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A short and stereoselective synthesis of functionalized pentenomycin derivatives

Faiz Ahmed Khan,* Jyotirmayee Dash and Bhimsen Rout

Department of Chemistry, Indian Institute of Technology, IIT Kanpur, Kanpur 208 016, India

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Abstract—A short and stereoselective synthesis of 2-hydroxymethyl-4-deoxypentenomycin and 2-hydoxymethylpentenomycin derivatives is accomplished in five and seven steps starting from tetrabromonorbornyl derivatives in overall yields of 41% and 38%, respectively.
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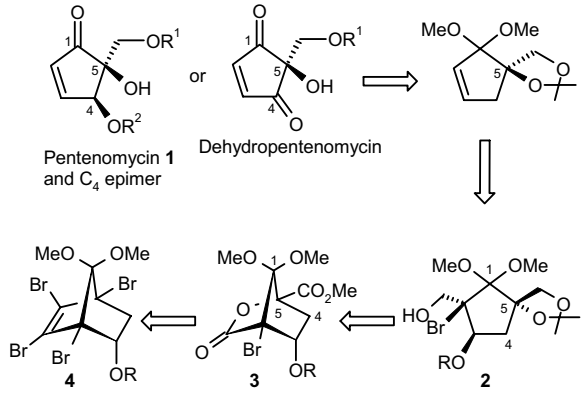
Pentenomycins comprise of a class of bioactive polyhydroxylated cyclopentenoid natural products, which exhibit moderate activity against Gram-positive and Gram-negative bacteria.[1] Smith and co-workers reported the first synthesis of all seven members of the pentenomycin family.[2] Among them, pentenomycin I **1** is usually referred to as pentenomycin, and has attracted substantial attention, as a result of this a number of syntheses have been reported.[2,3] The synthetic interest of various research groups toward these targets is due to their oxygenated skeleton, which has been found in a diverse range of biologically potent natural products, and due to the potential pharmacological importance of the cyclopentenone moiety, is a highly reactive functionality in a multitude of structurally complex antitumor agents.[2–4] We herein report a short and stereoselective synthesis of 2-hydroxymethyl-4-deoxypentenomycin **11** and 2-hydroxymethylpentenomycins **22** and **23** starting from tetrabromonorbornyl derivatives using methodologies recently developed in our laboratory.[5,6]

Our synthetic approach to pentenomycin analogues is based on the regio- and stereoselective formation of bridged lactones **3** derived from tetrabromonorbornyl derivatives **4** via the corresponding diketones.[5b,6e] The key feature of our retrosynthetic analysis (Scheme 1) is to install the C-5 tertiary center present next to a carbonyl group in a stereoselective manner; this is also a structural feature in many naturally occurring molecules.[2,3,7]

A simple LAH reduction of the bicyclic lactone **3** would lead to the formation of oxygenated cyclopentane skeleton **2**, from which the synthesis of **1** could be achieved by suitable functional group transformations.

For the synthesis of pentenomycins, we initially started with ethyl vinyl ether adduct **6**. The adduct was prepared in 85% yield from 1,2,3,4-tetrabromo-5,5-dimethoxycyclopenta-1,3-diene **5** and ethyl vinyl ether in benzene in a sealed tube at 140–150 °C for 30 h. The adduct **6** was oxidized to the corresponding α-diketone **7** in near quantitative yield (Scheme 2). The alkaline H_2O_2 cleavage reaction of **7** furnished a single regioisomer of the bromolactone **8** in 78% yield.[6e] Hydrodebromination of the bridged lactone **8** by radical reaction[5a]



Scheme 1. Retrosynthetic scheme of our approach to pentenomycin derivatives.

Keywords: Pentenomycins; Tetrabromonorbornyl derivatives.
* Corresponding author. Tel.: +91 512 2597864; fax: +91 512 2597436; e-mail: faiz@iitk.ac.in

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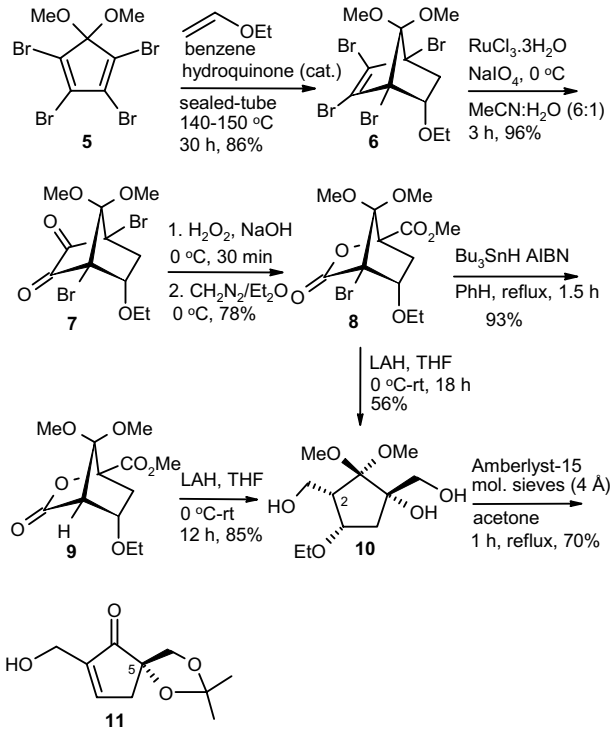
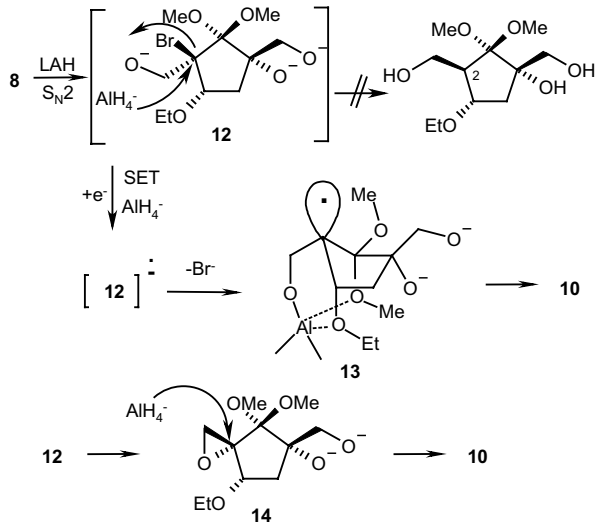


Scheme 2. Synthesis of 2-hydroxymethyl-4-deoxypentenomycin derivative **11**.

followed by LAH reduction of the resulting bicyclic lactone **9** furnished the polyhydroxylated cyclopentanoid derivative **10**, an advanced intermediate of pentenomycin. The polyhydroxylated cyclopentanoid **10** possesses the required C-5 tertiary center present in pentenomycins as well as other naturally occurring molecules[7] and could serve as a crucial intermediate in the synthesis of carbocyclic nucleosides.[8]

Surprisingly, LAH reduction of bromolactone **8** in THF also furnished compound **10** directly in 56% yield from **8**. The enone moiety of pentenomycin was simply obtained by treating **10** with Amberlyst-15 in acetone to give the 2-hydroxymethyl-4-deoxypentenomycin derivative **11** in 70% yield. All the three desired reactions, viz, protection of the vicinal diol as an acetonide, deprotection of the dimethyl acetal and elimination of the ethoxy substituent gratifyingly took place in a single pot. This demonstrates a very short and stereoselective sequence for the synthesis of the 2-hydroxymethyl-4-deoxypentenomycin derivative **11** in five steps in an overall yield of 41% starting from the tetrabromonorbornyl derivative **6** (Scheme 2).

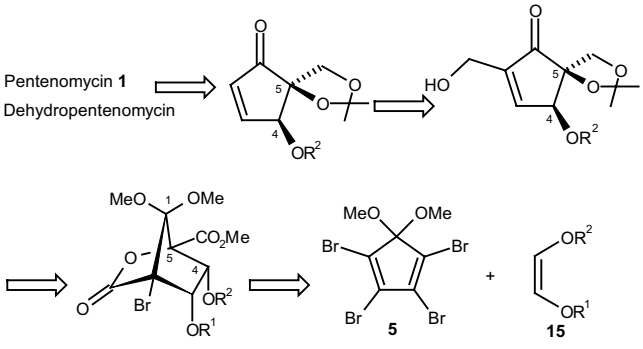
The formation of cyclopentanoid derivative **10** with retention of stereochemistry at C-2 via both the pathways (**8**→**9**→**10** and **8**→**10**) rules out an S_N2 pathway and reveals that an electron-transfer radical mechanism is perhaps operative during LAH reduction of bromolactone **8**.[9] A plausible mechanism for the LAH reduction of **8** is depicted in Scheme 3. The S_N2 reaction at the sterically hindered C-2 carbon as shown in **12** is apparently not feasible. The formation of **10** could be



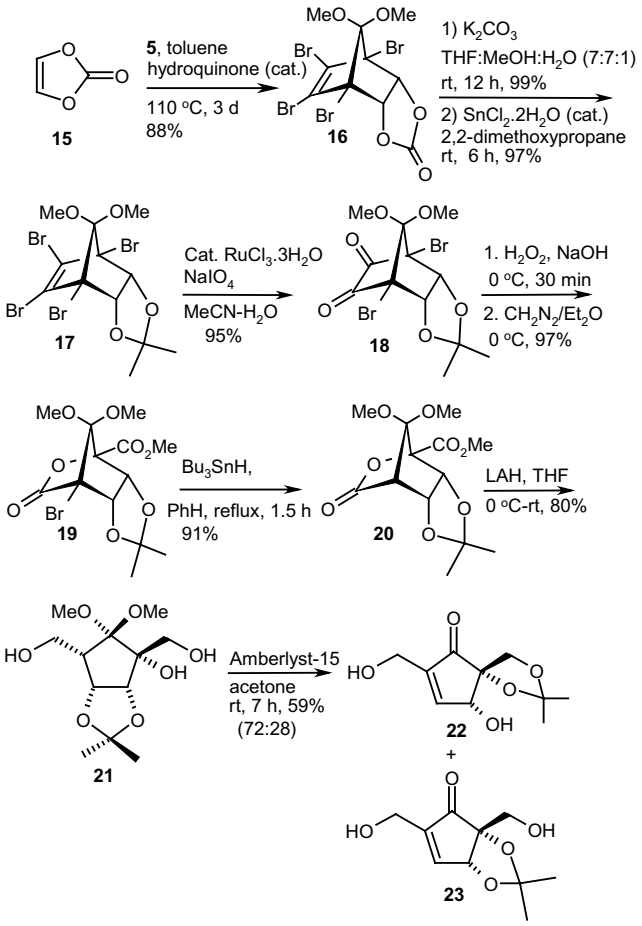
Scheme 3. SET mechanism in the LAH reduction of bromolactone **8**.

explained on the basis of a SET pathway involving an electron transfer from LAH to an intermediate **12**, formed from **8**, to generate the corresponding radical anion. On losing a bromide ion, this radical anion would produce radical species **13**, which then abstracts a hydrogen atom to give **10**. Due to chelation, hydrogen abstraction takes place from the β-face only to give a single product. However, at this stage, it is difficult to rule out an alternative pathway via formation of the epoxide **14** from **12** and subsequent epoxide opening, involving two inversions, eventually leading to **10** with net retention of stereochemistry.

At this juncture we wanted to install the hydroxyl group at C-4, a required feature of the pentenomycin structure. Preliminary attempts using SeO_2 led to an intractable mixture of products. To avoid the difficulties encountered during allylic oxidation we decided to explore the inherent flexibility of our synthetic scheme to incorporate the C-4 hydroxyl group at an early stage by choosing dienophiles of type **15** as presented in the retrosynthetic analysis (Scheme 4). The key feature of the retrosynthesis shown is to establish the C-5 tertiary center as well as the C-4 stereocenter at an early stage in a stereoselective manner.



Scheme 4. Retrosynthetic analysis of pentenomycin.



Scheme 5. Synthesis of 2-hydroxymethylpentenomycin derivatives **22** and **23**.

Vinylene carbonate **15** was used as the dienophile of choice for carrying out the synthesis (Scheme 5). A Diels–Alder reaction between tetrabromodimethoxycyclopentadiene **5** and **15** furnished the *endo* adduct **16** in 88% yield. Since the carbonate is sensitive to subsequent steps, it was deprotected to the diol following a recent literature procedure[10] and then reprotected as acetonide **17**. We then performed the same sequence of reactions as depicted in Scheme 2. The acetonide **17** was oxidized to the yellow crystalline diketone **18** in near quantitative yield, which was further cleaved to furnish bromolactone **19** in 97% yield. It is important to note that although we characterized all the intermediates thoroughly, the reactions up to the bridged-lactone **19**, starting from the tetrabromo adduct **16**, could be carried out without any column chromatographic purification. The crude reaction mixtures were pure enough to be used directly in subsequent steps, which is highly gratifying in a multi-step synthesis. The reductive hydrodebromination of **19** followed by LAH reduction of the reduced lactone **20** furnished the polyhydroxylated cyclopentanoid derivative **21** (Scheme 5).

Highly oxygenated cyclopentanoid **21** is a useful template that could serve as a potential advanced intermediate in the syntheses of densely functionalized cyclopentanoids. The requisite tertiary center was acquired in a stereoselective manner and this advanced intermediate contains all the vital features of pentenomycin at C-1, C-4, and C-5. Once again, to our delight, subjecting the cyclopentanoid **21** to Amberlyst-15 in acetone furnished the products **22** and **23**, derived from four reactions that take place in a single pot: (i) protection of the vicinal diol, (ii) acetonide deprotection, (iii) deprotection of the dimethyl acetal, and finally, (iv) elimination of the hydroxy functionality leading to the formation of 2-hydoxymethylpentenomycin derivatives **22** and **23** in a ratio of 72:28 in 59% yield (Scheme 5).

We have accomplished a new synthesis of 2-hydroxymethyl-4-deoxypentenomycin derivative **11**, in a very short and stereoselective sequence of five steps in an overall yield of 41% starting from the tetrabromonorbornyl derivative **6**. The functionalized pentenomycin derivatives **22** and **23** were similarly synthesized very efficiently, avoiding laborious chromatographic purifications for the major part, with an overall yield of 38% starting from the tetrabromonorbornyl derivative **16**.

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