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A new synthesis of (±)-homosarkomycin ethyl ester

Ali Samarat,[a] Valérie Fargeas,[b] Jean Villiéras,[b] Jacques Lebreton[b] and Hassen Amri[a,*]

[a]*Laboratoire de Chimie Organique et Organométallique, Faculté des Sciences, Campus Universitaire, 1060 Tunis, Tunisia*
[b]*Laboratoire de Synthèse Organique, UMR-CNRS 6513, Faculté des Sciences et de Techniques, BP 92208-2, rue de la Houssinière, 44322 Nantes-Cedex 3, France*

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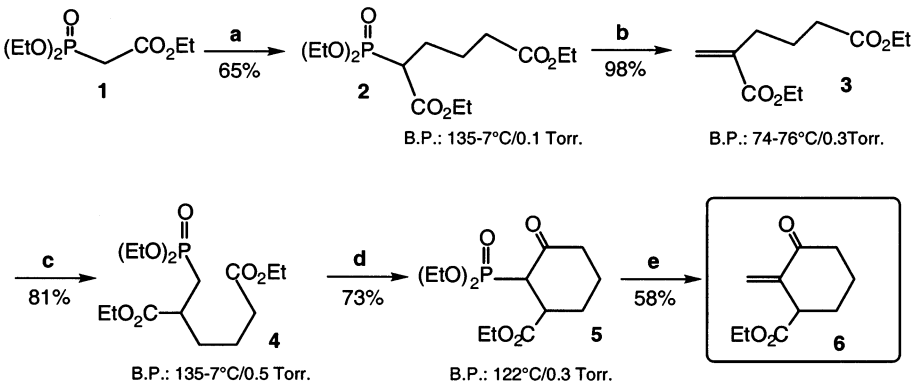
Abstract—A new and efficient synthesis of (±)-homosarkomycin ethyl ester **6**, an antitumor antibiotic is described. The successful synthetic approach to **6** uses β-ketophosphonate **5** as a key intermediate.

Sarkomycin is known to display a powerful inhibitory effect on Ehrlich ascites tumors in mice.[1] As a result of the biological activities associated with sarkomycin and some analogues, among them homosarkomycin,[2] many syntheses of these targets have been reported as multi-step syntheses[3–5] with low overall yields. We have previously described a short large-scale synthesis of (±)-sarkomycin esters[6] and derivatives[7] including a cyclic β-ketophosphonate as a key intermediate. In continuation of our interest in the synthesis of biological compounds,[8] we report herein, a short synthesis of (±)-homosarkomycin ethyl ester **6** using low cost products and methodology (Scheme 1).

At first, the coupling between commercially available triethyl phosphonoacetate **1** and ethyl bromobutyrate leads to the functional phosphonate **2** in 65% yield. Methylenation of **2** by the Wittig–Horner reaction using paraformaldehyde and potassium carbonate as a base, provides in an excellent yield (98%) the desired diethyl α-methylene adipate **3**. The addition of diethyl phosphite salt to diester **3** affords the Michael adduct **4** (81%), which was cyclized using ^{t}BuOK in anhydrous tetrahydrofuran to give the key β-ketophosphonate intermediate **5**. Introduction of the exocyclic methylene group was performed by means of the Wittig–Horner reaction under heterogeneous liquid–liquid conditions in the presence of aqueous formaldehyde (30%) and potassium carbonate to give (±)-homosarkomycin ethyl ester **6** in 58% yield. Spectroscopic data[9] are in accord with the structure **6**.



Scheme 1. *Reagents and conditions*: (a) NaH, Br-$(CH_2)_3$-COOEt, THF, reflux, 8 h; (b) $(HCHO)_n$, K_2CO_3, THF, reflux, 4 h; (c) $(EtO)_2P(O)H$, K_2CO_3, 75°C, 16 h; (d) ^{t}BuOK, THF, 0°C, rt, 2 h; (e) HCHO (30%), K_2CO_3, THF/H_2O, rt,1 h.

Keywords: (±)-homosarkomycin ethyl ester; phosphonic acid derivatives; Wittig reactions; Michael reactions.
* Corresponding author. Fax: +216 1 885 008; e-mail: hassen.amri@fst.rnu.tn

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In summary, a simple and efficient synthesis of (±)-homosarkomycin ethyl ester was accomplished in only five steps in 22% overall yield from commercially available phosphonate **1**. Studies directed towards the synthesis of (±)-homosarkomycin analogues (from substituted ω-bromobutyrates or from ω-bromopentanoate) are in progress, as well as the biological evaluation, the results of which will be reported in due course.

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9. Synthesis of homosarkomycin ethyl ester **6**: To a mixture of β-ketophosphonate **5** (3.06 g, 10 mmol) in 10 mL of THF and 30% aqueous formaldehyde (2 mL) is added a gelatinous solution of potassium carbonate (2.76 g, 20 mmol) diluted in water (2 mL). The heterogeneous reaction mixture is stirred for 1 h at room temperature then treated with water. The solution is then extracted with ether. The combined organic layers are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (hexane: EtOAc, 9:1, $R_f = 0.8$) to afford (±)-homosarkomycin ethyl ester **6**. Spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (t, 3H, $J = 7$ Hz); 2.36 (m, 6H); 3.64 (m, 1H); 4.15 (q, 2H, $J = 7$ Hz); 5.54 (d, $J = 1.4$ Hz, 1H); 6.16 (d, $J = 1.4$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.2 (CH_3), 22.7 (CH_2), 23.6 (CH_2), 29.7 (CH_2), 33.1 (CH), 60.2 (CH_2O), 125.6 (=CH_2), 142.1 (=C), 172.3 (COO), 210.4 (CO). MS (70 eV, m/z): 182 (M^+, 4), 155 (96), 127 (78), 109 (47), 99 (100), 81 (52), 29 (34).