to the hydrolytic stability of the P–C bond.[2] Derivatives containing the phosphonate system have been shown to possess a broad range of useful pharmacological activities, and are used as herbicides,[3] antibiotics,[4] antiviral agents,[5] anti-HIV agents,[6] and blood pressure regulators.[7]

During recent years there has been considerable investigation on α-hydroxy phosphonates and the corresponding α-hydroxy phosphonic acids. In particular, α-hydroxy phosphonates have been shown to possess a wide range of biological activities.[8] Many of these compounds have exhibited antibacterial, antivirus, antibiotic, pesticidal and antitumor activities.[9,10] Furthermore, many α-functionalized phosphonates, such as α-amino,[11] α-acetoxy,[12] α-halo,[13] and α-keto phosphonates[14] are prepared from α-hydroxy phosphonates.

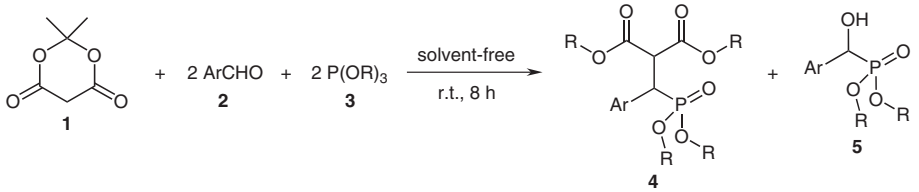
This broad range of applications has made the development of new and efficient phosphonate syntheses very valuable. Consequently, a variety of phosphonate syntheses have been reported in the literature. To the best of our knowledge, there are only two reports for the preparation of β-phosphono malonates by Enders et al. in which reaction of phosphorus nucleophiles and α,β-unsaturated malonates under catalytic conditions has led to interesting products.[15]

Due to the unique properties of P-containing organic compounds, the development of synthetic methods which enable facile access to these useful entities are desirable. As part of our current studies on the development of efficient and facile methods for the preparation of biologically active organic compounds from readily available building blocks,[16] herein we report a novel reaction leading to β-phosphono malonates and α-hydroxy phosphonates.

Thus, a mixture of Meldrum's acid (**1**), a benzaldehyde **2**, and a trialkyl phosphite **3** was stirred at ambient temperature under solvent-free conditions. The progress of the reaction was monitored by TLC. The reaction went to completion within eight hours to afford the corresponding dialkyl 2-[(dialkoxyphosphoryl)arylmethyl]malonates **4a–i** and dialkyl hydroxy(aryl)methylphosphonates **5a–i**. ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of compounds **4** and **5** in good yields. The results are summarized in Scheme 1 and Table 1.[17]

All dialkyl hydroxy(aryl)methylphosphonates **5a–i** are known compounds and were characterized by comparison of their physical and spectral data with those of authentic samples reported in the literature.[18–21]

The structures of dialkyl 2-[(dialkoxyphosphoryl)arylmethyl]malonates **4** were deduced on the basis of IR, ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectroscopy, mass spectrometry and elemental analysis. The IR spectrum of **4a**



Scheme 1 Reaction between Meldrum's acid, benzaldehydes and trialkyl phosphites

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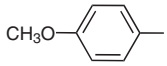
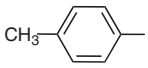
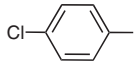
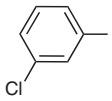
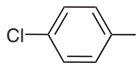
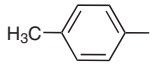
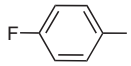
Table 1 Synthesis of β-Phosphono Malonates **4** and α-Hydroxyphosphonates **5**

Entry	Ar	R	Yield (%) of **4**[a]	Mp (°C) of **4**	Yield (%) of **5**[a]
1		Me	**4a**, 45[15b]	80–81	**5a**, 41[18]
2		Me	**4b**, 43	94–95	**5b**, 42[19]
3		Me	**4c**, 42[15b]	103–104	**5c**, 40[19]
4		Me	**4d**, 47	95–96	**5d**, 39[19]
5		Me	**4e**, 42	102–103	**5e**, 43[20]
6		Et	**4f**, 46	colorless liquid	**5f**, 40[18]
7		Et	**4g**, 41	colorless liquid	**5g**, 45[21]
8		Et	**4h**, 44	colorless liquid	**5h**, 46[21]
9		Et	**4i**, 43	colorless liquid	**5i**, 43[21]

[a] Isolated yields.

showed absorptions at 1735 and 1014 cm^{-1} indicative for C=O and P–O bonds, respectively. The mass spectrum of **4a** displayed the molecular ion [M^+] peak at m/z = 330, which was 32 mass units (a MeOH) more than that of the 1:1:1 adduct of Meldrum's acid, benzaldehyde and trimethyl phosphite with the loss of an acetone molecule. The ^{1}H NMR spectrum of **4a** showed two singlets (δ = 3.38 and 3.78) arising from the two ester methoxy groups. Two doublets were observed (δ = 3.44 and 3.64; $^3J_{PH}$ = 10.7, 10.9 Hz, respectively) for the two diastereotopic $POCH_3$ groups. Two doublets of doublet were seen [δ = 3.97 ($^2J_{PH}$ = 20.4 Hz, $^3J_{HH}$ = 11.8 Hz) and δ = 4.20 ($^3J_{PH}$ = 10.2 Hz, $^3J_{HH}$ = 11.8 Hz)] for the PCHCH moiety, along with characteristic signals with appropriate chemical shifts for the five aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed characteristic signals at δ = 43.7 (as a doublet, $^1J_{PC}$ = 139.2 Hz, due to P–CH), 52.6 and 53.0 (due to the two CO_2CH_3 groups), 52.9 and 53.8 (as two doublets, $^2J_{PC}$ = 7.0, 6.5 Hz, respectively, arising from the two diastereotopic $POCH_3$ groups), and 53.1 for PCHCH moiety. Two characteristic resonances were observed at δ = 166.9 (as a doublet, $^3J_{PC}$ = 21.2 Hz) and 167.6 for the two carbonyls of the malonate moiety as well as three CHs and a quaternary carbon with appropriate chemical shifts and multiplicities for the phenyl substituent. The ^{1}H decoupled ^{31}P NMR spectrum of **4a** showed a signal at δ = 26.67 in agreement with the proposed structure.[17]

As shown in Scheme 2, there are three possible conformational diastereomers for β-phosphono malonates **4**, as a result of rotational barrier around C–C single bond. On the basis of the J values in the ^{1}H NMR and ^{13}C NMR spectra, the approximate weight of the individual rotamers in the equilibrium can be determined. For example in the ^{1}H NMR spectral data of **4a**, the observed vicinal coupling constant for the two H atoms is $^3J_{HH}$ = 11.8 Hz, which is in close proximity to that of two vicinal H atoms with an *anti* relationship, and is far from the expected J value for the other two rotamers with a gauche relation of these two vicinal H atoms, i.e. the equilibrium is shifted in favor of rotamer **4a-I**. This conclusion is confirmed by the ^{13}C NMR data of **4a**. One of the two carbonyl C atoms is gauche to the P atom with no observed coupling, while the other is in a 180° torsional angle (*anti* relationship) with $^3J_{PC}$ = 21.2 Hz (Figure 1).

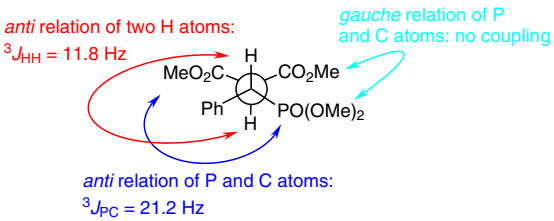
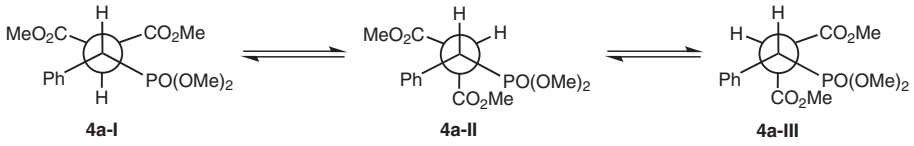
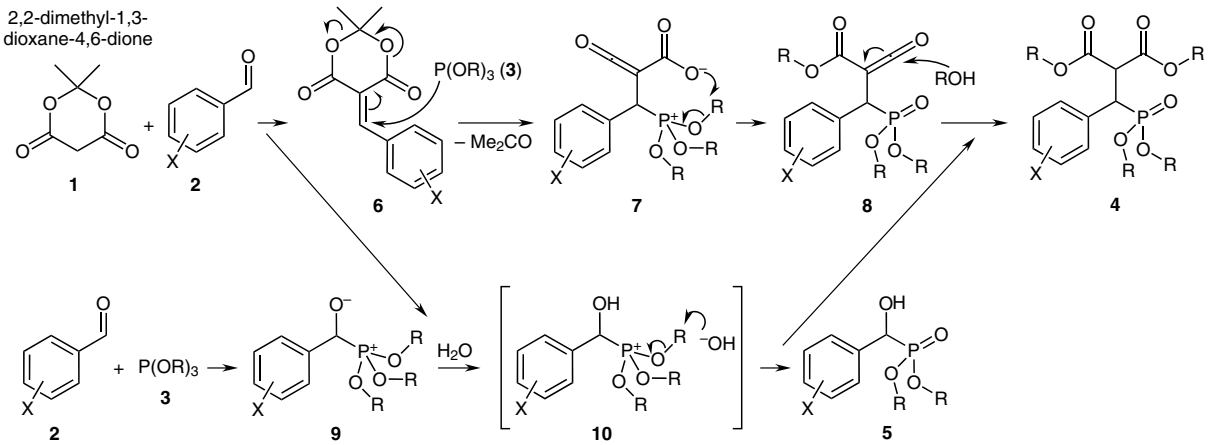


Figure 1 J values in the favored rotamer of **4a**

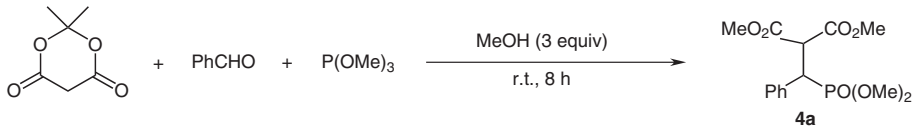
Although no detailed mechanistic studies have been carried out, a possible explanation for the reaction is proposed in Scheme 3. First Meldrum's acid (**1**) may condense with the aldehyde **2** to give 5-arylmethylidene Meldrum's acid intermediate **6**. Conjugate addition of the phosphite **3** on **6**, may lead to formation of the ketene phosphonium carboxylate intermediate **7** by removal of an acetone molecule. Next, the alkyl group of the phosphonium moiety may be attacked by the adjacent carboxylate group to afford the ketene phosphonate intermediate **8**. On the other hand, nucleophilic attack of another trialkyl phosphite **3** on the aldehyde **2**, may lead to formation of the phosphonium alkoxide intermediate **9**, which may be protonated by the H_2O generated from the condensation of Meldrum's acid and the aldehyde, to give α-hy-



Scheme 2 Three possible conformational diastereomers of **4a**



Scheme 3 Possible mechanism for the formation of dialkyl 2-[(dialkoxyphosphoryl)arylmethyl]malonates **4** and dialkyl hydroxy(aryl)methylphosphonates **5**



Scheme 4 Reaction between Meldrum's acid, benzaldehyde and trimethyl phosphite in the presence of MeOH

droxy phosphonium hydroxide **10**. Then nucleophilic attack of hydroxide ion on the alkyl group of the phosphonium moiety may lead to formation of the α-hydroxy phosphonates **5** by removal of an alcohol molecule. Finally, this alcohol molecule may attack on the ketene group of phosphonate **8** to afford β-phosphono malonates **4**.

When the reaction was carried out by the use of equimolar ratios of Meldrum's acid, benzaldehyde and trimethyl phosphite in the presence of MeOH (3 equiv), ^{1}H NMR analysis of the reaction mixture clearly indicated formation of **4a** (Scheme 4). Our attempts to detect the other product **5a** were not successful.

In conclusion, we have developed a one-pot reaction between Meldrum's acid, aldehydes and trialkyl phosphites for the preparation of β-phosphono malonates and α-hydroxy phosphonates which are of potential synthetic interest. Solvent-free and mild conditions, ambient temperature and good yields of the products are the main advantages of this reaction. The reactions were performed under neutral conditions, and the starting materials and reagents have been mixed without any activation or modification.

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References and Notes

(1) (a) Horiguchi, M. *Biochim. Biophys. Acta* **1972**, *261*, 102. (b) Hildebrand, R. L. *The Role of Phosphonates in Living Systems*; Hildebrand, R. L., Ed.; CRC Press: Boca Raton, **1983**.

(2) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (b) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622.

(3) (a) Duke, S.; Lydon, J. *Weed Technol.* **1987**, *1*, 122. (b) Leason, M.; Cunliffe, D.; Parklin, D.; Lea, P. J.; Miflin, B. J. *Phytochemistry* **1982**, *21*, 855. (c) Diddens, H.; Zähner, H.; Kraas, E.; Göhring, W.; Jung, W. G. *Eur. J. Biochem.* **1976**, *66*, 11.

(4) (a) Christiansen, B. G.; Leanza, W. J.; Beattie, T. R.; Patchett, A.; Arison, B. H.; Ormond, R. E.; Kuehl, F. A.; Albers-Schonberg, G.; Jardetzky, O. *Science* **1969**, *166*, 123. (b) Glamowski, E. J.; Gal, G.; Purick, R.; Davidson, A. J.; Sletzinger, M. *J. Org. Chem.* **1970**, *35*, 3510. (c) Giordano, C.; Castaldi, G. *J. Org. Chem.* **1989**, *54*, 1470. (d) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassal, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature (London)* **1978**, *272*, 56.

(5) (a) Van Herrewege, Y.; Penne, L.; Vereecken, C.; Fransen, K.; Van Der Groen, G.; Kestens, L.; Balzarini, J.; Vanham, G. *Aids Res. Human Retroviruses* **2002**, *18*, 1091. (b) Guan, H.-P.; Qiu, Y.-L.; Ksebati, M. B.; Kern, E. R.; Zemlicka, J. *Tetrahedron* **2002**, *58*, 6047. (c) Aquaro, S.; Calio, R.; Balzarini, J.; Bellocchi, M. C.; Garaci, E.; Perno, C. F. *Antiviral Res.* **2002**, *55*, 209.

(6) (a) Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000**, 698. (b) Camp, N. P.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047.

(7) Kido, Y.; Hamakado, T.; Anno, M.; Miyagawa, E.; Motoki, Y. *J. Antibiot.* **1984**, *37*, 965.

(8) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.

(9) (a) Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van Den Oord, J.; De Clercq, E.; Andrei, G. *Antimicrob. Agents Chemother.* **2002**, *46*, 3356. (b) Hammerschmidt, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 341. (c) Jennings, L. J.; Macchia, M.; Parkin, A. *J. Chem. Soc., Perkin Trans. 1*

1992, 2197. (d) Sikorski, J. A.; Miller, M. J.; Braccoli, D. S.; Cleary, D. J.; Corey, S. D.; Font, K. J.; Gruys, K. J.; Han, C. Y.; Lin, K.-C.; Pansegrau, P. D.; Ream, J. E.; Shnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur* **1993**, *76*, 115.
(10) Peters, M. L.; Leonard, M.; Licata, A. A. *Cleve. Clin. J. Med.* **2001**, *68*, 945.
(11) Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051.
(12) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 1771.
(13) Eymery, F.; Lorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 2671.
(14) Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 6720.
(15) (a) Enders, D.; Tedeschi, L. *Org. Lett.* **2001**, *3*, 3515. (b) Enders, D.; Tedeschi, L.; Förster, D. *Synthesis* **2006**, 1447.
(16) (a) Adib, M.; Sheikhi, E.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2012**, *68*, 3377. (b) Adib, M.; Sheikhi, E.; Bagheri, M.; Bijanzadeh, H. R.; Amanlou, M. *Tetrahedron* **2012**, *68*, 3237. (c) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191. (d) Adib, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2011**, 619. (e) Adib, M.; Karimzadeh, M.; Mahdavi, M.; Sheikhi, E.; Mirzaei, P. *Synlett* **2011**, 834. (f) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Tetrahedron* **2010**, *66*, 9263. (g) Adib, M.; Mohamadi, A.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2010**, 1606. (h) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Synthesis* **2010**, 4082.
(17) **General Procedure for the Preparation of Compounds 4 and 5, Exemplified on 4a and 5a**: A mixture of benzaldehyde (2 mmol), Meldrum's acid (1 mmol), and trimethyl phosphite (2 mmol) was stirred at ambient temperature for 8 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the products were purified by column chromatography using *n*-hexane–EtOAc (2:1) as eluent. The solvent was removed and the products were obtained.

Dimethyl 2-[(Dimethoxyphosphoryl)phenylmethyl]-malonate (**4a**): yield: 0.149 g (45%); white powder; mp 80–81 °C. IR (KBr): 1735 (C=O), 1498, 1440, 1312, 1244, 1212, 1161, 1046, 1014 (PO), 916, 856, 829, 728 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.38 (s, 3 H, CO_2CH_3), 3.44 (d, $^3J_{PH}$ = 10.7 Hz, 3 H, $POCH_3$), 3.64 (d, $^3J_{PH}$ = 10.9 Hz, 3 H, $POCH_3$), 3.78 (s, 3 H, CO_2CH_3), 3.97 (dd, $^3J_{HH}$ = 11.8 Hz, $^2J_{PH}$ = 20.4 Hz, 1 H, PC*H*CH), 4.20 (dd, $^3J_{HH}$ = 11.8 Hz, $^3J_{PH}$ = 10.2 Hz, 1 H, PCHC*H*), 7.21–7.34 (m, 5 H, 5 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 43.7 (d, $^1J_{PC}$ = 139.2 Hz, PCH), 52.6 (CO_2Me), 52.9 (d, $^2J_{PC}$ = 7.0 Hz, POMe), 53.0 (CO_2Me), 53.1 (PCH*C*H), 53.8 (d, $^2J_{PC}$ = 6.5 Hz, POMe), 127.9, 128.6 (2 × CH), 129.6 (d, $^3J_{PC}$ = 5.9 Hz, CH), 133.2 (d, $^2J_{PC}$ = 7.0 Hz, C), 166.9 (d, $^3J_{PC}$ = 21.2 Hz, C=O), 167.6 (C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 26.67 (P=O). MS (EI): *m*/*z* (%) = 330 (40) [M^+], 299 (13), 271 (91), 266 (34), 239 (100), 211 (16), 189 (36), 177 (6), 161 (16), 149 (22), 131 (55), 121 (70), 109 (25), 103 (36), 93 (16), 77 (20), 59 (11). Anal. Calcd for $C_{14}H_{19}O_7P$ (330.27): C, 50.91; H, 5.80. Found: C, 50.7; H, 5.9.

Diethyl 2-[(Diethoxyphosphoryl)(4-fluorophenyl)-methyl]malonate (**4i**): yield: 0.174 g (43%); colorless liquid. IR (KBr): 1740, 1735 (C=O), 1604, 1510, 1447, 1369, 1300, 1226, 1161, 1099, 1019 (PO), 962, 849, 794 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.12 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.22, 1.30 (2 × t, *J* = 7.1 Hz, 6 H, 2 × CH_2CH_3), 3.75–4.05 (m, 7 H, 3 × CH_2CH_3, PC*H*CH), 4.13 (dd, $^3J_{HH}$ = 11.3 Hz, $^3J_{PH}$ = 11.1 Hz, 1 H, PCHC*H*), 4.16 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.98 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{FH}$ = 8.5 Hz, 2 H, 2 × CH), 7.30–7.36 (m, 2 H, 2 × CH). ^{13}C NMR (128.5 MHz, $CDCl_3$): δ = 13.6, 14.0 (2 × $CO_2CH_2CH_3$), 16.2 (d, $^3J_{PC}$ = 5.8 Hz, $POCH_2CH_3$), 16.3 (d, $^3J_{PC}$ = 6.2 Hz, $POCH_2CH_3$), 43.1 (d, $^1J_{PC}$ = 140.0 Hz, PCH), 53.5 (PCH*C*H), 61.7, 62.0 (2 × $CO_2CH_2CH_3$), 62.4 (d, $^2J_{PC}$ = 6.9 Hz, $POCH_2$), 63.1 (d, $^2J_{PC}$ = 6.7 Hz, $POCH_2$), 115.3 (d, $^2J_{FC}$ = 21.3 Hz, CH), 129.5 (dd, $^2J_{PC}$ = 7.1 Hz, $^4J_{FC}$ = 2.7 Hz, C), 131.5 (dd, $^3J_{FC}$ = 7.7 Hz, $^3J_{PC}$ = 6.3 Hz, CH), 162.3 (d, $^1J_{FC}$ = 250.3 Hz, CF), 166.5 (d, $^3J_{PC}$ = 20.0 Hz, C=O), 167.1 (C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 24.25 (P=O). MS (EI): *m*/*z* (%) = 404 (38) [M^+], 359 (20), 339 (11), 331 (100), 312 (28), 293 (16), 285 (91), 265 (28), 257 (43), 247 (16), 229 (67), 219 (43), 201 (13), 191 (15), 179 (34), 149 (94), 121 (32), 109 (31), 101 (21), 91 (9), 83 (38), 65 (8), 55 (13). Anal. Calcd for $C_{18}H_{26}FO_7P$ (404.37): C, 53.47; H, 6.48. Found: C, 53.5; H, 6.3.
(18) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 165.
(19) Seven, O.; Polat-Cakir, S.; Hossain, M. S.; Emrullahoglu, M.; Demir, A. S. *Tetrahedron* **2011**, *67*, 3464.
(20) Yang, F.; Zhao, D.; Lan, J.; Xi, P.; Yang, L.; Xiang, S.; You, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5646.
(21) Wu, Q.; Zhou, J.; Yao, Z.; Xu, F.; Shen, Q. *J. Org. Chem.* **2010**, *75*, 7498.

