Realisation of highly stereoselective dihydroxylation of a cyclopentene in the synthesis of (−)-aristeromycin

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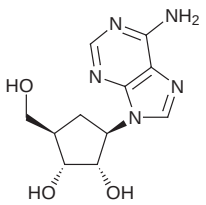
A 2-furyl group was used as a synthetic equivalent of the CH_2OH at the 4′ position of aristeromycin, and dihydroxylation of the cyclopentene possessing the furyl group proceeded highly stereoselectively to produce the key diol for the synthesis of (−)-aristeromycin.

Aristeromycin **1** is a carbocyclic analogue of adenosine and its unique biological properties and structure have attracted considerable interest among organic chemists. Total syntheses of **1** have been reported and are summarised in several reviews.[1] In order to improve or use the biological properties of **1**, analogues of **1** have also been synthesised. Among these syntheses, the strategy of utilizing the monoacetate of *cis* cyclopent-4-ene-1,3-diol (*i.e.* **2**)† as the starting material, which



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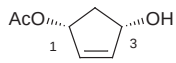

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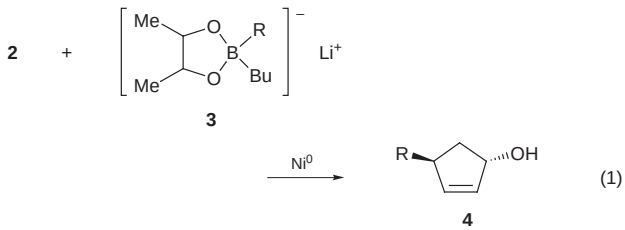
was originally reported by Deardorff,[2] is attractive especially in that (i) both enantiomers are readily available[3] and (ii) installation of the substituents onto the cyclopentene ring of **2** simply accomplishes a synthesis of **1**. Several groups have published syntheses of **1** along this line, and the efficiency in installing the nitrogen-containing moiety and "CH_2OH" group has also been improved.[4] The stereoselectivity of the dihydroxylation, however, still remains at low levels.[2,4,5] Recently, an explanation for the low selectivity of the dihydroxylation was proposed by Katagiri.[6] Namely, the cyclopentene possessing the requisite 'CH_2OR' group at the 4′ position (aristeromycin numbering) and a heteroatom at the 1′ position adopts minor and major conformers, and the dihydroxylation of the latter inevitably produces a mixture of stereoisomeric diols. Therefore, a new approach, whereby dihydroxylation would take place stereoselectively, is required in order to use the convenient monoacetate **2** as a starting material for **1**.

Recently, we reported a nickel-catalysed coupling reaction of **2** and lithium borates **3**, where aryl, furyl and alkenyl groups (R) on the borates can be transferred onto **2** (eqn. 1).[7] This reaction proceeds stereo- and regio-selectively to furnish *trans* 1,4-products **4**, for the first time, as the major products. These groups (R) are all candidates for 'CH_2OR' and are bigger than 'CH_2OR'. Consequently, even in the *undesired* conformer of the cyclopentene possessing such a group (R) and a nitrogen atom at the 4′ and 1′ positions, respectively, the approach from the β-face would be prevented more effectively than that with CH_2OR as the R group. Our proposal is illustrated in Fig. 1. To examine the above idea, we chose the furyl group (R = 2-furyl) as a 'CH_2OR' precursor and succeeded in the stereoselective synthesis of acetonide **11**. Hydrolysis of **11** to aristeromycin has already been established.[4b,8] In addition, **11** is an important starting compound for the synthesis of analogues and supermolecules containing aristeromycin.[9]



The synthetic route is summarised in Scheme 1. The cyclopentenol **4a** was prepared from (1*R*)-acetate **2** (> 95% ee)[3c] and lithium 2-furylborate **3** (R = 2-furyl). Reaction of **4a** with $(PhO)_2P(O)N_3$[10] proceeded selectively to afford **5**‡ as the sole product. The key dihydroxylation was examined under various conditions and the results are summarised in Table 1. A 4 : 1 ratio of the desired product **6** and the stereoisomer **12** was obtained in good yield when the reaction was carried out at room temperature (entry 1). Although the ratio was definitely higher than previously reported ones, it was still low from a synthetic point of view. Fortunately, reaction at lower temperature (0 °C) resulted in a substantially higher ratio of 14 : 1 (entry 2). Since the observed coupling constant between Ha and Hc of **5** (J_{ac} = 5.4 Hz) indicates that **5** does take both the desired and undesired conformers according to Katagiri,[6] it is clear that the observed high stereoselectivity is provided by the furyl group. Use of acetone as solvent slightly decreased the ratio (entry 3). Double diastereoselectivity between chiral **5** and the Sharpless reagent (AD-mix-α or –β),[11] was also examined. Unfortunately, better selectivity (*i.e.* ratio of **6** to **12**) was not attained (entries 4 and 5). A reagent lacking the chiral ligand for AD-mix resulted in a similar ratio (entry 6).[12]

Since separation of the diols **6** and **12** by chromatography was not an easy task due to their similar mobility on TLC, the mixture was transformed into the corresponding acetonides **7** and **13**, which were easily separated by chromatography. The furyl group of **7** was then transformed into a CO_2Me group by oxidation using $NaIO_4$ and $RuCl_3$ catalyst followed by esterification with CH_2N_2 to afford **8** in 80% yield. Treatment of **8** with $LiAlH_4$ effected reduction of the ester and the azide

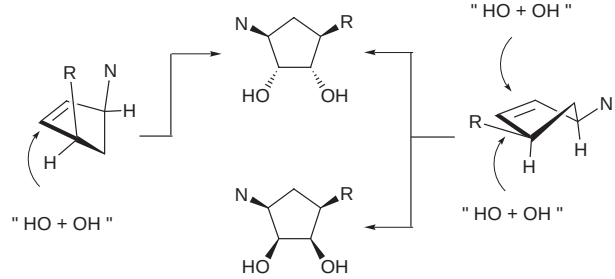
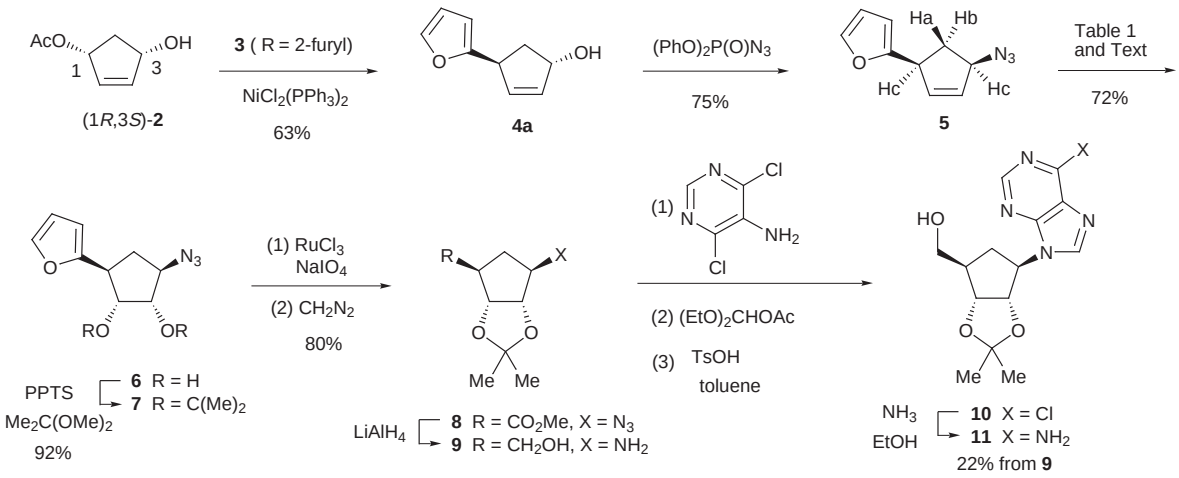


Fig. 1 Desired (left) and undesired (right) conformers for dihydroxylation.

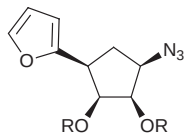


Scheme 1

Table 1 Dihydroxylation of **5**

Entry	Reagent	Conditions	Ratio[a] **6**:**12**	Yield (%)[b]
1	OsO_4,[c] NMO	MeCN–Bu^{t}OH–H_2O (4:1:1), room temp., 16 h	4:1	71
2	OsO_4,[c] NMO	MeCN–THF–Bu^{t}OH–H_2O (4:2:1:1), 0 °C, 7 h	14:1	72
3	OsO_4,[c] NMO	Acetone–THF–H_2O (8:4:1), 0 °C, 7 h	11:1	65
4	AD-mix-α	Bu^{t}OH–H_2O (1:1), 0 °C, 24 h	3:1	—[d]
5	AD-mix-β	Bu^{t}OH–H_2O (1:1), 0 °C, 24 h	6:1	34
6	OsO_4,[e] $K_3Fe(CN)_6$, K_2CO_3	Bu^{t}OH–H_2O (1:1), 0 °C→ room temp., 24 h	4:1	—[d]

[a] Ratios were determined by ^{1}H NMR. [b] Isolated yields. [c] 3 mol%. [d] Not determined. [e] 1.25 mol%.



12 R = H
13 R = C(Me)$_2$

groups to afford **9**. The amino group of **9** was converted to a chloropurine moiety using the standard procedure. Finally, reaction of **10** with NH_3 gave the acetonide of aristeromycin **11**, whose ^{1}H NMR (300 MHz) spectrum was fully coincident with the reported data.[13] Use of EtOH for this transformation proved to be better than the standard solvent of MeOH since NH_3–MeOH gave the corresponding methoxide as a by-product. The deprotection of **11** to aristeromycin has already been published.[8]

Since high stereoselection in the dihydroxylation was achieved using the furyl group, it is possible that an aryl or alkenyl group may control the dihydroxylation and that such a group, after being installed onto the cyclopentene ring, can be transformed by taking advantage of their reactivity into various polyoxygenated side chains at the 4' position. These modifications are important for the next generation of carbocyclic sugars.

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Notes and references

† For convenience, one enantiomer is shown.

‡ *Selected data* for **5**: δ_H(300 MHz, $CDCl_3$) 1.93 (dt, *J* 14, 5.4, 1H), 2.76 (dt, *J* 14, 8.3, 1H), 3.92–4.00 (m, 1H), 4.41–4.49 (m, 1H), 5.91 (dt, *J* 5.7, 2.4, 1H), 6.04–6.10 (m, 2H), 6.30 (dd, *J* 3.0, 1.8, 1H), 7.34 (d, *J* 2, 1H).

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