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Stereoselective synthesis of (−)-ara-cyclohexenyl-adenine

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Abstract—A stereoselective synthesis leading to (−)-ara-cyclohexenyl-adenine is described. The synthesis starts from methyl-α-D-glucopyranose and involves an isomerization step, selective protection/deprotection chemistry, a Ferrier rearrangement and a Mitsunobu reaction. This is the first total synthesis of an enantiomeric pure ara-type cyclohexenyl nucleoside.

Modified nucleosides represent the most important class of antiviral compounds.[1,2] In the category of nucleoside analogues with a 'six-membered' carbohydrate mimic potent antiherpes activity has been found in the series of cyclohexenyl nucleosides.[3]

The synthesis of (±)-ara-cyclohexenyl-adenine[4] and of (±)-ribo-cyclohexenyl-adenine[5] has been described (Fig. 1). These nucleoside analogues were synthesized, likewise, because of their potential biological importance as antiviral agent. The obtained racemic mixtures[4,5] can be used for a first antiviral screening assay, but are neither useful for incorporation studies in oligonucleotides nor for enzymatic studies. The approach of separating a racemic mixture into enantiomers was less appealing for compound **1** as its total synthesis from furan and acrylic acid[4] had several drawbacks, a.o. the non-selectivity of protection–deprotection chemistry for the secondary alcohol groups and the time consumption and low yield of some reactions.

Therefore, we envisaged a stereoselective synthesis of compound **1**, starting from naturally occurring carbohydrates. Initially, our synthetic approach was based on the palladium catalyzed asymmetric allylic alkylation reaction, described for the synthesis of (+)- and (−)-cyclophellitol.[6] However, we were not very successful in carrying out this reaction in good and reproducible yields. The synthesis of the cyclohexenyl scaffold, which is used for the synthesis of the nucleoside analogues, is based on the work of Jung and Choe who synthesized

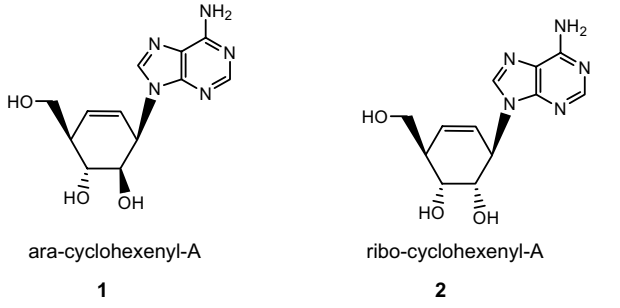

Figure 1. Structure of ara-cyclohexenyl-adenine and ribo-cyclohexenyl-adenine.

cyclophellitol from D-mannose.[7] Our variant on this carbohydrate-based approach starts from commercially available and inexpensive methyl-α-D-glucopyranose (**3**).

First, the 4- and 6-OH groups of methyl-α-D-glucopyranose were protected with a benzylidene group (Scheme 1), followed by a two-step selective benzoylation of the 2-OH group via a stannylidene intermediate.[8] The free 3-OH group was protected with the acid labile tetrahydropyranyl group. After removing the benzoyl protecting group in basic circumstances, the free 2-OH was oxidized to a keto function and converted into a methylene group using Wittig conditions. The intermediate keto compound **9** was not purified.

During the hydroboration reactions of **10** (Scheme 2), the tetrahydropyranyl group was partially removed to give a mixture of unprotected and protected compounds. Therefore, we preferred to change the 3-OH protecting group. The tetrahydropyranyl group was

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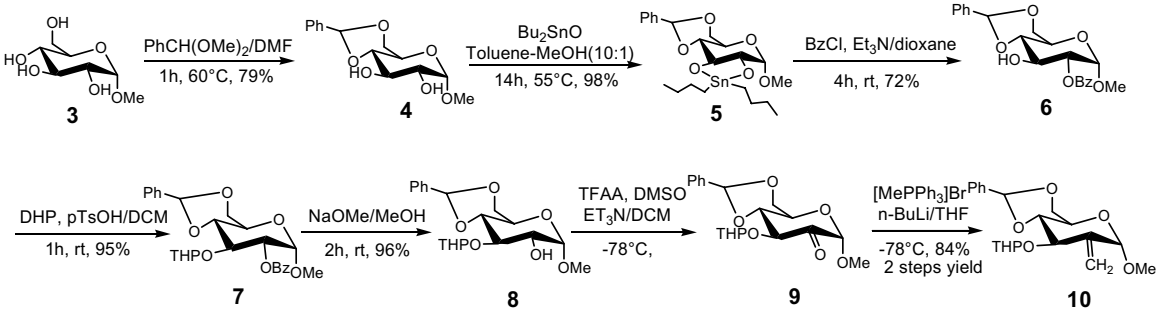
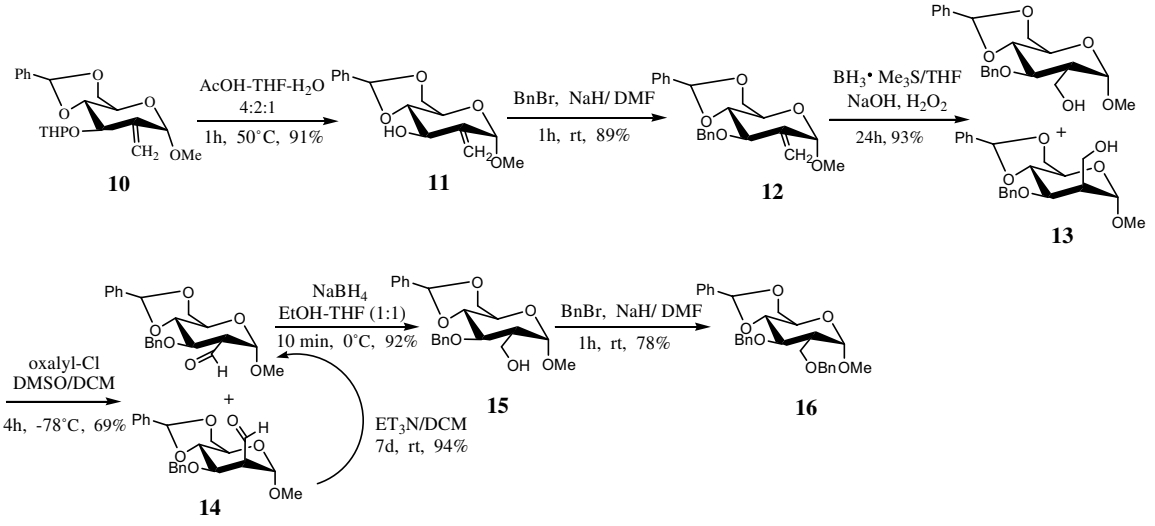
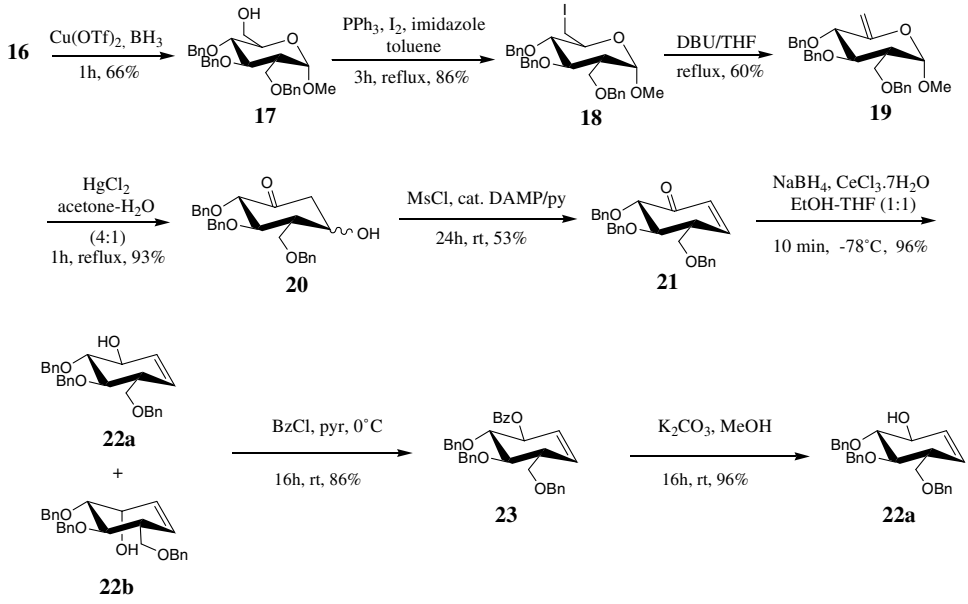


Scheme 1.

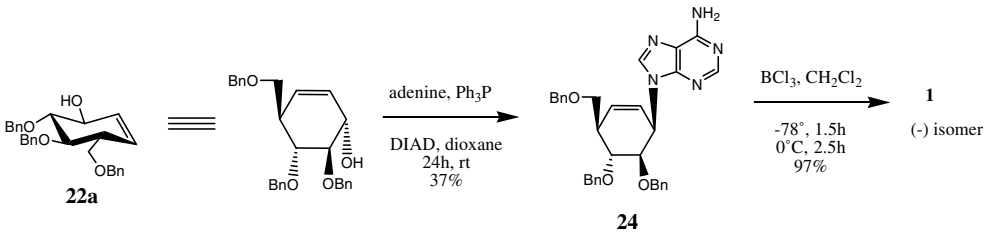


Scheme 2.



Scheme 3.

selectively removed using mild acidic conditions and reprotected using benzyl bromide/NaH to give compound **12**. Hydroboration of **12** gives a 1:1 mixture of diastereomers with a 2-hydroxymethyl group in the [*R*] or [*S*] configuration. Since we only need the compound with an equatorial hydroxymethyl group ([*R*] configura-



Scheme 4.

tion), we carried out an isomerization step to convert the 2-[*S*] stereogenic centre into a 2-[*R*] stereogenic centre. Therefore, the mixture of primary alcohols (**13**) was oxidized and the obtained mixture of aldehydes (**14**) was isomerized under mild basic conditions followed by reduction using sodium borohydride. This approach was previously described by Jung and Choe.[7] It should be noted that the success of this approach is highly dependent on the purity of the starting materials (otherwise the isomerization reaction is getting very slow). The primary hydroxyl group was protected with a benzyl group to obtain compound **16**.

Selective cleavage of the benzylidene-acetal bond was achieved using BH_3·THF and $Cu(OTf)_2$[9] (Scheme 3), without observing the formation of the 6-O-benzyl protected side compound.

This selective deprotection is needed to obtain the exocyclic methylene compound **19** by an iodination-elimination step (Scheme 3). The desired enone **21** is then obtained by a Ferrier rearrangement[7,10] followed by an elimination reaction. Selective reduction of the keto group of **21** was, however, not absolute and a mixture of two diastereoisomers **22a** and **22b** were obtained in a ratio of 94:6. As the separation of **22a** and **22b** by column chromatography is tedious, we preferred to protect the free HO group by benzoylation which resulted into a more easily separable mixture of compounds. Removal of the benzoyl protecting group of **23** yielded **22a**.

Introduction of the adenine base moiety was carried out under Mitsunobu type conditions[11] (Scheme 4) and all the benzyl protecting groups can be removed smoothly using BCl_3 in CH_2Cl_2.[12] The obtained ara-cyclohexyl-A is a mimic of a natural nucleoside in the D-configuration and shows an $[\alpha]_D$ value of −83.0 (CH_3OH, *c* 1).[13] When tested in the replicon system (HCV) the compound proved to be inactive.

In conclusion, the first stereoselective total synthesis of an ara-type cyclohexenyl nucleoside is described, starting from a commercially available carbohydrate.

References and notes

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13. *Compound* **1**: A 1 M solution of BCl_3 in CH_2Cl_2 (7.4 ml, 7.4 mmol) was added to a stirred solution of compound **24** (270 mg, 0.493 mmol) in CH_2Cl_2 (9.9 ml) at −78 °C. Stirring was continued under N_2 at −78 °C for 1.5 h. Then, the mixture was allowed to warm slowly to 0 °C over 2.5 h. Next, it was cooled again to −78 °C and MeOH was added (5 ml). After 5 min, the cooling was removed and the mixture was concentrated. The residue was concentrated three times from MeOH to remove all $B(OMe)_3$. The residue was chromatographed (CH_2Cl_2–MeOH: 4/1) to give compound **1** as a white, amorphous solid (132 mg, 97%). HRMS: 278.1238 ($M+H^+$), calcd: 278.1253. ^1H NMR (500 MHz, CD_3OD): δ 8.20 (s, 1H, H-2′ or H-8′), 8.16 (s, 1H, H-2′ or H-8′), 6.10 (ddd, $J = 1.4$, 2.6, 9.9 Hz, 1H, H-5), 5.85 (ddd, $J = 2.7$, 4.6, 9.9 Hz, 1H, H-6), 5.46 (m, 1H, H-1), 3.99 (dd, $J = 5.2$, 9.3 Hz, 1H, H-2), 3.91 (dd, $J = 4.0$, 10.6 Hz, 1H, H-7a), 3.84–3.89 (m, 2H, H-3, H-7b), 2.38 (m, 1H, H-4) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ 157.25, 151.60, 119.96 (C-4′, C-5′, C-6′), 153.46, 142.61 (C-2′, C-8′), 135.82 (C-5), 124.09 (C-6), 72.33 (C-2), 68.69 (C-3), 62.73 (C-7), 54.57 (C-1), 47.99 (C-4) ppm. $[\alpha]_D$ −83.0 (CH_3OH, *c* 1). Elem. Anal. Calcd for $C_{12}H_{15}N_5O_3$ (MW 277.1): C, 51.96; H, 5.46; N, 25.27. Found: C, 51.87; H, 5.40; N, 25.31.