Synthetic Methods Hot Paper

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Synthesis of (Carbo)nucleoside Analogues by [3+2] Annulation of Aminocyclopropanes**

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Abstract: *(Carbo)nucleoside derivatives constitute an important class of pharmaceuticals, yet there are only few convergent methods to access new analogues. Here, we report the first synthesis of thymine-, uracil-, and 5-fluorouracil-substituted diester donor–acceptor cyclopropanes and their use in the indium- and tin-catalyzed [3+2] annulations with aldehydes, ketones, and enol ethers. The obtained diester products could be easily decarboxylated and reduced to the corresponding alcohols. The method gives access to a broad range of new (carbo)nucleoside analogues in only four or five steps and will be highly useful for the synthesis of libraries of bioactive compounds.*

The natural nucleosides constitute the building blocks of DNA and RNA. The interaction of enzymes and other biomolecules with nucleosides is essential for the regulation of genetic expression and cell replication. Therefore, the nucleoside scaffold constitutes a privileged structure in medicinal chemistry (Figure 1).[1] In addition to bioactive natural products, such as the antiviral and antibiotic aristeromycin (**1**), more than 45 FDA-approved drugs are nucleoside analogues. Besides only slightly modified analogues, such as cytarabine (**2**) and telbivudine (**3**), more elaborated compounds derived from thymine have been successful, such as the carbonucleoside stavudine (**4**), the anti-HIV front drug azidothymidine (**5**), and the fluorinated floxuridine (**6**). Nevertheless, resistances are emerging in viral infections, and less toxic anti-cancer agents would be highly desirable, calling for the development of new bioactive nucleoside analogues.

The synthesis of nucleoside analogues has been the focus of intensive effort since several decades.[2] Nevertheless, most methods are based on a linear approach involving first the synthesis of a ribose analogue followed by introduction of the nucleobase, either by formation of the C–N bond using a substitution reaction from an acetate **I** (Vorbrüggen reaction)[2b] or a condensation reaction from an aminoglycoside **II**[2a] (Scheme 1A). This approach is efficient if the targeted analogue is similar to a natural ribose derivative, but can involve a long multi-step sequence if a more elaborate scaffold is desired.[3] This is particularly true for carbonucleoside analogues, for which elegant synthetic approaches involving ring-closing metathesis,[3a] Pauson–Khand[3b] or desymmetrization starting from cyclopentadiene and proceeding via diols,[3c–e] Vince lactam,[3f,g] or nitroso cycloaddition reactions[3h] have been developed.

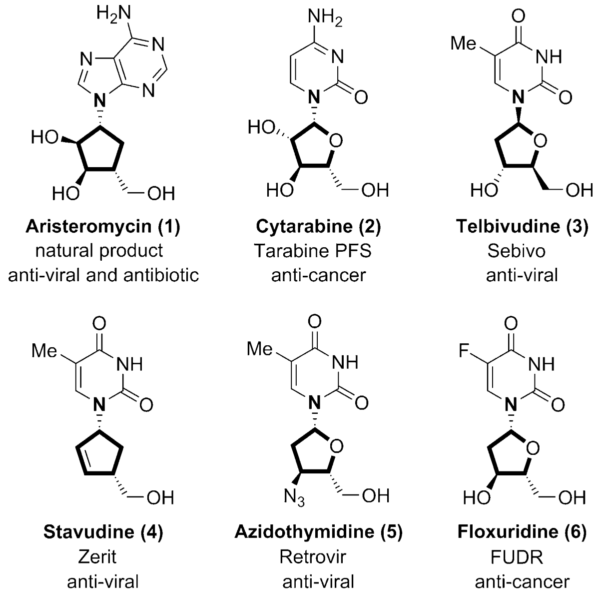

Figure 1. Natural and synthetic bioactive nucleoside analogues.

Our group has introduced the use of imide-substituted diester cyclopropanes in [3+2] annulation reactions.[4] With this new class of donor–acceptor cyclopropanes,[5] access to intermediates of type **II** became possible (Scheme 2B). Nevertheless, the efficiency of the annulation process was mitigated by the necessary removal of the phthalimide group followed by DNA-base construction, which would add several steps to the synthetic sequence. Furthermore, the deprotection of the pththalimide group could not be achieved on the tetrahydrofurylamines.

If a DNA-base could be used as amino substituent on the cyclopropane, a more efficient synthesis would become possible (Scheme 1C). Herein, we report the successful implementation of this strategy, including: 1) the first efficient three-step synthesis of thymine/uracil donor–acceptor cyclopropanes, 2) their successful [3+2] cycloaddition with enol ethers, aldehydes and ketones, and 3) their further derivatization to access hydroxylated analogues.

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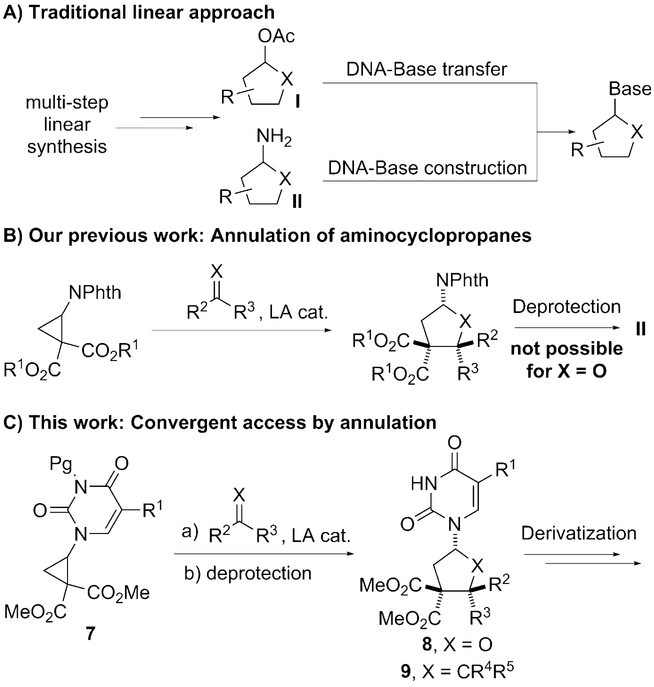
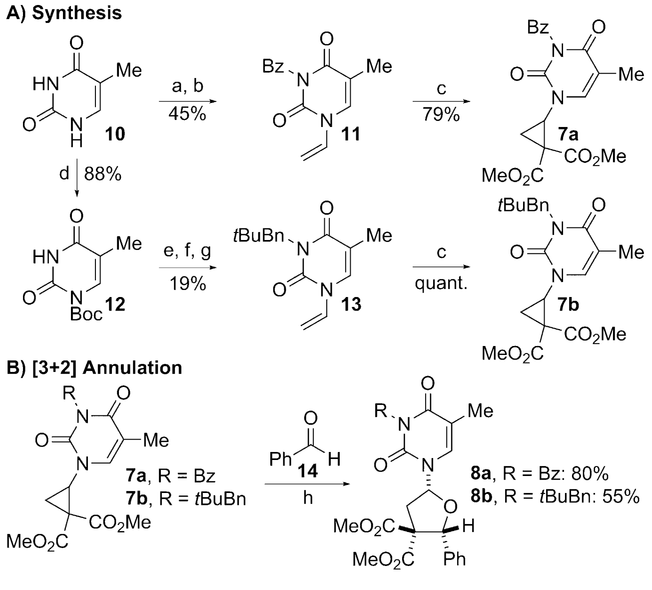
In our work with phthalimide-substituted cyclopropanes, modulating the electronic density on the nitrogen was essential for a successful annulation reaction. Based on the fact that thymine and phthalimide have similar pK_a values (8.3 and 9.9, respectively), we started our investigations with thymine-substituted cyclopropanes (Scheme 2 A). Cyclopropane **7a** was easily accessed by selective mono-benzoylation of thymine (**10**),[6] followed by Pd-catalyzed vinylation under slightly modified reported conditions[7] and cyclopropanation using Du Bois' Rhodium–espino complex.[8] As N3-selective *tert*-butylbenzylation was not possible, a longer sequence involving temporary Boc protection of the N1 nitrogen was necessary in the case of cyclopropane **7b**.[9]



Scheme 1. A) Traditional approach, B) our previous work, and C) new strategy to access (carbo)nucleoside analogues. Phth = Phthamoyl, Pg = protecting group, LA = Lewis acid.

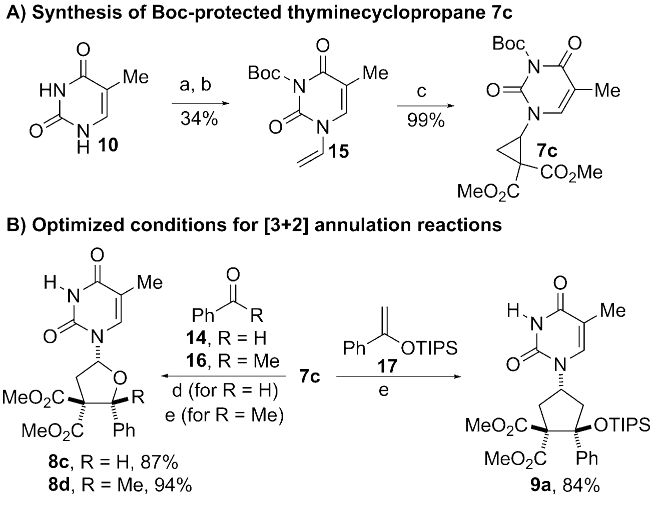


Scheme 2. A) Synthesis of aminocyclopropanes **7a** and **7b** and B) first attempts of [3+2] annulation. Reaction conditions: a) BzCl, pyridine, CH_3CN, 69%. b) 4 mol% Na_2PdCl_4, vinylacetate, 80 °C, 65%. c) 0.2 mol% $[Rh_2(esp)_2]$, diazodimethylmalonate, CH_2Cl_2. d) Boc_2O, DMAP, CH_3CN. e) *t*BuBnBr, NaH, DMF, 0 °C, quant. f) K_2CO_3, MeOH, 81%. g) 4 mol% Na_2PdCl_4, vinylacetate, 80 °C, 23%, h) 5 mol% $Fe_2O_3{\cdot}Al_2O_3$, CH_2Cl_2.

With aminocyclopropanes **7a** and **7b** in hand, we first examined the iron-catalyzed [3+2] annulation reaction with benzaldehyde (**14**) (Scheme 2 B).[4c] The reaction was successful for both substrates **7a** and **7b**. Nevertheless, we were never able to remove either of the protecting groups on the nitrogen of thymine. We decided consequently to turn to the easily removable *tert*-butoxy carbonyl (Boc) protecting group.

Due to the incompatibility of the Boc group with the vinylation conditions, a method to access selectively N1-vinyl thymine prior to introduction of the Boc group was required. All the reported methods to access this substrate proceeded with low yield and reproducibility in our hands.[10] Nevertheless, we discovered that N1-selective Pd-catalyzed vinylation was possible in 45% yield from thymine itself in presence of trimethylsilyltriflate (TMSOTf) as additive (Scheme 3 A). Boc-protection[11] and cyclopropanation then proceeded in good yields, giving access to **7c** in only three steps.

First attempts towards the annulation of **7c** with benzaldehyde (**14**) using an iron catalyst gave the desired product only in low yield (< 27%). This was due to loss of the Boc protecting group during both reaction and purification. Changing to $In(OTf)_3$ as catalyst[12] and direct Boc deprotection of the crude product by heating in ethanol at 70 °C afforded the desired NH-free product **8c** in 87% yield (Scheme 3 B). Aminocyclopropane **7c** could also be used in other [3+2] annulation processes involving either ketones[4b]



Scheme 3. A) Synthesis of aminocyclopropanes **7c** and B) optimized conditions for [3+2] annulation reactions. Reaction conditions: a) 4 mol% $Pd(OAc)_2$, vinylacetate, TMSOTf, 70 °C, DMF, 45%. b) Boc_2O, DMAP, CH_2Cl_2, 75%. c) 0.02 mol% $[Rh_2(esp)_2]$, diazodimethylmalonate, CH_2Cl_2. d) 20 mol% $In(OTf)_3$, CH_2Cl_2; then EtOH, 70 °C. e) 10 mol% $SnCl_4$, CH_2Cl_2, −20 °C; then EtOH, 70 °C.

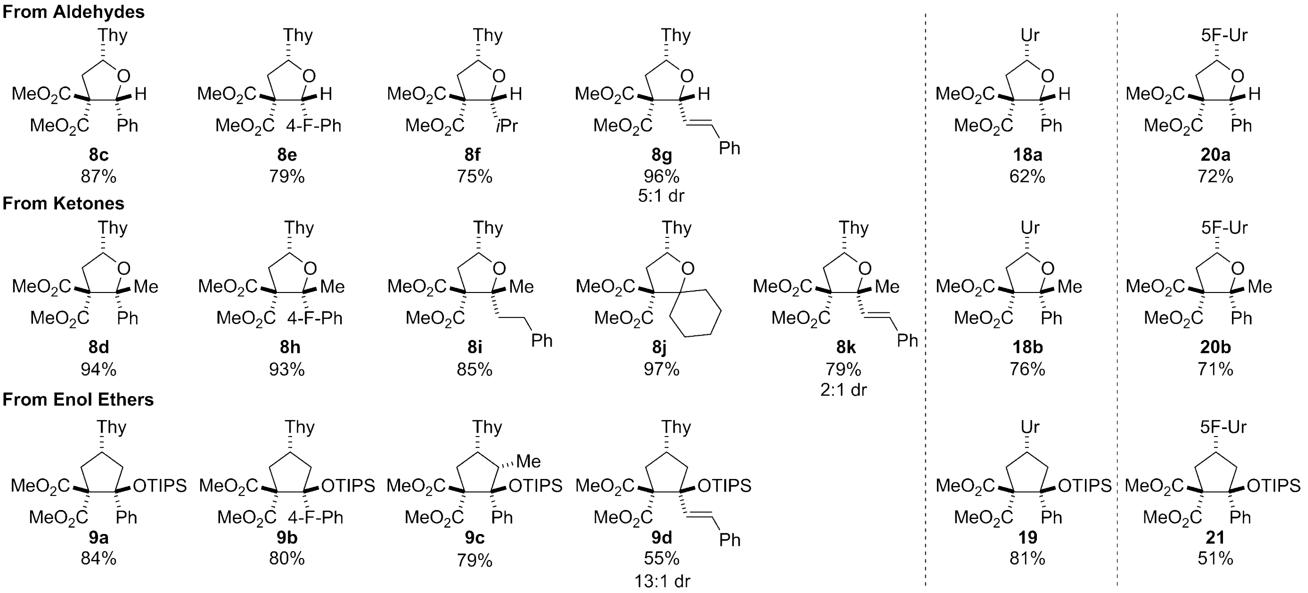
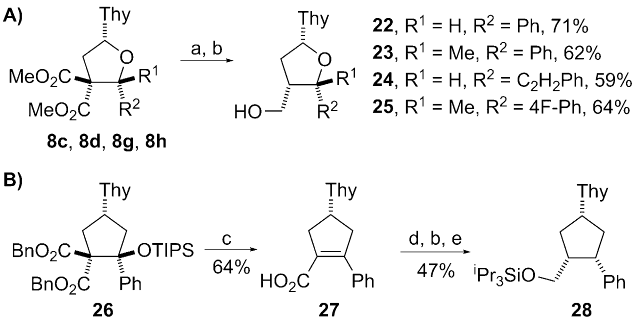


Figure 2. Scope of the [3+2] annulation reaction. The reactions were run on 0.40 mmol scale using the conditions of Scheme 3 and isolated yields after column chromatography are given. See Supporting Information for full experimental details. Thy = thymine, Ur = uracil, 5F-Ur = 5-fluorouracil.

or silyl enol ethers[4a] to give tetrahydrofuryl amine **8d** and cyclopentyl amine **9a** in 94% and 84% yield, respectively. In this case, the lower reactivity of **7c** compared with phthalimide-substituted cyclopropanes required the use of a higher temperature (−20 instead of −78 °C) in the tin-catalyzed process.

We then turned to the investigation of the scope of the [3+2] annulation (Figure 2).[13] The reaction was successful in the case of aromatic (products **8c** and **8e**), aliphatic (products **8f**) and vinylic aldehydes (product **8g**). Excellent diastereoselectivity (> 20:1) was observed, except for product **8g** (5:1). The same was also true for ketones (products **8d** and **8h–k**), although the diastereoselectivity was lower for vinylic ketones (product **8k**). With enol ethers, more substituted derivatives, such as tetrasubstituted cyclopentane **9c**, could also be accessed. The [3+2] annulation product was obtained in 55% yield with a dienol ether as partner (product **9d**). Finally, modification of the thymine substituent was also examined. Both cyclopropanes derived from uracil and 5-fluorouracil could also be used in the annulation reaction with aldehydes, ketones, and enol ethers (products **18–21**).[14]

For most nucleoside drugs enzymatic phosphorylation of a hydroxy group is an important step in the mode of action.[1] Modification of the obtained products to include hydroxy group(s) would be consequently highly rewarding in the quest of new bioactive compounds. To reach this goal, saponification followed by decarboxylation of diester **8c** gave access to a single isomer of the corresponding carboxylic acid,[15] which could be reduced to primary alcohol **22** in 71% overall yield (Scheme 4A). The same sequence was also successful for styrene derivative **8g**, giving the corresponding alcohol **24** in 59% yield. Products **8d** and **8h** could also be converted into the desired alcohols **23** and **25** in 62 and 64% yield respectively. In the case of the carbonucleoside analogues, dibenzylester cyclopentylamine **26** could be converted into the corresponding diacid by hydrogenation.[16] Heating the neat crude diacid to 80 °C led then to decarboxylation and silyl ether elimination to give acid **27** (Scheme 4B). Pd-catalyzed hydrogenation followed by acid reduction gave the corresponding unstable saturated alcohol, which was isolated as silyl ether **28**.



Scheme 4. Modification of A) the tetrahydrofuran and B) the cyclopentane products. Reaction conditions: a) KOH, MeOH. b) $BH_3 \cdot SMe_2$, THF. c) 10% Pd/C, 1 atm H_2, EtOH, 57 °C, then neat, 80 °C. d) 5% Pd/C, 1 atm H_2, EtOH, 85%. e) iPr_3SiCl, DMF, imidazole, 55% over two steps.

In conclusion, we have reported the first synthesis of nucleobase-substituted diester cyclopropanes and their use in cycloaddition with aldehydes, ketones, and enol ethers. This new transformation gave access in a few steps to important nucleoside analogues, which were easily modified to give hydroxylated derivatives. Future work will focus on the synthesis of a broader range of analogues to build up a chemical library for biological testing and extending the scope of the reaction to the purine class of nucleobases.

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[11] Cyclopropanation in absence of the Boc protecting group was not successful.

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[13] The stereochemistry of compounds **8e**, **8i**, and **9a** has been determined by X-ray crystallography. CCDC 995573, 994735, and 994948 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The stereochemistry of the other compounds has been assigned by analogy or NMR experiments. See Supporting Information for further details.

[14] The uracil- and 5-fluorouracil-substituted cyclopropanes were obtained using a similar synthetic sequence. In the case of the 5-fluorouracil derivatives, it was necessary to use a more stable benzoyl protecting group. See Supporting Information for further details.

[15] The diastereoselectivity in the decarboxylation step was usually high (>5:1, >20:1 for **8c**). The products are obtained under kinetic control, but the rationalization of the high selectivity will require further investigations.

[16] Cyclopentylamine **26** was obtained in 94% yield from the [3+2] annulation of the corresponding dibenzylester-substituted cyclopropane with enol ether **17**.