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First synthesis of (±)-bis-homosarkomycin ethyl ester

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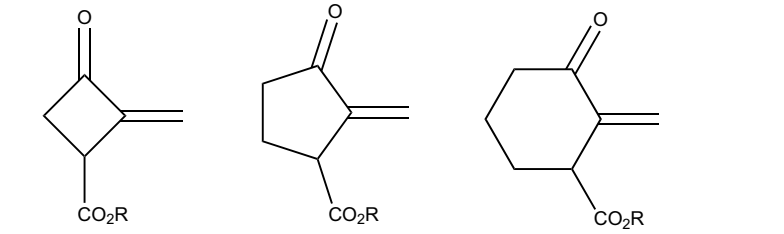
Abstract—A five step synthesis of (±)-bis-homosarkomycin ethyl ester **6** has been achieved starting from commercially available ethyl phosphonoacetate and ethyl 5-bromovalerate. The successful synthetic approach to **6** uses α-methylene pimelate **3** as a key intermediate.

α-Methylene cycloalkanones are integral building blocks in many bioactive natural and unnatural products.[1] Among them, sarkomycin[2–4] and related compounds[5,6] have attracted considerable attention due to their interesting anti-tumour activity.[7] The broad spectrum of biological activity of these compounds encouraged us to start an extensive program for the search for new synthetic methods.[8] In this area, we previously reported a short large-scale synthesis of (±)-sarkomycin esters[9] and derivatives[10] as well as a successful preparation of (±)-homosarkomycin ethyl ester.[11] In this work, we applied our methodology to the synthesis of the seven membered-ring analogue (±)-bis-homosarkomycin ethyl ester **6**, which has never been documented in the literature excepted the ethylidene derivative reported in the Li's work[12] (Scheme 1).

We envisaged that the Horner–Wadsworth–Emmons reaction in heterogeneous medium would be a powerful and practical route to the diester **3**, which has also been reported by Knochel and co-workers,[13] a key intermediate for this total synthesis. The diethyl α-methylene pimelate **3** was prepared in two steps from commercially available triethyl phosphonoacetate **1**. Firstly, an efficient coupling between the anion of phosphonate **1** and commercially available ethyl 5-bromovalerate in THF under reflux provided the bifunctional phosphonate **2** in 70% yield. Methylenation of phosphonate **2** via the Horner–Wadsworth–Emmons reaction using paraformaldehyde and anhydrous solid potassium carbonate as a base, led to the key diethyl α-methylene pimelate **3** in excellent yield (96%) and high purity.



norsarkomycin ester[6] sarkomycin ester[9] homosarkomycin ester[11]

Scheme 1.

Keywords: Horner–Wadsworth–Emmons reaction; Functional phosphonoacetate; Michael addition; Cyclisation.
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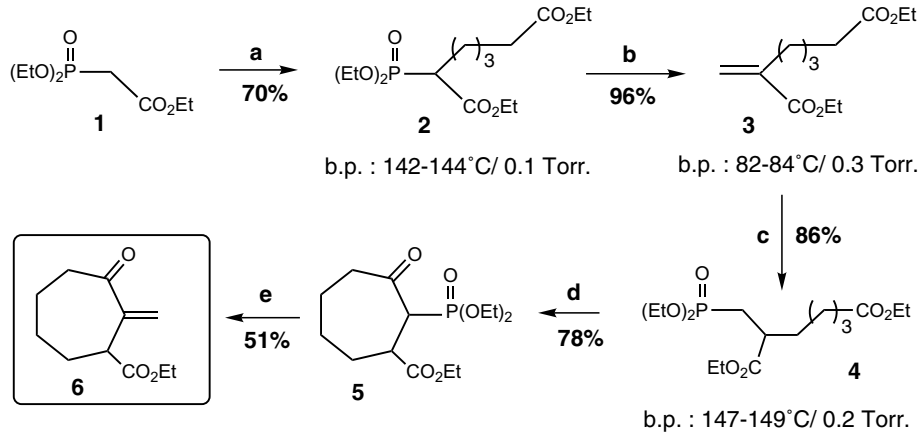

Scheme 2. Reagents and conditions: (a) NaH, $Br(CH_2)_4CO_2Et$, THF, reflux, 12 h; (b) $(HCHO)_n$, K_2CO_3, THF, reflux, 8 h; (c) $(EtO)_2P(O)H$, K_2CO_3, HSTBA (3 mol%), THF, reflux, 24 h; (d) NaH, DME, reflux, 36 h; (e) HCHO (30% aq), K_2CO_3, THF/H_2O, rt, 2 h.

The addition of the diethyl phosphite salt to the diester **3**, in the presence of a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate (HSTBA) as phase transfer reagent, led to the Michael adduct **4** in good yield (86%). The Dieckman-like cyclisation of phosphonate **4** using sodium hydride as a base in anhydrous DME gave rise to the β-ketophosphonate **5** as a mixture of two diastereoisomers in 78% yield. Introduction of the exocyclic moiety was then carried out via the Horner–Wadsworth–Emmons reaction in an heterogeneous medium in the presence of aqueous formaldehyde (30%) and a concentrated (10 M) potassium carbonate solution in THF, to give (±)-bis-homosarkomycin ethyl ester **6** in moderate yield (51%). Spectroscopic data[14] were in accord with the structure **6** (Scheme 2).

In conclusion, we have reported a short and efficient route for the first synthesis of (±)-bis-homosarkomycin ethyl ester **6** using readily available and inexpensive starting materials. The synthesis requires only five steps, proceeds in 23% overall yield, thus demonstrating the synthetic potential of the Horner–Wadsworth–Emmons reaction under heterogeneous conditions. Efforts are underway to extend this strategy to the preparation of heterocyclic analogues. Work along these lines and biological evaluation of these compounds are currently in progress.

References and notes

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14. Synthesis of (±)-bis-homosarkomycin ethyl ester **6**: To a mixture of β-ketophosphonate **5** (1.60 g, 5 mmol) in 5 mL of THF and 30% aqueous formaldehyde (1 mL) was added a solution of potassium carbonate (1.38 g, 10 mmol) in water (1 mL). The heterogeneous reaction mixture was stirred for 2 h at room temperature then treated with water. The solution was then extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 9/1, $R_f = 0.75$) to afford (±)-bis-homosarkomycin ethyl ester **6** as a yellow liquid. Spectroscopic data: IR (film) cm^{-1}: 1734, 1714, 1630. ^1H NMR (300 MHz, $CDCl_3$): 1.34 (t, 3H, $J = 7$ Hz), 1.52–2.12 (m, 6H), 2.42 (m, 2H), 3.54 (m, 1H), 4.23 (q, 2H, $J = 7$ Hz), 5.72 (s, 1H), 6.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0 (CH_3), 23.9 (CH_2), 25.6 (CH_2), 29.7 (CH_2), 43.1 (CH_2), 52.4 (CH), 61.7 (CH_2O), 148.3 (=CH_2), 153.0 (=C), 173.1 (COO), 206.1 (CO). HRMS (EI) calcd for $C_{11}H_{16}O_3$ (M^+) 196.2429, found 196.2457.