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Stereoselective synthesis of (−)- and (+)-pentenomycins using RCM☆

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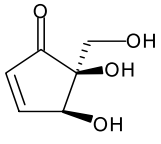
Abstract—An efficient synthesis of enantiopure (−)- and (+)-pentenomycins are described by reductive iodo elimination and ring-closing metathesis (RCM), as the key steps. The first synthesis of the unnatural (+)-isomer is described.

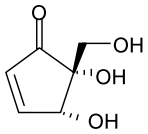
Highly oxygenated cyclopentenoid[1] skeletons are of increasing interest because of their variety of biological activities, such as, glycosidase inhibitors[1d] and amino-glycosidase antibiotics.[1e] (−)-Pentenomycin **1** isolated from culture broths of *Streptomyces eurythermus* by Umino and co-workers in 1973,[2] is known to exhibit potential antibiotic activity. It shows moderate activity against a variety of both gram positive and gram negative bacteria including *Neisseria meningitidis* and *Neisseria gonorrhoeae*.[2] Thus, the synthesis of pentenomycin **1** have attracted considerable attention from synthetic chemists due to its fascinating structural, stereochemical and biological properties. Although its structure seems to be simple, its synthesis is not an easy task owing to its sensitivity towards acids and bases, and also due to the presence of a tertiary chiral center.

Even though synthetic approaches to (−)-pentenomycin **1** have been reported, including racemic,[3] as well as enantiopure,[3d,4] there were no reports on the synthesis of unnatural (+)-pentenomycin **2**. Herein we report a common strategy for an efficient synthesis of (−)- and (+)-pentenomycins **1** and **2** starting from commercially available D-mannose and D-ribose, respectively, by using reductive iodo elimination under sonication and RCM.[5]



(-)-Pentenomycin

1



(+)-Pentenomycin

2

For the synthesis of (−)-pentenomycin **1**, D-mannose was taken as starting material (Scheme 1). First, D-mannose was converted to 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **3**. The hydroxymethyl group was introduced with aqueous CH_2O in the presence of K_2CO_3 to afford **4**.[6] The primary hydroxyl group in **4** was protected as a silyl ether to give **5** by treating **4** with TBDPS-Cl and imidazole. The hydroxy compound **5** was converted to the methyl ether **6** by treating with MeI, and NaH in THF. Selective acetonide deprotection gave diol **7**. Cleavage of diol **7** with $NaIO_4$, followed by reduction with $NaBH_4$ afforded the alcohol **8**. Treatment of **8** with I_2, PPh_3 and imidazole furnished iodo compound **9**.[7]

When iodo compound **9** was subjected to reductive elimination by treatment with activated Zn under sonication conditions,[5] aldehyde **10** was produced. The crude aldehyde **10** was treated with vinylmagnesium bromide to afford the corresponding allylic alcohol **11** as a mixture of diastereomers. Treatment of **11** with Grubbs' catalyst (0.1 equiv.) yielded **12**. PDC oxidation of **12** gave the cyclopentenone **13**. Removal of the silyl group of **13** with HF–Py gave crystalline alcohol **14** (mp 62–64°C, lit.:[2b,4a] 63–66°C, $[\alpha]_D^{25}=+22.0$ (*c* 1.0, $CHCl_3$). Deprotection of the acetonide with 90% TFA[4a] culminated in an efficient synthesis of the target, (−)-pentenomycin **1**, whose spectral (^1H and ^{13}C) and physical data were in agreement with reported values. $[\alpha]_D^{25}=-30.2$ (*c* 0.29, EtOH), lit.:[3,4] $[\alpha]_D^{21}=-32.0$ (*c* 0.3, EtOH).

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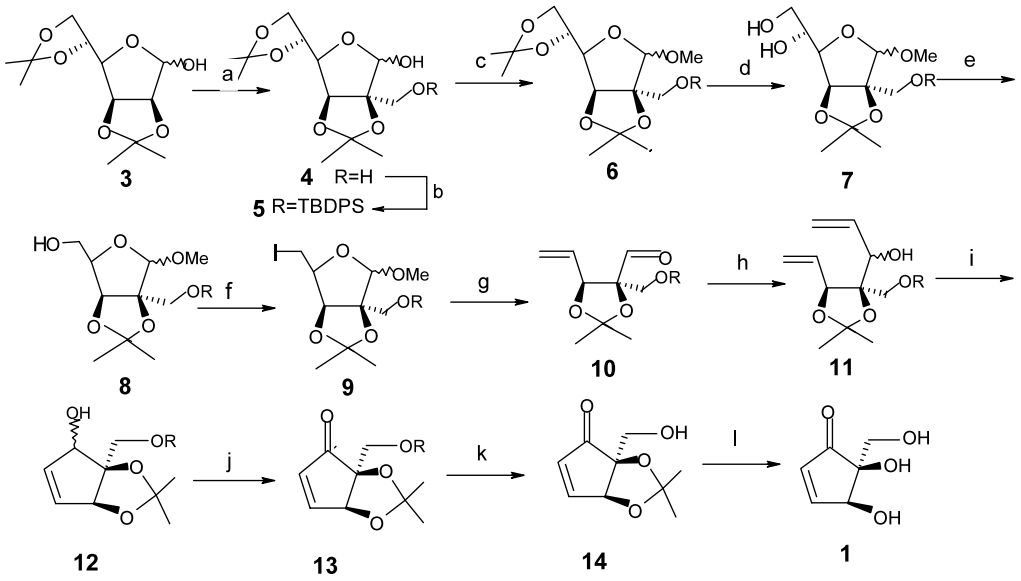
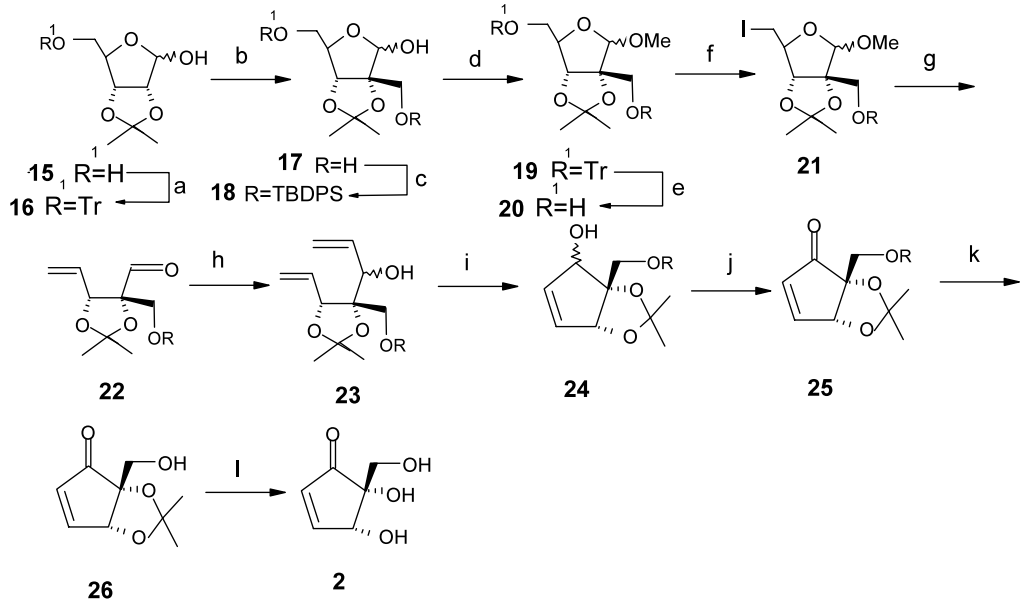


Scheme 1. *Reagents and conditions*: (a) aq. CH_2O, K_2CO_3, MeOH, 85°C, 48 h; 85%; (b) TBDPS–Cl, imidazole, DMAP (cat.), CH_2Cl_2, 0°C–rt, 6 h; 79%; (c) MeI, NaH, THF, 0°C–rt, 3 h; 91%; (d) 60% AcOH, rt, 24 h; 73%; (e) i. $NaIO_4$, THF:H_2O (4:1), 0°C–rt, 6 h; (ii) $NaBH_4$, MeOH, 0°C–rt, 30 min; 82% (for two steps); (f) I_2, PPh_3, imidazole, toluene, 120°C, 8 h; 76%; (g) activated Zn,))))), THF:H_2O (4:1), rt–50°C, 5 h; (h) vinylmagnesium bromide, THF, 0°C, 2 h; 72% (for two steps); (i) Grubbs' catalyst ($(PCy_3)_2Cl_2RuCHPh$) (0.1 equiv.), CH_2Cl_2, rt, 6 h; 84%; (j) PDC, CH_2Cl_2, 0°C–rt, 30 h, 78%; (k) HF–Py, Py, THF, 0°C–rt, 48 h; 60%; (l) 90% TFA, rt, 30 min, 67%.

We further explored the same strategy for the synthesis of unnatural (+)-pentenomycin **2**, starting from commercially available D-ribose. D-Ribose was converted to 2,3-*O*-isopropylidene-D-ribose **15**. The primary hydroxyl group in **15** was selectively protected with trityl chloride to give **16**, which was then subjected to the aqueous CH_2O, K_2CO_3 conditions to afford hydroxymethyl compound **17**. Compound **17** was treated with TBDPS–Cl and imidazole to give silyl ether **18**. Treatment of **18** with MeI and NaH, yielded methyl ether derivative **19**. Under HCO_2H:Et_2O (1:1) conditions detritylation took place to afford alcohol **20**.[8] Compound **20** was converted to iodo compound **21** with I_2, PPh_3 and imidazole.



Scheme 2. *Reagents and conditions*: (a) Tr–Cl, Et_3N, DMAP (cat.), CH_2Cl_2, 0°C–rt, 10 h; 70%; (b) aq. CH_2O, K_2CO_3, MeOH, 85°C, 10 h; 83%; (c) TBDPS–Cl, imidazole, DMAP (cat.), CH_2Cl_2, 0°C–rt, 3 h; 83%; (d) MeI, NaH, THF, 0°C–rt, 3 h; 79%; (e) HCO_2H:Et_2O (1:1), 0°C–rt, 1 h; 53%; (f) I_2, PPh_3, imidazole, CH_2Cl_2, 0°C–rt, 12 h; 65%; (g) activated Zn,))))), THF:H_2O (4:1), rt–50°C, 5 h; (h) vinylmagnesium bromide, THF, 0°C, 2 h, 87% (for two steps); (i) Grubbs' catalyst ($(PCy_3)_2Cl_2RuCHPh$) (0.1 equiv.), CH_2Cl_2, rt, 6 h; 80%; (j) PDC, CH_2Cl_2, 0°C–rt, 30 h; 80%; (k) HF–Py, Py, THF, 0°C–rt, 48 h; 63%; (l) 90% TFA, rt, 30 min, 53%.

Reductive elimination of **21** with activated Zn under sonication conditions yielded olefinic aldehyde **22** (Scheme 2), which was further treated with vinylmagnesium bromide giving allyl alcohol **23**. Finally (+)-pentenomycin **2** was synthesized via **26** (mp 63–65°C, $[\alpha]_D^{25} = -21.16$ (*c* 1.0, $CHCl_3$)) using the conditions described in Scheme 1 for (−)-pentenomycin **1**. The spectroscopic (^1H and ^{13}C) data for **2** were in agreement with the (−)-isomer **1**. $[\alpha]_D^{25} = +30.1$ (*c* 0.1, EtOH).

In summary, we have used a common strategy for the synthesis of (−)- and (+)-pentenomycins[9] using reductive iodo elimination and RCM, starting from commercially available D-mannose and D-ribose respectively in good yields.

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