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A NEW SYNTHESIS OF SARKOMYCIN

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Summary: A novel and short synthesis of (±)-sarkomycin is described.

Recent studies have led to the synthesis of sarkomycin 1[1], a compound discovered by Umezawa[2a] which was subsequently shown to have an inhibitory effect on Erlich ascites tumors in mice[2b]. We wish to report a new approach to this important compound, utilizing as a key intermediate 3-dimethoxymethyl-2-carboxymethylcyclopentanone 2, a useful synthon in organic synthesis[3,4,5] of cyclopentanoids derivatives, obtained in high yield by the known procedure from α-tropolone[4,5].

The original synthetic route involves the treatment of 2 with lithium borohydride in methanol at -78°C to give in 95% yield a diastereomeric mixture of the alcohols 3[5], in a ratio of 85:15 α:β of isomeric compounds[3a,5]. Further reduction using lithium aluminium hydride(LAH) in THF at room temperature furnished in 90% yield the diols 4[5] as a white oil after chromatograph purification: IR (neat) 3500, 1140, 1110, 1050 cm^{-1}; NMR (CCl_4)δ_{TMS} 4.25 (m, 1H), 4.10 (d, J=6Hz, 1H), 3.85 (d br, 2H), 3.10 (s, 6H)[6]. Protection as the mono-trimethylsilyl derivative (5), followed by chromium trioxide-pyridine oxidation of the remaining hydroxyl group gave the ketone 6 in 75% overall yield: IR (neat) 1730, 1160, 1075, 1040 cm^{-1}; NMR ($CDCl_3$)δ_{TMS} 4.15 (d, J=6Hz, 1H), 3.95 (d, J=6Hz, 2H), 3.12 (s, 6H)[6]. Several attempts to obtain sarkomycin 1, via the enone derivative from 6 by cautious acid treatment[7] followed by oxidation with pyridinium chlorochromate were unsuccessful.

Thus, an alternative route was developed that consists of direct reduction of 2[3,4,5] with an excess of LAH[8] in a mixture of THF:DME to furnish the hydroxy-olefin 7, in 40% yield after purification by chromatography: IR (neat) 3560, 1632, 1150, 1110, 1050 cm^{-1}; NMR ($CDCl_3$) δ_{TMS} 5.15 and 4.90 (m, 1H each), 4.28 (m, 1H), 4.15 (d, J=6Hz, 1H), 3.15 (s, 6H). Attempts to liberate the aldehyde function of 7 by treatment with Amberlite IR-120 in acetone[3a] gave only an intractable brown-oil as product. Finally, the synthesis of 1 was accomplished by careful oxidation of 7 with an excess of Jones reagent[9], immediately followed by treatment of the unstable product with diazomethane in ether to give 1a[1c] in ca. 20% overall yield: IR (neat) 1735, 1720, 1630 cm^{-1}; NMR ($CDCl_3$)δ_{TMS} 6.15 (d, J=2Hz), 5.60 (d, 2Hz), 3.68 (s, 3H). (±) Sarkomycin (1) can be prepared from 1a using the published procedure[1a] to hydrolyse the ester

derivative.

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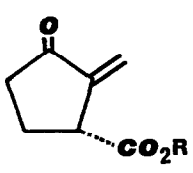
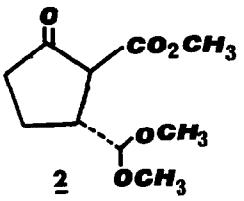


1 R=H
1a R=CH3



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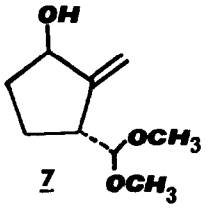

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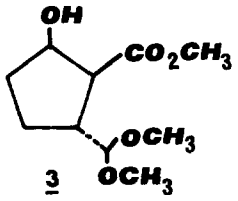

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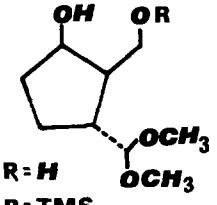
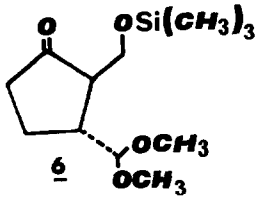


4 R=H
5 R=TMS



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6. Satisfactory PMR, IR and MS data were obtained for the compounds reported herein.

7. cf. ref. 1d.

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