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An Integrated Chemoenzymatic Synthesis of Enantiopure (-)-(1*R*,5*S*)-Cyclosarkomycin: a Sarkomycin Precursor

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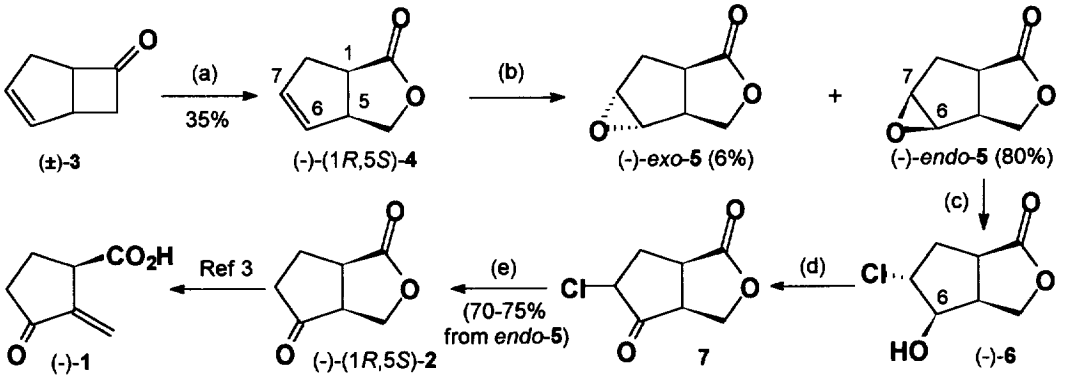
Abstract: *A five-step chemoenzymatic synthesis of (-)-(1R,5S)-cyclosarkomycin 2 has been achieved starting from commercial racemic bicycloheptenone 3. The strategy developed involved - as key steps - an enantioselective microbiologically catalyzed Baeyer-Villiger oxidation followed by a chemical regioselective epoxide ring opening.* © 1997, Published by Elsevier Science Ltd. All rights reserved.

The antibiotic (-)-(*R*)-sarkomycin **1,** isolated from the soil microorganism *Streptomyces erythrochromogenes* in 1954, has been shown to exhibit a potential antitumor activity.[1] We report herein an enantioselective total synthesis of (-)-(1*R*,5*S*)-cyclosarkomycin **2**,[2] a precursor of (-)-(*R*)-**1** which can be easily converted into sarkomycin by acidic treatment[3], starting from the enantiopure bicyclic lactone (-)-(1*R*,5*S*)-**4**. We have shown previously that this lactone is obtainable *via* microbiological (i.e. bacterial) oxidation of the commercially available racemic ketone **3**.[4] Moreover, we have observed recently that this same lactone could be obtained even more conveniently (35% yield, ee > 98%), using the fungus *Cunninghamella echinulata* (NRRL 3655).[5] Obviously, further transformation of this chiron into the target molecule **2** required the regioselective introduction of an hydroxyl function at C(6). Various attempts, including hydrohalogenation[6] or hydroboration[7] of the double bond of **4**, failed in our hands. We finally directed our efforts towards the regioselective ring-opening[8] of the corresponding epoxide **5**. This was obtained by treatment of **4** with *m*-chloroperbenzoic acid

Scheme 1: Synthetic way to the (-)-(1*R*,5*S*)-cyclosarkomycin 2



Conditions: (a) Culture of *C. echimulata*. (b) 1.1 eq. MCPBA, CH_2Cl_2, 0 °C to rt, 12h. (c) ~3 eq. TMSCl, ~5 eq. Zn, Et_2O, 0 °C to rt, 1 h (d) 1.2 eq. Dess-Martin reagent, CH_2Cl_2, rt, 10 min. (e) ~5 eq. Zn, AcOH, rt, 15 min.

(MCPBA) which afforded, after crystallisation, a mixture of diastereomeric epoxides **5** in 80% and 6% yield,respectively.[9] Since it was difficult to unambiguously deduce the correct stereochemistry of either these isomers from their ^{1}H NMR analysis, this was achieved using X-Ray crystallography, which indicated that the minor isomer -which occurred to give better crystals- was of *exo* configuration.[10,11] We therefore examined the regiocontrolled ring-opening of the (major) *endo*-**5** epoxide using various nucleophiles.[8] The best results were obtained under treatment of *endo*-**5** with an excess of zinc dust and trimethylsilyl chloride[12] in diethylether[13] at 0 °C, which led almost with an excellent selectivity (> 95%) to the desired chloroalcohol **6** in 75% yield after purification.[14] The crude product was further oxidized using the Dess Martin reagent[15] into the chloroketone **7** which was directly treated with zinc in acetic acid to afford, after crystallisation, the desired (-)-(1*R*,5*S*)-cyclosarkomycin **2** (ee > 98%,[16])($[\alpha]_D^{18}$ = -388 (c = 1, CH_2Cl_2) (literature[2c] $[\alpha]_D^{25}$ = -415 (c=0.92, CH_2Cl_2)).

In conclusion, an efficient five-step synthesis of enantiopure (-)-(1*R*,5*S*)-cyclosarkomycin **2** has been achieved. It is to emphasize that this implies a resolution process *as a first step* (an important feature for industrial applications allowing to avoid undesired enantiomeric ballast over the synthesis). Also, it can be seen that this strategy, which leads presently to a 21% overall yield (and thus already compares very favourably with those previously described[2]), could certainly be further optimised as far as the yield of the biooxidation is concerned.

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6. Upon treatment of **4** with *N*-bromoacetamide in acetone/water (9/1) at 0 °C, the corresponding bromoalcohol isomers were obtained as a 1:1 mixture, in high yield.
7. Racemic **4** has previously been described to be converted with diborane into a 3/1 mixture of the C-6 and C-7 alcohols but we were unable to reproduce this result. See ref. 3.
8. For some recent examples see: Bonini, C.; Righi, G. *Synthesis* **1994**, 225-238 and literature cited.
9. (-)-*endo*-epoxide **5**: $[\alpha]_D^{18}$ = -38 (c = 1.5, CH_2Cl_2), mp 67-68 °C, ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.05 (dd, *J* = 14.8 and 7.8, 1H); 2.55 (d, *J* = 14.8, 1H); 3.0-3.1 (m, 2H); 3.59 (s, 1H); 3.62 (d, *J* = 2.0, 1H); 4.44 (dd, *J* = 9.2 and 6.4, 1H); 4.54 (d, *J* = 9.2). ^{13}C NMR (62.5 MHz): 31.1 (C8), 40.2 (C1), 40.6 (C5), 58.6 (C6), 59.8 (C7), 68.3 (C4), 178.8 (C2).
10. In the literature (ref. 3), the major isomer was assigned an *exo configuration*.
11. Colourless crystals grown from Et_2O/ CH_2Cl_2: monoclinic, space group *Pmca*, a = 7.793(2), b = 10.253(3), c = 16.238 (4) Å.
12. Vankar, Y.D.; Chaudhuri, N.C.; Rao, C.T. *Tetrahedron Lett.* **1987**, *28*, 551-554. Using this procedure we were however unable to remove the chlorine atom in the same step, as described for the other substrates in this work.
13. Attempts to perform the same reaction in CH_2Cl_2 led to a 8:2 mixture of **6**, along with its regioisomer, in 50-60% yield.
14. Surprisingly, under these conditions, *exo*-epoxide **5** gave the hydroxy-7-chloro-6 regioisomer of **6** with a good selectivity.
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16. Enantiomeric excesses were determined by chiral GC analysis using a 25 m capillary column Lipodex E (Macherey-Nagel) at 160 °C and a racemic sample as reference: (-)-(1*R*,5*S*)-cyclosarkomycin **2** t_R = 15.5 min and (+)-(1*S*,5*R*)-**2** t_R = 16.8 min.

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