A Simple Synthesis of (±)-Sarkomycin

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Abstract: A facile 6-step route to (±)-sarkomycin in 17% overall yield has been described via Michael addition of nitromethane to 2-hydroxymethyl-2-cyclopentenone, oxone-induced oxidative Nef reaction, and acid catalyzed dehydration.

Key words: 2-hydroxymethyl-2-cyclopentenone, nitromethane, Michael addition, oxidative Nef reaction, oxone, (±)-sarkomycin synthesis

The α-methylene ketone and lactone functionalities are found to be present in a great number of compounds having anticancer properties. The simplest of those, sarkomycin (1), was produced by a strain of the soil microorganism *Streptomyces erythromogenes* and reported to show powerful inhibitory effect on Ehrlich ascites tumors in mice. Sarkomycin (1) selectively inhibits DNA synthesis and it has been suggested that the site of the inhibition is DNA polymerase, probably at the sulfhydryl group. Structural determination studies revealed that sarkomycin (1) possesses a single asymmetric center with R stereochemistry. Since its isolation in 1953 by Umezawa et al., several elegant synthetic routes to this rather unstable natural product, its corresponding esters, and analogs (Figure 1) have been reported in view of their promising biological activity. In spite of the huge amount of effort, most of these syntheses are not suitable for the preparation of sarkomycin on a large scale as they involve either the use of unstable starting material or complicated experimental procedure involving low yield steps. In continuation of our ongoing studies towards the synthesis of bioactive natural products, herein we report a simple synthesis of (±)-sarkomycin via the first efficient Michael addition of nitromethane to 2-hydroxymethyl-2-cyclopentenone (Scheme 1).

Reaction of 2-cyclopentenone (4) with aqueous formaldehyde in the presence of imidazole as a catalyst gave 2-hydroxymethyl-2-cyclopentenone (5) in 85% yield. There are other conditions reported in the literature to obtain such type of Baylis–Hillman adducts; but we found the present conditions to be the most fruitful for the preparation of compound 5. Many bases such as DABCO, tetramethylguanidine, and triethylamine were tried for the

![Scheme 1](image-url)
high yielding Michael addition of nitromethane to enone 5, however, the best result was obtained using Triton B as a base,\textsuperscript{13} affording trans-nitro compound 6 in 93% yield. Ketalization of the carbonyl in 6 (89%) followed by protection of the hydroxy group as its THP ether yielded 8 in 80% yield. After this step we did the first very clean oxone induced modified Nef\textsuperscript{10} reaction on 8 to obtain 9 in ca. 100% yield. As per the reported procedure,\textsuperscript{7b} the treatment of 9 with dilute HCl under the conditions described by Marx et al. provided (±)-sarkomycin (10) in only 30% yield. The analytical and spectral data obtained for compound 10 were in complete agreement with reported data.\textsuperscript{7i}

In summary, we have demonstrated a simple and short synthesis of (±)-sarkomycin. The simplicity of reaction conditions used, especially the Triton B catalyzed Michael addition of nitro methane to 5 in the presence of a free hydroxyl group as well as the clean oxone-induced Nef reaction are noteworthy. We feel that the present approach is general and it will be useful for the synthesis of analogs homosarkomycin and bishomosarkomycin.

Melting points are uncorrected. \textsuperscript{1H} NMR spectra were recorded on Bruker AC 200 NMR spectrometer (200 MHz) with TMS as an internal standard. The \textsuperscript{13}C NMR spectra were recorded on Bruker MSL 300 NMR spectrometer (75 MHz) and Bruker DRX 500 NMR spectrometer (125 MHz). Some of the compounds show splitting for two/three carbon in the \textsuperscript{13}C NMR spectra due to the presence of the tetrahydropyranoyl group or due to the formation of a spiro skeleton in the ketal protected form. Column chromatography was carried out on ACME silica gel (60–120 mesh). Petroleum ether with a bp range of 60–80 °C was used. Commercially available nitromethane, dihydropyran, ethylene glycol, and oxone were used.

2-Hydroxymethyl-2-cyclopentanone (5)

To a mixture of 2-cyclopentenone (4: 9.8 g, 120 mmol) and aq formaldehyde (30%, 24 mL, 240 mmol) in anhyd nitromethane (20 mL) was added PPTS (251 mg, 1 mmol) and the reaction mixture was stirred at r.t. for 5 h. The reaction mixture was then acidified to pH 5 with HCl (1.5 M) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL). The organic layer was washed with aq NaHCO\textsubscript{3} (30 mL), brine (30 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. Concentration of the organic layer in vacuo gave a thick yellow oil, which was purified by silica gel column chromatography (petroleum ether–EtOAc, 1:1) to obtain 5 as a thick yellow oil; yield: 16.09 g (93%).

IR (Neat): 3449, 1531 cm\textsuperscript{-1}.

\textsuperscript{1H} NMR (CDCl\textsubscript{3}, 200 MHz): d = 1.40–2.00 (m, 11 H), 2.55–2.85 (m, 2 H), 4.37 (br s, 2 H), 7.55 (br s, 1 H).

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IR (Neat): 3449, 1531 cm\textsuperscript{-1}.

\textsuperscript{1H} NMR (CDCl\textsubscript{3}, 200 MHz): d = 1.40–2.00 (m, 11 H), 2.55–2.85 (m, 2 H), 4.37 (br s, 2 H), 7.55 (br s, 1 H).

IR (Neat): 3449, 1531 cm\textsuperscript{-1}.
1H NMR (CDCl$_3$, 200 MHz): $\delta$ = 1.15–2.10 (m, 10 H), 2.50–2.70 (m, 1 H), 2.70–2.90 (m, 1 H), 3.35–4.00 (m, 8 H), 4.60 (br s, 1 H), 6.31 (br s, 1 H).

13C NMR (CDCl$_3$, 75 MHz): $\delta$ = 19.2, 25.3, 30.4, 35.6, 35.8, 46.0, 48.7, 61.9, [64.3, 64.8 (1 C)], 66.2, [70.2, 70.4 (1 C)], 98.7, 116.6, [177.1, 178.4 (1 C)].

Anal. Calcd for C$_7$H$_8$O$_3$: C, 60.00; H, 5.75. Found: C, 60.03; H, 5.77.

Anal. Calcd for C$_{14}$H$_{22}$O$_6$: C, 58.73; H, 7.74. Found: C, 58.77; H, 7.74.

2-Methylene-3-oxo-cyclopentanecarboxylic Acid [(±)-Sarkomyacin, 10]

A solution of 9 (572 mg, 2 mmol) in HCl (0.5 N; 15 mL) was stirred at r.t. for 10 h and then extracted with CHCl$_3$ (3 × 20 mL). The combined organic layer was extracted with cold NaHCO$_3$ (5%; 30 mL) and the aqueous layer was reacidified with dil. HCl and again extracted with CHCl$_3$ (2 × 10 mL). Concentration of the organic layer gave essentially pure 10 as a thick oil; yield: 84 mg (30%).

IR (CHCl$_3$): 2943, 1723 cm$^{-1}$.

1H NMR (CDCl$_3$, 200 MHz): $\delta$ = 2.10–3.20 (m, 4 H), 3.45–3.85 (m, 1 H), 4.60 (br s, 1 H), 7.69.

5.70.

1H NMR (CDCl$_3$, 200 MHz): $\delta$ = 19.2, 25.3, 30.4, 35.6, 35.8, 46.0, 48.7, 61.9, [64.3, 64.8 (1 C)], 66.2, [70.2, 70.4 (1 C)], 98.7, 116.6, [177.1, 178.4 (1 C)].

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References

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