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Synthesis of enantiomeric cyclosarcomycins

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Based on chiral cyclopentene blocks 2 and 3, enantiomeric cyclosarcomycins 4 and 5 were obtained and characterised.

Chiral cyclopentene blocks are important building templates at the synthesis of cyclopentenone antibiotics, prostaglandins, carbanucleosides, *etc*.[1–4] Earlier, we have developed a practical pathway to produce diastereomeric cyclopentene **2** and **3**[5] from available bicycle **1** and (+)-α-methylbenzylamine. Here, we consider the developed conversion of **2** and **3** into enantiomeric cyclosarcomycins **4** and **5**. Cyclosarcomycin **4** is a stable precursor of natural cyclopentanoid, sarcomycin A **6**.

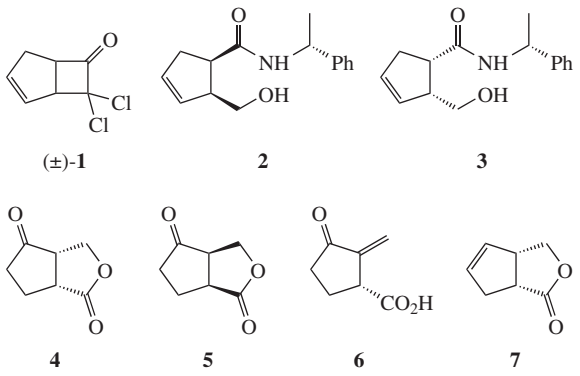


Figure 1 Structures of basic initial and target compounds.

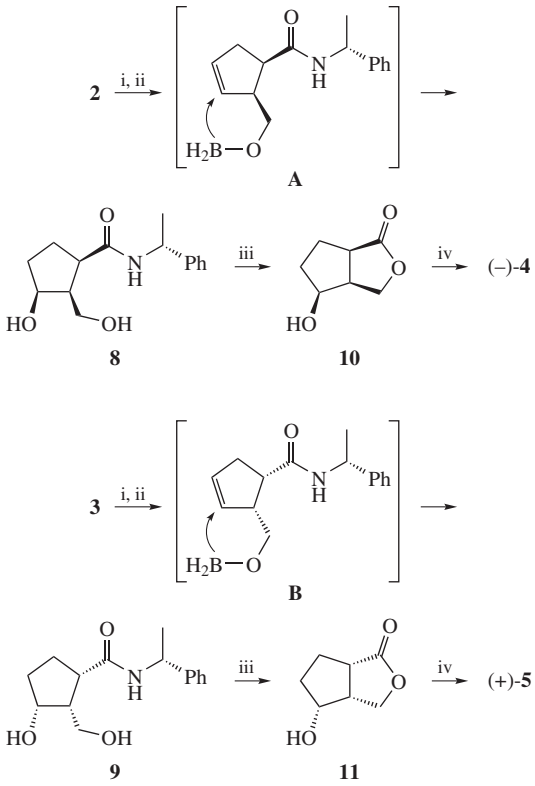
Firstly, (–)-*R*-sarcomycin A **6** was isolated from soil microorganisms *Streptomyces erythrochromogenes* in 1954.[6] It possesses antibiotic and antitumor properties and is used in Japan for the chemotherapy of tumoral diseases.[7]

There are many publications on the synthesis of (–)- and (±)-**6**, esters, nor- and homoanalogues, cyclosarcomycin, dihydrosarcomycin, *etc*.[8–13]

The regioselective introduction of the oxo function into a cyclopentene ring is a principal problem of the approaches to cyclosarcomycins **4** and **5** from cyclopentenes **2** and **3**. To resolve this problem, we propose the hydroboration–oxidation process directly with borane. In this case, the hydroxyl-directed[14] intramolecular hydroboration becomes possible (Scheme 1).

Note that, for the similar synthesis of racemic **6** from lactone **7**, Hudlicky also used the tandem reactions of hydroboration–oxidation and oxidation by the Jones reagent to introduce the oxo function.[15] However, in this case, the regioselectivity of hydroboration was low, and a significant amount of useless regioisomeric ketone was formed in addition to product **6**.

As it was expected, the hydroboration–oxidation reactions of compounds **2** and **3** proceeded to form only diols **8** and **9**.[†,‡] The acidic hydrolysis of compounds **8** and **9** gave hydroxylactones **10** and **11**, respectively.[§] The following oxidation by pyridinium chlorochromate led to expected optically pure (–)- and (+)-cyclo-



Scheme 1 Synthesis of cyclosarcomycins **4** and **5**. *Reagents and conditions*: i, BH_3·THF, THF, 1 h; ii, 20% NaOH, 35% H_2O_2, 3 h, 90–92%; iii, 9 N H_2SO_4–dioxane (1:2), reflux, 4 h, 83–86%; iv, PCC, CH_2Cl_2, room temperature, 4 h, 74–77%.

sarcomycins **4** and **5** (Scheme 1),[¶] which can be transformed into (–)- and (+)-sarcomycins **6** using known methods.

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† *Typical procedure for the synthesis of amidodiols* **8** *and* **9**. Amidoalcohol **2** (500 mg, 2 mmol) in 15 ml of dry THF was cooled to 0 °C under argon and treated dropwise with 4 ml of a 1 M solution (2 equiv.) of a borane–THF complex. The cooling bath was removed after the addition (2 min), and the mixture was stirred at room temperature for 2 h, whereupon excess BH_3 was decomposed by the addition of 1 ml of H_2O. The reaction mixture was cooled in ice, 1.2 ml of 3 M NaOH solution was added followed by 1 ml of 30% H_2O_2, and the entire mixture was then heated at 50 °C for 1 h. The reaction mixture was cooled, acidified with 2 ml of 3 M HCl, and stirred at room temperature for 0.5 h, then it was partitioned between brine and diethyl ether and extracted. The organic layers were combined, dried, and evaporated to give an oil, which was chromatographed [15 g of silica, $CHCl_3$:MeOH (10:1)] to give 480 mg (92%) of amidodiol **8**.

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‡ *(1*R*,2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)*-N*-(1-phenylethyl)cyclopentanecarboxamide* **8**: yellow crystalline solid, yield 92%, mp 97–99 °C, $[\alpha]_D^{16}$ +47.5 (*c* 1.25, CH_2Cl_2). IR (Nujol mull, ν/cm^{-1}): 3307, 2968, 2870, 1632, 1533, 1369, 1236, 1045, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (d, 3H, Me, *J* 7.1 Hz), 1.86–2.18 (m, 5H, 2-H, 4-H and 5-H), 2.89 (q, 1H, 1-H, *J* 8.3 Hz), 3.49 (d, 2H, OH and CH_2–O, *J* 5.3 Hz), 3.54–3.63 (br. s, 2H, OH and CH_2–O), 4.22 (q, 1H, 3-H, *J* 5.3 Hz), 5.05 (quint., 1H, C*H*–Ph, *J* 7.1 Hz), 6.56 (d, 1H, N–H, *J* 7.1 Hz), 7.22–7.33 (m, 5H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.65 (Me), 26.83 (C-5), 33.63 (C-4), 46.25 (C-1), 48.96 (*C*HPh), 52.56 (C-2), 61.83 (CH_2O), 75.69 (C-3), 126.10, 127.36, 128.63, 143.09 (Ph), 174.25 (C=O). MS (APCI), *m*/*z* (%): 264 [MH$^+$] (100), 246 (98.5), 228 (8.6). Found (%): C, 68.27; H, 7.63; N, 5.09. Calc. for $C_{15}H_{21}NO_3$ (%): C, 68.44; H, 7.98; N, 5.32.

*(1*S*,2*R*,3*R*)-3-Hydroxy-2-(hydroxymethyl)*-N*-(1-phenylethyl)cyclopentanecarboxamide* **9**: white crystalline solid, yield 90%, mp 104–106 °C, $[\alpha]_D^{16}$ +78.1 (*c* 0.965, CH_2Cl_2). IR (Nujol mull, ν/cm^{-1}): 3296, 2964, 2872, 1635, 1533, 1368, 1237, 1045, 693. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (d, 3H, Me, *J* 6.9 Hz), 1.82–2.16 (m, 5H, 2-H, 4-H and 5-H), 2.89 (q, 1H, 1-H, *J* 8.5 Hz), 3.63 (d, 2H, OH and CH_2–O, *J* 5.6 Hz), 3.78–3.98 (br. s, 2H, OH and CH_2–O), 4.23 (q, 1H, 3-H, *J* 6.1 Hz), 5.04 (quint., 1H, C*H*–Ph, *J* 6.9 Hz), 6.82 (d, 1H, N-H, *J* 6.9 Hz), 7.21–7.35 (m, 5H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.93 (Me), 26.64 (C-5), 33.57 (C-4), 46.11 (C-1), 49.00 (*C*HPh), 52.54 (C-2), 61.91 (CH_2O), 75.51 (C-3), 126.14, 127.39, 128.72, 143.16 (Ph), 174.32 (C=O). MS (APCI), *m*/*z* (%): 264 [MH$^+$] (100), 246 (91.8), 228 (10.2). Found (%): C, 68.19; H, 7.74; N, 5.14. Calc. for $C_{15}H_{21}NO_3$: C, 68.44; H, 7.98; N, 5.32.

§ *General procedure for the synthesis of compounds* **10** *and* **11**. 9 N solution of H_2SO_4 (1 ml) was added to a stirred solution of amidodiol **9** (100 mg, 0.4 mmol) in dioxane (2 ml) at room temperature. The mixture was refluxed for 3 h and monitored by TLC (ethyl acetate–light petroleum, 1:1), cooled to room temperature, and concentrated in a vacuum. The residue was diluted with water (4 ml) and extracted with diethyl ether (3×7 ml). The combined extracts were washed with saturated brine, dried over Na_2SO_4 and concentrated in a vacuum. Purification of the products by column chromatography (ethyl acetate–light petroleum, 1:1) afforded hydroxylactone **11** (45 mg, 83%) as a white crystalline solid.

*(3*aR*,4*R*,6*aS*)-4-Hydroxyhexahydro-1*H*-cyclopenta[*c*]furan-1-one* **11**: yield 83%, mp 76–78 °C, $[\alpha]_D^{16}$ +81.0 (*c* 1.15, CH_2Cl_2). IR (Nujol mull, ν/cm^{-1}): 3323, 2962, 2922, 2853, 1737, 1458, 1387, 1194, 1146, 1037, 962. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62–1.87 (m, 2H, 5-H and 6-H), 2.01–2.12 (m, 1H, 5-H), 2.18–2.36 (m, 1H, 6-H), 2.82–2.93 (m, 1H, 3a-H), 2.94–3.04 (br. s, 1H, OH), 3.15 (td, 1H, 6a-H, *J* 2.3, 9.0 Hz), 4.03 (dd, 1H, 3-H, *J* 3.7, 9.5 Hz), 4.15–4.21 (m, 1H, 4-H), 4.49 (t, 1H, 3-H, *J* 9.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.86 (C-6), 34.05 (C-5), 43.03 (C-6a), 48.00 (C-3a), 70.62 (C-3), 79.05 (C-4), 180.82 (C=O). MS (APCI), *m*/*z* (%): 143 [MH$^+$] (100), 125 (9.3). Found (%): C, 58.97; H, 6.93. Calc. for $C_7H_{10}O_2$ (%): C, 59.15; H, 7.04.

¶ *General procedure for the synthesis of compounds* **4** *and* **5**. Solid pyridinium chlorochromate (PCC) (604 mg, 2.8 mmol) was added to a solution of hydroxylactone **11** (200 mg, 1.4 mmol) in CH_2Cl_2 (15 ml) at room temperature. After stirring for 4 h, Et_2O (20 ml) was added and the reaction mixture was filtered on a pad of Celite, and concentrated. The residue was purified by column chromatography on SiO_2. Elution with hexane–EtOAc (1:1) gave ketolactone **5** as a white crystalline solid.

*(3*aR*,6*aS*)-Tetrahydro-1*H*-cyclopenta[*c*]furan-1,4(3*H*)-dione* **5**: yield 74%, mp 58–60 °C, $[\alpha]_D^{16}$ +362.5 (*c* 1.17, CH_2Cl_2). IR (Nujol mull, v/cm^{-1}): 2955, 2920, 2853, 1759, 1735, 1456, 1379, 1169, 1119, 1024, 952. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.17–2.57 (m, 4H, 5-H and 6-H), 2.97–3.07 (m, 1H, 3a-H), 3.37–3.45 (m, 1H, 6a-H), 4.42 (dd, 1H, 3-H, *J* 7.5, 9.5 Hz), 4.48 (dd, 1H, 3-H, *J* 2.2, 9.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.60 (C-6), 36.51 (C-5), 41.45 (C-6a), 47.71 (C-3a), 68.67 (C-3), 178.27 (C-1), 216.92 (C-4). MS (APCI), *m*/*z* (%): 139 [MH$^+$] (100). Found (%): C, 59.73; H, 5.63. Calc. for $C_7H_8O_2$ (%): C, 59.99; H, 5.75.