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The polyhydroxy cyclopentene, a total synthesis of (–)-pentenomycin

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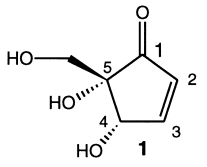
Abstract

The functionalized cyclopentene **2** was converted in five steps to (–)-pentenomycin **1**.

Keywords: cyclopentenes; cyclopentenones; cyclization; antibiotics.

The pentenomycin antibiotics have attracted considerable attention due to its wide range of structural and stereochemical features and biological activities.[1a] Pentenomycin **1** was isolated by Umino and co-workers in 1973 from the culture broths of *Streptomyces eurythermus*,[1b,c] while epipentenomycin the C-4 diastereomer, was isolated from carpophores of *Perziza* sp.[2] There have been several approaches[3] to synthesize these antibiotics and their derivatives however, an expeditious and efficient approach is still needed.



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In connection, we recently reported the synthesis of a polyhydroxylated cyclopentene **2**,[4] a useful template that can be widely utilized in synthesis of highly functionalized five-membered rings. The synthesis of **2** was done via a ring closing metathesis (RCM) in five steps with a 90% yield. A comparison of cyclopentene **2** with pentenomycin **1** indicates that the stereochemistry around the C-4 and C-5 are identical. Therefore, logical retrosynthetic analysis suggests that our key cyclopentene intermediate **2** can be converted to pentenomycin **1**, via elaboration of precursor **3** (Scheme 1).

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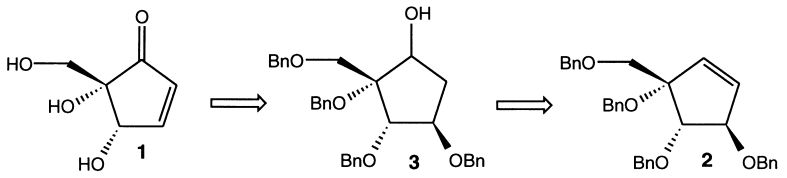
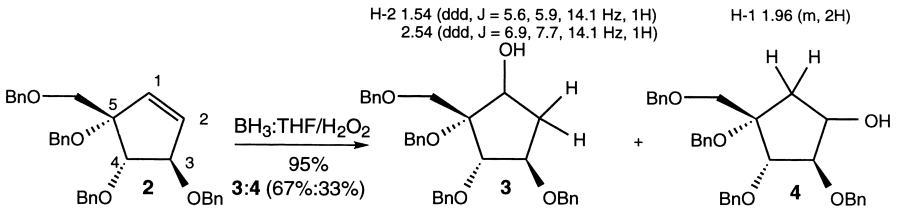


Scheme 1.

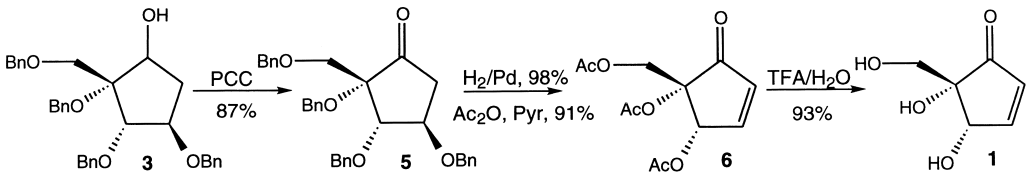
Thus, compound **2** was treated with BH_3:THF to give the two regioisomeric alcohols **3** and **4** (2:1) (Scheme 2). The use of BH_3:SMe_2 gave no additional selectivity while catecholborane and 9-borobicyclo[3.3.1]nonane gave no reaction.[5] The structural identification of these regioisomers **3** and **4** were based on the coupling constants of the new methylene protons at C-2 and C-1, respectively (Scheme 2).



Scheme 2.

Compound **3** was oxidized by PCC to afford the corresponding ketone **5** (Scheme 3). Additional confirmation of the regiochemistry of the carbonyl group came from the coupling constants of the C-2 methylene protons of **5**, where two signals at δ 2.30 (dd, J = 7.7, 20.0 Hz, 1H) and δ 2.79 (dd, J = 7.4, 20.0 Hz, 1H) were observed. However, the corresponding ketone of the other regioisomer **4** showed only one signal for the C-1 protons at δ 2.61 (d, J = 3.7 Hz, 2H).

The ketone **5** was hydrogenated, then treated with pyridine/acetic anhydride to furnish the acetylated enone **6**. Deprotection of the acetate **6** with trifluoroacetic acid/H_2O afforded (–)-pentenomycin **1** (Scheme 3). The ^1H and ^{13}C NMR of **6** and **1** were identical with those reported in the literature.[1,2,6]



Scheme 3.

In summary, a concise and efficient synthesis of the (–)-pentenomycin **1** was demonstrated in five steps (46% yield), using our key polyhydroxy cyclopentene intermediate **2**.

Acknowledgements

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6. For compound **1**: ^{1}H NMR (D_2O, 270 MHz) δ 3.61 (ABq, $\Delta\delta = 0.07$ ppm, 2H, J = 11.6 Hz), 4.72 (dd, J = 1.2, 2.7 Hz, 1H), 6.34 (dd, J = 1.2, 6.2 Hz, 1H), 7.74 (dd, J = 2.7, 6.2 Hz, 1H) ^{13}C NMR (D_2O, 67.5 MHz) δ 63.3, 71.7, 76.3, 133.5, 164.6, 209.8.