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A Novel Free-Radical Approach to Methylenomycin B[1]

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ABSTRACT

A new free-radical strategy for the synthesis of α-functionalized diethyl β-ketophosphonates utilizing diethyl β-ketophosphonyl α-radical is exemplified by the formal synthesis of methylenomycin B—a cyclopentanoid antibiotic. © *1997 John Wiley & Sons, Inc.*

Methylenomycin B-**8** is an antibiotic isolated from the culture broth of *Streptomyces* species by Haneishi et al.[2,3]. This highly substituted cyclopentenone has attracted the attention of many research groups and is usually regarded as an object for testing new synthetic methodologies [4]. In the course of our recent investigations on the synthesis and reactions of α-phosphonyl radicals, a new, free-radical approach for the synthesis of highly substituted phosphonates has been developed [5].

In this article, we would like to present an extension of this useful methodology to the formal synthesis of methylenomycin B. The essence of the new concept is the synthesis and utilization of the α-phosphonyl radical **3**, generated from the suitably α-substituted β-ketophosphonate **2**. Thus, starting from diethyl 2-oxo-*n*-butylphosphonate **1** or diethyl methylthiomethylphosphonate **4**, α-chloro-, α-bromo-, and α-methylthioderivatives **2** were prepared as the radical **3** precursors (Scheme 1). For further functionalization, the precursors **2** were submitted to the free-radical reaction with the commercially available isopropenyl acetate **5** using the *n*-Bu_3SnH/AIBN (α,α-azabisisobutyronitrile) reagents system. This reaction afforded the corresponding adduct **6** as a mixture of diastereomers in the yields and the P/R ratios (product/reduced substrate) given in Scheme 1. In a typical experiment, the *n*-Bu_3SnH/AIBN reagents system was added with a syringe pump to a stirred solution of a mixture of the radical precursor **2** and isopropenyl acetate **5** (10 eq.) in refluxing toluene under argon over 3 or 4 hours. Then, the resulting adduct **6** [6] was hydrolyzed under acidic conditions and oxidized with $Na_2Cr_2O_7/H_2SO_4$ to give the desired 1,4-diketone **7**. The latter has been earlier synthesized by us and was easily converted to methylenomycin B-**8** in a two-step reaction involving base-catalyzed cyclization and the Horner–Wittig reaction with formaldehyde [7]. It is interesting to note that hydrolysis of the acetate function in **6** under acidic conditions in the absence of oxidant led to the unexpected formation of the β-phosphorylated dihydrofuran **9** (Scheme 1). The reaction proceeds in quantitative yield in a large excess of refluxing methanol in the presence of concentrated hydrochloric acid over 24 hours. The formation of **9** [8] may involve two reversible processes (removal of the acetate function in **6** and nucleophilic attack of the free hydroxyl group at the carbonyl moiety) and irreversible removal of water from the cyclic product formed. An alternative mechanism that would involve the carbophilic attack of the enol hydroxyl at the protonated C–OH or C–OAc is less probable, since formation of the enol form of the β-ketophosphonate is suppressed in methanol. The structure of **9** was confirmed by ^{1}H-, ^{13}C-, and ^{31}P-NMR as well as UV, IR, and MSCI techniques. The final assignment was established using 2D ^{1}H–^{1}H (COSY) and ^{1}H–^{13}C

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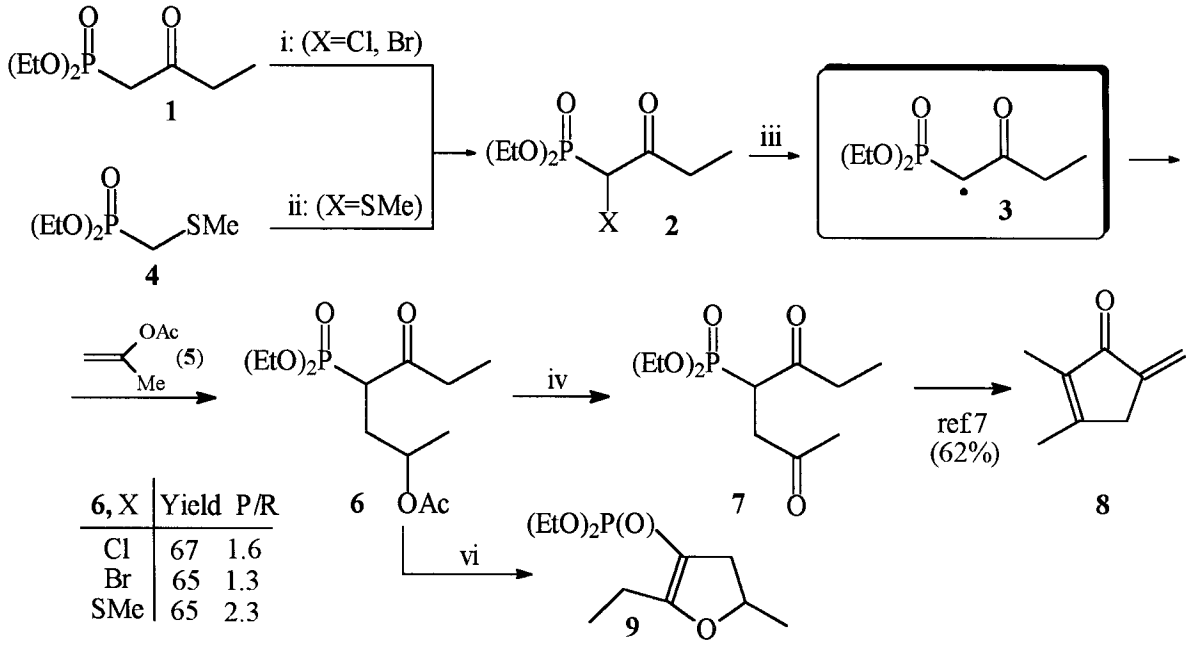
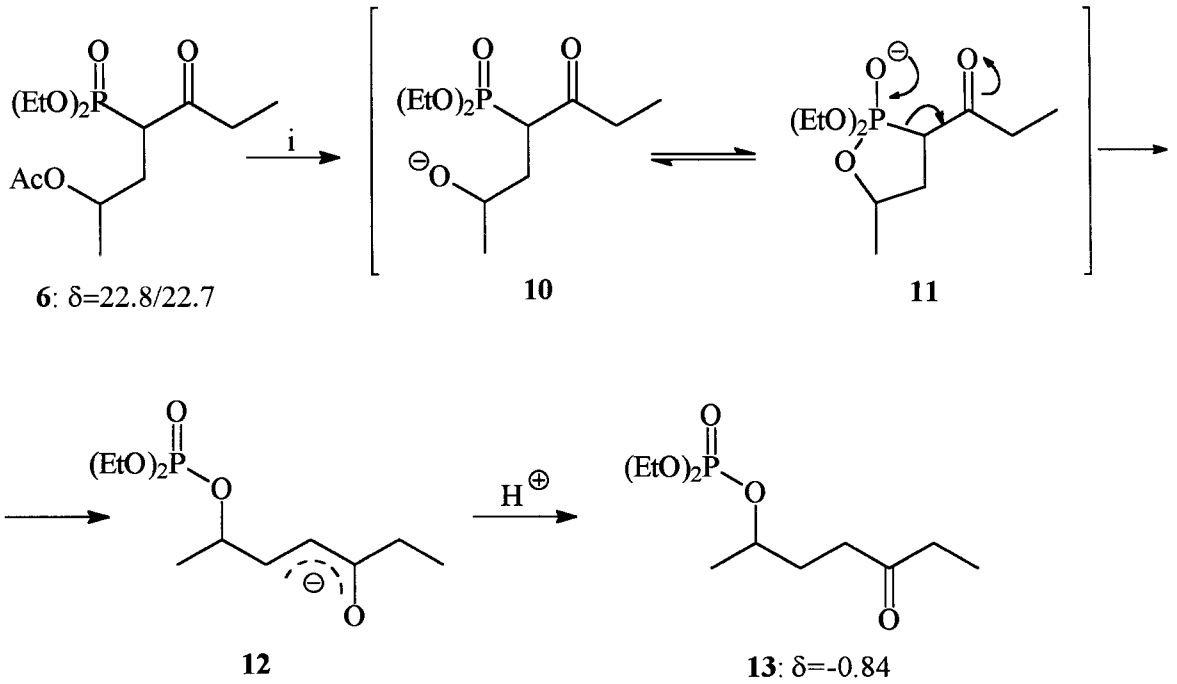


SCHEME 1 i: (X = Cl) – SO_2Cl_2(2 eq.)/CCl_4/0°↗25°C (80%) then $Na_2S_2O_5$/$NaHCO_3$/MeOH/H_2O (80%); (X = Br) – NaH or Et_3N/Br_2(49%); ii: (X = SMe)-*n*-BuLi/EtCOOMe/ – 78°C↗25°C, THF (68%); iii: *n*-Bu_3SnH (1.5 eq.)/AIBN (20%)/toluene, reflux (yields are based on the starting phosphonate); iv: $Na_2Cr_2O_7/H_2SO_4$, reflux (15%); vi: MeOH (0.1 mmol/100 mL)/HCl(conc.), reflux, 24 h (100%).



SCHEME 2 i: 3% KOH/H_2O/EtOH, 25°C 24 h (100% yield) or KCN/EtOH (96%), reflux, 6 h (100% yield) or NH_4OH (25%)/MeOH/H_2O, 25°C, 24 h (85% yield).

correlations. The hydrolysis of the acetate in **6** under basic conditions led to the formation of the phosphate **13** [9], also in a quantitative yield (Scheme 2). The reaction proceeds via two steps, the first undoubtedly being hydrolysis of the acetate function. The second consists in nucleophilic attack of the oxyanion **10** at the phosphoryl phosphorus leading most probably via a five-membered oxyphosphorane intermediate **11** to the rearranged product **12** and, after protonation, to **13**. The driving force for this new example of phosphoryl group migration from carbon to oxygen is the high nucleophilicity of the oxyanion toward phosphorus and stabilization of the enolate anion formed [10].

In conclusion, we have reported the first preparation of the β-ketophosphonyl radical **3** and its application to the synthesis of the functionalized β-ketophosphonate **6**, which was a key substrate in a new, formal synthesis of methylenomycin B-**8**. Further investigation on the scope and limitation of this new, free-radical reaction of the α-phosphonyl radical of type **3** with alkenes will be published in due course.

REFERENCES

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[4] (a) J. Mathew: Synthetic Approaches to Methylenomycin B and Analogs, in G. Lukacs (ed): *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbiological Products,* Springer Verlag, Berlin, Vol. 2, pp. 435–474 (1993). (b) M. Mikołajczyk: Cyclopentanoid Antibiotics: New Syntheses Based on Organophosphorus and Organosulfur Reagents, in K. Kröhn, H. Kirst, H. Maag (eds): *Antibiotics and Antiviral Compounds—Chemical Synthesis and Modifications,* VCH, Weinheim, pp. 205–213 (1993).

[5] P. Bałczewski, M. Mikołajczyk, *Synthesis, 392,* 1995, see also Ref. 1.

[6] **6**:0.01 mmHg/150°C (Kugelrohr); ^{1}H-NMR ($CDCl_3$; 200 MHz); δ = 1.04, 1.05 (2 × t, 3H, $^3J_{H\text{-}H}$ = 7.2 Hz, C(O)$CH_2\underline{CH_3}$); 1.18, 1.20 (2 × d, $^3J_{H\text{-}H}$ = 6.2 Hz, CH$\underline{CH_3}$); 1.30 (t, 6H, $^3J_{H\text{-}H}$ = 7.1 Hz, $\underline{CH_3}CH_2OP$ in one diastereomer); 1.31 (dt, 6H, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{H\text{-}P}$ = 0.3 Hz; $\underline{CH_3}CH_2OP$ in the second diast.); 1.95, 2.00 (2 × s, 3H, OAc); 1.78–2.10 (m, 2H, PCH$\underline{CH_2}$); 2.29–2.52 (m, 2H, C(O$\underline{CH_2}CH_3$); 3, 19 (ddd, 1H, $^3J_{HH}$ = 11.8, 2.2 Hz, $^2J_{H\text{-}P}$ = 25.4 Hz, PCH in one diast.); 3.30 (ddd, 1H, $^3J_{H\text{-}H}$ = 9.3, 3.5 Hz; $^2J_{H\text{-}P}$ = 24.2, PCH in the second diast.); 4.20–4.40 (m, 4H, $CH_3\underline{CH_2}OP$), 4.70–4.92 (m, 1H, CHOAc); ^{31}P-NMR ($CDCl_3$); δ = 22.8/22.7; ^{13}C-NMR ($CDCl_3$, 75 MHz δ = 7.3 (s, C(O)$CH_2\underline{CH_3}$); 16.3 (d, $^3J_{C\text{-}P}$ = 5.2 Hz; POC$H_2\underline{CH_3}$); 20.2, 21.17 (2 × s, PCH$\underline{CH_2}$); 32.5 (2 × s, C(O)$\underline{CH_2}$); 36.9, 37.8 (2 × s, C(O)$\underline{CH_2}$); 48.2, 49.8 (2 × d, $^1J_{C\text{-}P}$ = 124.6; 125.7 Hz; P$\underline{CH}$); 62.5–62.9 (m, PO$\underline{CH_2}CH_3$); 68.6, 70.3 (2 × d, $^3J_{C\text{-}P}$ = 15.6, 13.3 Hz, $\underline{CH}$OAc); 170.3, 170.5 (2 × s, OC(O)Me); 205.6, 205.7 $\underline{C}$(O)Et); MSEI (*m/z, %*) – 308 (M^+; 0.2); 257 (7); 237 (8); 208 (15); 165 (100); 163 (6); 137 (12); 109 (13); 57 (8); 43 (34); 29 (22). Anal. calcd for $C_{13}H_{25}O_6P$ = 308.31; C, 50.56; H, 8.17; H, 8. Found: C, 50.42; 29.

[7] M. Mikołajczyk, A. Zatorski, *J. Org. Chem., 56,* 1991, 1217.

[8] **9**: oil, prep. chrom. (benzene/acetone as eluent, v/v = 2/1); ^{31}p-NMR($CDCl_3$), S = 19.7 ppm; ^{1}H-NMR ($CDCl_3$, 300 MHz), δ = 1.08 (t, 3H, $^3J_{H\text{-}H}$ = 7.5 Hz, C(O)$CH_2\underline{CH_3}$); 1.29 (t, 6H, $^3J_{H\text{-}H}$ = 7.0 Hz, $\underline{CH_3}H_2OP$); 1.31 (d, 3H, $^3J_{H\text{-}H}$ = 7.5 Hz, C(O)$CH_2\underline{CH_3}$); 2.35 (dddt, 1H, $^3J_{H\text{-}P}$ = 14.0 $^3J_{H\text{-}H}$ 7.2, $^2J_{H\text{-}H}$ = 2.4, $^5J_{H\text{-}H}$ = 1.1 Hz, PCC$\underline{H_A}$); 2.52 (qdt, 2H, $^3J_{H\text{-}H}$ = 7.5, $^4J_{H\text{-}P}$ = 1.6, $^5J_{H\text{-}H}$ = 1.1 Hz, = C$\underline{CH_2}CH_3$); 2.89 (dddt, 1H, $^3J_{H\text{-}P}$ = 13.4, $^3J_{H\text{-}H}$ = 9.8, $^2J_{H\text{-}H}$ = 2.4, $^5J_{H\text{-}H}$ = 1.1 Hz, PCC$\underline{H_B}$); 3.95–4.10 (m, 4H, PO$\underline{CH_2}CH_3$); 4.67–4.78 (M, 1H, $\underline{CH}$–O); ^{13}C-NMR($CDCl_3$), δ = 11.67 (s, =C$CH_2\underline{CH_3}$); 16.28 (d, $^3J_{C\text{-}P}$ = 6.1 Hz, $\underline{CH_3}$ CH_2OP); 20.87 (s, =C$\underline{CH_2}$); 21.53 (s, OC$H\underline{CH_3}$); 38.49 (d, $^2H_{C\text{-}P}$ = 9.8 Hz, $\underline{PC}$ = $\underline{C}H_2$); 60.97 (d, $^2J_{C\text{-}P}$ = 4.8 Hz, $CH_3\underline{CH_2}OP$); 78.33 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, $\underline{CH}$–O); 91.17 (d, $^1J_{C\text{-}P}$ = 217.4 Hz, P–$\underline{C}$=), 118.70 (brs, =$\underline{C}$–O); UV (MeOH), λ = 228 nm; IR (film), ν = 1630 cm^{-1}, MSCI (isobutane); M + 1 = 249; MSEI (70 eV, *m/z, %*) – 248 (M^+, 100), 233 (20), 220 (30), 219 (26), 205 (17), 192 (31), 191 (54), 177 (25), 55 (16).

[9] **13**: oil, prep. chrom. (toluene/acetone as eluent, v/v-2/1), ^{1}H-NMR ($CDCl_3$, 200 MHz), δ = 1.05 (t, 3H, $^3J_{H\text{-}H}$ = 7.3 Hz, (O)$CH_2\underline{CH_3}$); 1.19–1.36 (m, 9H, 2 × $\underline{CH_3}CH_2OP$, $\underline{CH_3}CH$); 1.78–2.00 (m, 2H, CHC$\underline{H_2}$), 2.44 (q, $^3J_{H\text{-}H}$ = 7.3 Hz, (O)C$\underline{CH_2}CH_3$); 2.56 (t, 2H, $^3J_{H\text{-}H}$ = 7.3 Hz, $\underline{CH_2}$C(O)CH_2CH_3), 4.08 (2 × dq, 4H, $^3J_{H\text{-}H}$ = $^3J_{H\text{-}P}$ = 7.1 Hz, 2 × $CH_3\underline{CH_2}OP$), 4.47 (m, 1H, $\underline{CH}$OP); ^{31}P-NMR ($CDCl_3$), δ = 0.84; MSEI (15 eV, *m/z %*) – 266 (M^+, 1), 195 (32), 155 (74), 127 (16), 113 (12), 112 (100), 83 (57), 57 (20). Anal. calcd. for $C_{11}H_{23}O_5P$ = 266.09, C, 49.65; H, 8.71. Found: C, 45.51; H, 8.84.

[10] Recently, the diphenylphosphinoyl modifications of this migration has been published: A. Nelson, S. Warren, *Tetrahedron Lett., 37,* 1996, 150, and references cited therein.