Communications

Prins Desymmetrization of a C_2-Symmetric Diol: Application to the Synthesis of 17-Deoxyroflamycoin

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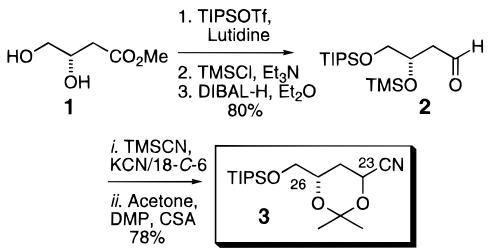
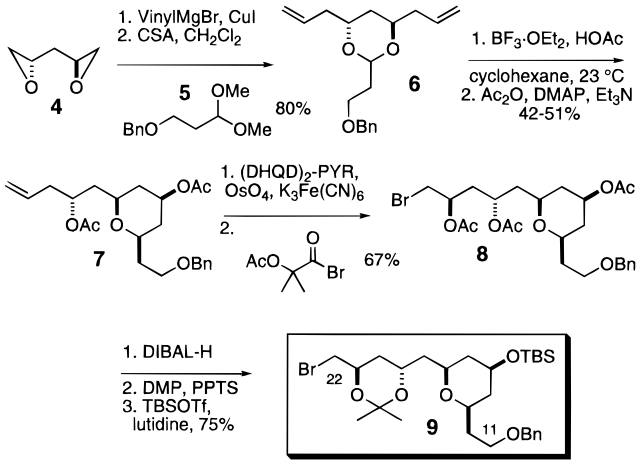
Roflamycoin is an ion-channel-forming polyene macrolide antibiotic that shows significant antifungal activity.[1,2] We recently reported the first total synthesis of roflamycoin.[3] One of the principle stumbling blocks in that synthesis was the introduction of the acid-labile hemiacetal ring. We were interested in preparing analogs of roflamycoin to evaluate the structural requirements for ion-channel activity, and it was clear that the presence of the hemiacetal ring would make analog synthesis more difficult. Is the hemiacetal ring really necessary for biological activity? Amphotericin B analogs in which the hemiacetal position is modified range from equipotent to less active by a factor of 16 in a fungistatic assay.[4] Presumably, the hemiacetal group in roflamycoin plays a structural role by defining the conformation in one of the two turn regions of the macrocycle, but that role could also be played by an appropriately substituted tetrahydropyran ring. The tetrahydropyran analog of roflamycoin would not show the acid sensitivity of the natural product and would have a clearly defined structure as there could be no possible equilibration between the ketone form and the two possible hemiacetal forms that is possible in the case of roflamycoin. Thus, 17-deoxyroflamycoin was selected as the first roflamycoin analog for synthesis and biological evaluation.

Natural roflamycoin was assembled from three segments, a C11−C26 bromide, C23−C26 cyanohydrin acetonide **3**, and C27−C35 cyanohydrin acetonide **12**.[3] The two latter components could be reused in a synthesis of 17-deoxyroflamycoin, and a new C11−C26 tetrahydropyran segment (**9**) would be substituted for the original bromide. The TIPS-protected cyanohydrin acetonide **3** is a key building block in the synthesis in that it is first alkylated with the C11−C26 bromide and then converted into C26-iodide **11** for subsequent alkylation of nitrile **12**. Thus, compound **3** is a four-carbon syn-1,3-diol synthon that can be used repeatedly to build up a polyol chain and is the linchpin in the convergent roflamycoin strategy.[5] Cyanohydrin acetonide **3** was prepared as a single enantiomer from methyl (*S*)-3,4-dihydroxybutyrate, **1**, itself available in two steps from (*S*)-malic acid (Scheme 1).[6] Sequential silylations and reduction gave aldehyde **2**, which was treated with TMSCN and KCN/18-crown-6 catalysis followed in one pot by acetonide protection to give cyanohydrin acetonide **3**. Preparation of compound **3** required six steps and proceeded in 32% overall yield from (*S*)-malic acid.

Scheme 1



Scheme 2



Synthesis of 17-deoxyroflamycoin required substituting C11−C22 tetrahydropyran segment **9** for the protected C17−ketone segment used in the synthesis of natural roflamycoin.[3] The synthesis of tetrahydropyran **9** is designed around an unusual Prins cyclization−desymmetrization reaction outlined in Scheme 2.[7] Desymmetrization of a C_2-symmetric substrate requires selective monofunctionalization, and an intramolecular Prins cyclization automatically generates a monofunctionalized product.[8] Diepoxide **4** was reacted with vinyl Grignard and catalytic CuI to give (4*R*,6*R*)-nona-1,8-diene-4,6-diol.[9] Acetal exchange with **5** gave the cyclic acetal **6** in 80% overall yield. Intramolecular Prins cyclization of **6** under conditions optimized for acetate trapping[10] gave tetrahydropyran **7** in 42−51% yield. The relatively low yield in the cyclization was due to the presence of the benzyl ether: the corresponding acetaldehyde acetal cyclized in 80% yield under the same conditions.[11] The final stereogenic centers were introduced by Sharpless asymmetric dihydroxylation, which gave a ca. 8:1 mixture of stereoisomers.[12,13] Monobromide formation using Moffatt's reagent,[14] followed by standard reprotection chem-

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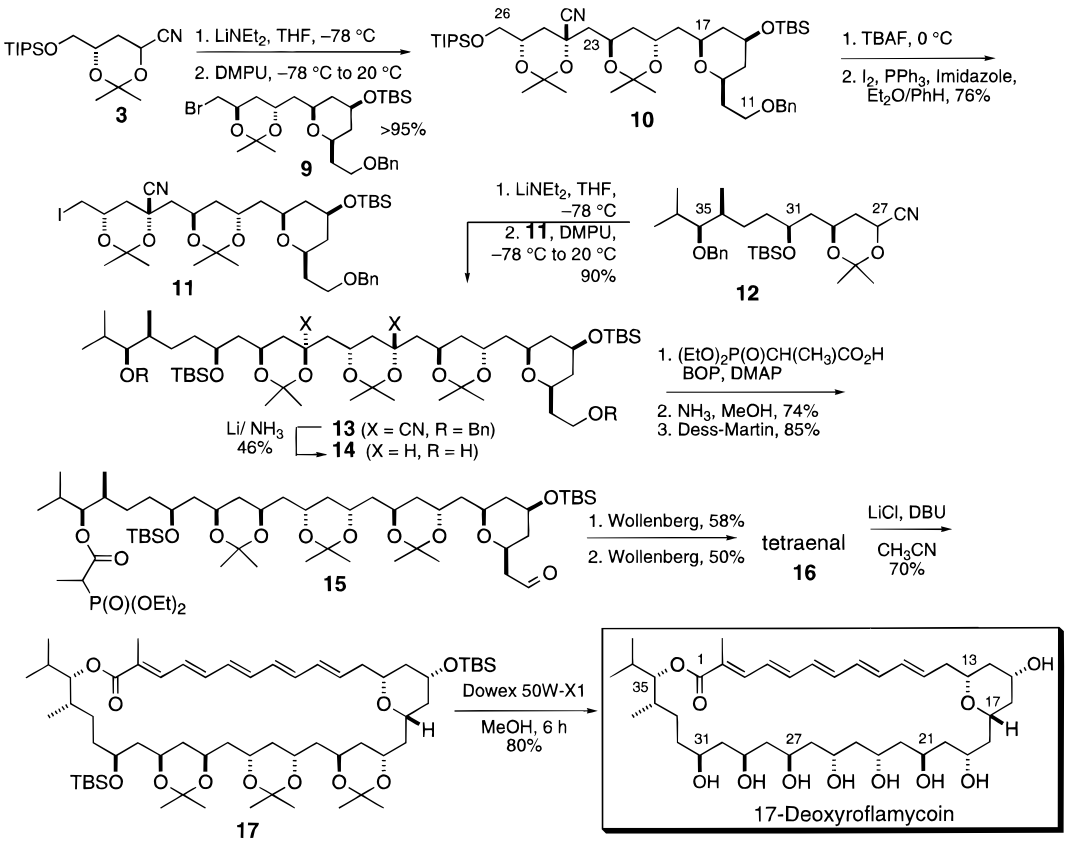
Scheme 3



istry, gave the tetrahydropyran **9** in good overall yield.[13] The key Prins desymmetrization reaction allowed tetrahydropyran **7** to be prepared as a single stereoisomer in just three steps from diepoxide **4**, and the C11−C22 building block **9** was prepared in only eight steps from diepoxide **4**.

The synthesis of 17-deoxyroflamycoin is illustrated in Scheme 3. The synthetic plan closely follows that used in the total synthesis of natural roflamycoin.[3] The anion of nitrile **3** (2.1 equiv) was alkylated with bromide **9** to give **10** in almost quantitative yield. Deprotection and iodination[15] of **10** gave the C26 iodide **11** that was ready for the second alkylation reaction. Alkylation of 2.6 equiv of the anion from **12** with **11** gave dinitrile **13** in 90% yield, and reductive decyanation removed the nitrile and benzyl groups to give protected polyol **14** as a single stereoisomer. Phosphonopropionate ester synthesis followed by oxidation gave the aldehyde **15**, and elaboration using two iterations of Wollenberg's procedure gave the tetraenal **16**.[3,16] Roush−Masamune cyclization gave an excellent yield of the pentaene macrocycle **17**, and a simple acid-catalyzed deprotection gave 17-deoxyroflamycoin in 80% yield. The NMR spectra of 17-deoxyroflamycoin were very similar to those of natural roflamycoin and showed the expected deviations due to the absence of the C17 oxygen atom. MS data, HPLC mobility, and the UV spectrum of 17-deoxyroflamycoin were all consistent with the assigned structure.

Roflamycoin shows antifungal activity with minimum inhibitory concentrations (MIC) of 32 and 64 μg/mL against *Candida albicans* and *Cryptococcus neoformans*, respectively, in disk-diffusion assays.[17] Synthetic 17-deoxyroflamycoin was not active against either of these organisms at 1280 μg/mL. Although the conformations of roflamycoin and 17-deoxyroflamycoin are very similar as judged by molecular modeling and the similarity between their NMR spectra, the latter compound is essentially inactive. The absence of the C17 oxygen shuts down fungistatic activity, but the question still remains whether the loss of biological activity is due to a loss of ion-channel activity. We are currently investigating this point. The C17 oxygen is crucial for antifungal activity, and future roflamycoin analogs will incorporate this functionality.

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Supporting Information Available: Experimental details for the preparation of 17-deoxyroflamycoin (14 pages).

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