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Concise synthesis of five-membered ring carbasugars based on key ring-closing metathesis

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ABSTRACT

A simple and efficient approach to the synthesis of five-membered ring carbasugars is achieved starting from readily available (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**) through key ring-closing metathesis (RCM) in high overall yield. We have also confirmed its viability by preparing the core bicyclo [3.1.0] hexane framework presented in the potent antiviral nucleoside N-MCT **1**.

Highly functionalized cyclopentanes appear as structural elements in biologically interesting compounds such as carbocyclic nucleosides[1] like aristeromycin[2] and carbovir[3] and in their own right as glycosidase inhibitors like the mannostatins,[4] allosamizoline,[5] trehazolin[6], and the synthetic Merrell Dow cyclopentylamine[7] (Fig. 1). These oxygenated cyclopentanes may be seen as carbocyclic sugar analogues, also known as carbasugars,[8] in which the ring oxygen of a furanose derivative has been replaced by a methylene group. Carbasugars lack the acetal function which is the characteristic of common monosaccharides. As carbohydrate analogues, they are stable to enzymatic hydrolysis in biological systems, and often display a range of biological activities, particularly as an antiviral agent.[9] A representative carbocyclic nucleoside analogue North-methanocarbathymidine (N-MCT **1**, Fig. 1), incorporating a pseudosugar with a fixed Northern conformation, exhibits potent antiherpetic activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2).[10]

After the pioneering synthesis of racemic pseudo-*R*-talopyranose (the first reported carbasugar) by McCasland in 1966,[11] numerous researchers have been challenged by the chemical synthesis of carbasugars and their efforts have resulted in the assembly of a growing repertoire of constructs possessing the most diverse structural and stereochemical arrangements. Two main approaches to the preparation of carbasugars have been either the synthesis using carbohydrates as starting materials to give optically pure compounds[12] or a total synthesis approach starting from racemic compounds such as norbornene[13] or achiral compounds as cyclopentadiene.[14]

While the first alternative bears the advantage of enantiomerically pure starting materials which also possess the required polyoxygenated framework, it is often difficult to interconvert one configuration to another without excessive use of protecting groups. The second access which usually starts from some cyclopentadiene-derived compounds often suffers from the necessity of getting enantiomerically pure material, thus requiring enzymatic[15] or chemical resolution[16] at some point in the synthesis, if optically active compounds are to be obtained.

In this Letter, we wish to report a new simple method for the preparation of five-membered ring carbasugars through key ring-closing metathesis (RCM) intermediates based on stereoselective reactions starting from the chiral pool. We have also confirmed its viability by preparing the core bicyclo [3.1.0] hexane framework to finish a formal synthesis of antiviral carbocyclic nucleoside analogue N-MCT **1**.

Commercially and inexpensively available D-mannitol was easily converted into (*R*)-2,3-*O*-isopropylideneglycer aldehyde **2** using a well-known procedure.[17] Treatment of the aldehyde **2** with allyl bromide in the presence of zinc dust and aqueous ammonium chloride solution in tetrahydrofuran at 0 °C afforded the corresponding homoallyl alcohol as a major diastereomer in favor of the anti-isomer[18] **3** (anti/syn 95:5, from ^{1}H NMR spectroscopy), which was used as such for further reaction (Scheme 1). The free hydroxy functionality in compound **3** was protected as its benzyl ether using sodium hydride and benzyl bromide in tetrahydrofuran to give compound **4**. In this step, the two isomers were easily separated by column chromatography. The pentylidene ketal-protecting group of **4** was hydrolyzed with 60% aqueous acetic acid, thereby giving the corresponding diol in 80% yield. The diol **5** was then treated with excess TBSCl in the presence of imidazole to provide the bis-TBS ether **6** in 85% yield after chromatographic purification. Selective removal of the primary TBS ether was achieved by treatment of **6** with PTSA (10%) in MeOH for 3 h.[19] This provided the mono-TBS ether **7** in 71% yield along with 25% of

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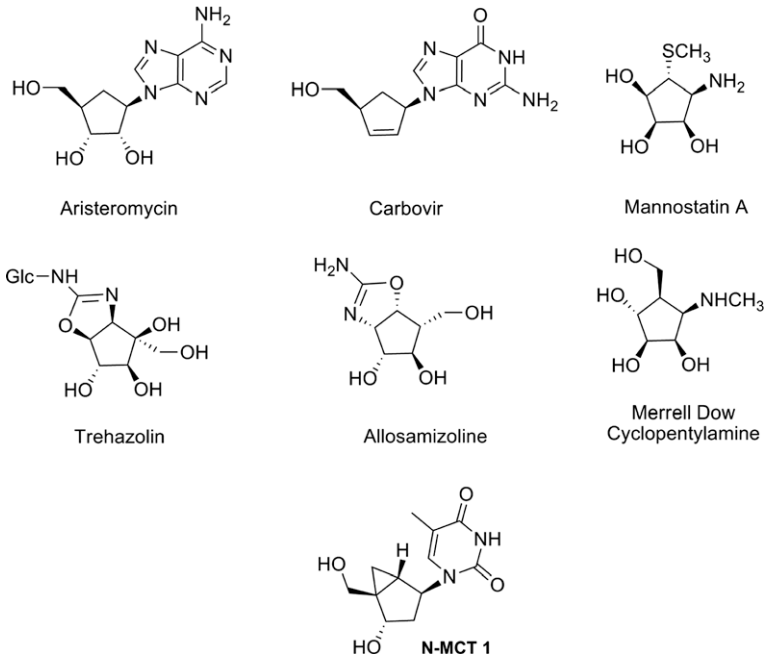
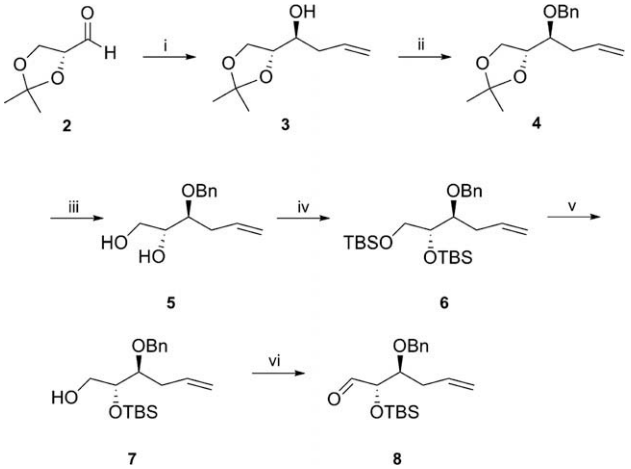


Figure 1. Some representative carbocyclic nucleosides and glycosidase inhibitors.

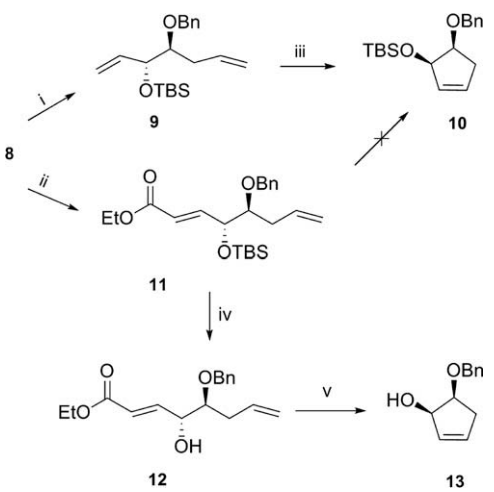
recovered **6**. It was necessary to stop this deprotection reaction short of completion in order to prevent competitive hydrolysis of the secondary TBS ether. Accordingly, resubjection of recovered **6** to the deprotection conditions provided additional quantities of **7**, and the total yield of **7** was 88% after one such recycle step. Oxidation of the primary alcohol was achieved with the Dess–Martin periodinane reagent in the presence of catalytic amount of pyridine.[20] The corresponding aldehyde **8** was produced in 90% yield, with no epimerization of the adjacent stereocenter. However, attempted oxidation of alcohol **7** under Swern conditions afforded a mixture of products.

The second olefin was introduced upon Wittig reaction of **8** with methylenetriphenylphosphorane. However, to prevent enolization of the aldehyde during the reaction, it was necessary to ensure that an excess of methyl triphenylphosphonium bromide relative to the *n*-butyllithium was used in the formation of the ylide. In practice, the reaction mixture was carried out with low yield and the starting material decomposed under the strong basic condition. An alternative strategy was the treatment of aldehyde **8** with (carbethoxymethylene)-triphenyl phosphorane ($Ph_3P{=}CHCO_2Et$) in THF furnished (2E)-2,7-diene **11** as the single product in excellent yield.

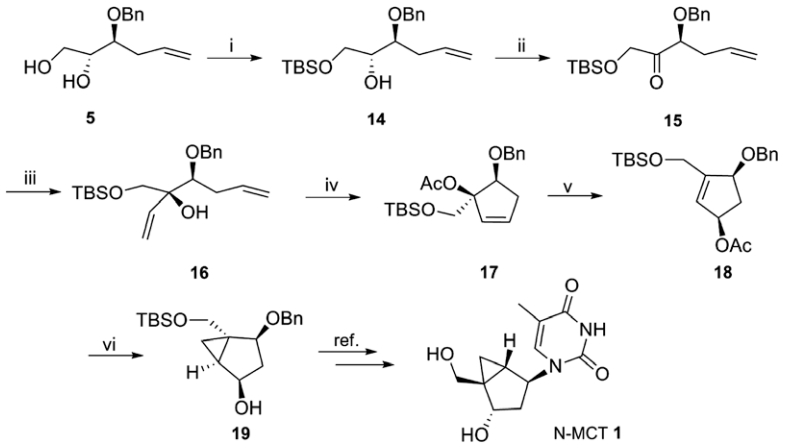
With diene substrates in hand, the key RCM reaction was explored. Our initial attempts involved the treatment of **9** with the Grubbs' first generation catalyst[21] (5 mol %) in CH_2Cl_2 to afford the corresponding cyclopentene **10** in moderate yield. Much higher yields were observed under the similar RCM condition using the Grubbs' second generation catalyst. Relative to the Grubbs' first generation catalyst, the second one is more convenient to use in that it is substantially more air stable.[22] Having in place the route to cyclopentene **10**, we next investigated the cyclization of diene **11** via RCM. A series of preliminary experiments using either first or second generation catalyst under a variety of reaction conditions



Scheme 1. Reagents and conditions: (i) $CH_2{=}CHCH_2Br$, Zn, NH_4Cl, 0 °C to rt, 4 h, 90%; (ii) BnBr, NaH, THF, 0 °C to rt, 5 h, 92%; (iii) 60% aq AcOH, rt, 12 h, 80%; (iv) TBSCl, imidazole, CH_2Cl_2, 16 h, 85%; (v) *p*-TsOH, MeOH, 0 °C, 2 h, 88%, after one recycle of recovered **6**; (vi) Dess–Martin reagent, CH_2Cl_2, overnight, 90%.



Scheme 2. Reagents and conditions: (i) $(Ph)_3PMeBr$, *n*-BuLi, THF, 50%; (ii) $Ph_3P{=}CHCO_2Et$, THF, 92%; (iii) 5 mol % 2nd Gen. Grubbs' cat., CH_2Cl_2, rt, 85%; (iv) TBAF, THF, 91%; (v) 10 mol % 2nd Gen. Grubbs' cat., $CHCl_3$, reflux, 80%.



Scheme 3. Reagents and conditions: (i) TBSCl, imidazole, THF, 0 °C, 8 h, 80%; (ii) Dess–Martin reagent, CH_2Cl_2, overnight, 98%; (iii) CH_2=CHMgBr, THF, −78 °C, 94%; (iv) (a) 5 mol % 2nd Gen. Grubbs' cat., CH_2Cl_2, rt, overnight; (b) Ac_2O, Et_3N, DMAP, two steps, 85%; (v) *p*-benzoquinone, $PdCl_2(MeCN)_2$, THF, 86%; (vi) (a) 1% NaOH, MeOH; (b) CH_2I_2, Et_2Zn, CH_2Cl_2, 82% (over two steps).

yielded no desired product probably due to the steric hindrance of TBS group. Deprotection of the silyl group of **11** with TBAF gave the corresponding alcohol **12**, which subsequently underwent the above-mentioned conditions also failed to get the target cyclized compound. Finally, we found that the improvement of catalyst up to 10 mol % together with $CHCl_3$ as a solvent under reflux was favored to form cyclopentene derivative **13** (Scheme 2).

After successful construction of the five-membered ring scaffold, we further applied this method for the formal synthesis of N-MCT **1**. As shown in Scheme 3, the primary hydroxy group of the diol **5** was selectively protected using equal equivalent TBSCl in the presence of imidazole in THF at lower temperature and then Dess–Martin oxidation of the secondary alcohol **14** to the ketone **15** was almost quantitative and no purification was necessary at this stage. An analogue of ketone **15** has been synthesized by Ludek and Marquez[23] starting from 2-deoxy-D-ribose. They also indicated that this compound did not show any signs of epimerization/racemization caused by a possible keto–enol tautomerism. Ketone **15** can also be considered as an erythrulose analogue and nucleophilic additions of organometallic compounds to the carbonyl group of this carbohydrate have been investigated in detail.[24] According to these studies, both benzyl-protected hydroxyl groups in α and α'-position competing in chelation of the metal and the carbonyl group usually lead to poor diastereoselectivities.[25] Fortunately, subsequent Grignard reaction with vinylmagnesium bromide in our approach showed exclusive stereoselectivity. We presumed that the steric hindrance of TBS group in **15** in accordance with the Felkin–Anh model favored the anti-addition of the Grignard reagent to the carbonyl group, affording diene **16** as a major product. After RCM conversion to the cyclopentenol with Grubbs' second generation catalyst and acetylation of the tertiary hydroxyl, compound **17** could be purified by column chromatography (85%, two steps). Finally, a palladium (II)-catalyzed rearrangement of the resulting allylic system **18**,[26] followed by a hydroxy-directed cyclopropanation under Simmons-Smith conditions gave the key carbobicyclic intermediate **19**[27] according to the published procedure,[28] providing the antiviral agent North-methanocarbathymidine (N-MCT, **1**) precursor in high yield.

In summary, we have presented a simple and efficient approach toward cyclopentene derivative **10** and **13**, containing the prerequisite five-membered ring framework presented in many potent bioactivity agents, such as N-MCT **1**. Utilizing cheap and plentiful (*R*)-2,3-*O*-isopropylidene glyceraldehyde **2** as starting material, we were able to introduce the desired *S*-configuration chiral center, which serves as an anchor for the stepwise buildup of the other necessary stereocenters. Meanwhile the double bond remaining in **10** and **13** possesses a useful reaction site so that polyhydroxylic groups were elaborated either by substrate-controlled diastereoselective epoxidation/epoxide opening or by direct dihydroxylation. Furthermore, we have finished the formal synthesis of N-MCT by preparing the key carbobicyclic intermediate **19** over nine steps in 25% overall yield under conditions that are ecologically friendlier than previous methods.

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27. *Compound* **19**: oil, $[\alpha]_D^{20}$ +19.0 (*c* 2.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.77 (s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 10.5 Hz, 1H), 4.04 (d, *J* = 6.0 Hz, 1H), 3.30 (d, *J* = 10.5 Hz, 1H), 2.17–2.10 (m, 1H), 1.65–1.53 (m, 1H), 1.30–1.15 (m, 2H), 0.93 (s, 9H), 0.63 (m, 1H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.01, 9.31, 19.21, 25.93, 26.61, 35.02, 36.08, 62.26, 71.32, 72.42, 80.58, 127.45, 127.54, 128.32, 138.34; ESIMS *m*/*z* 371.1 $[M+Na]^+$.
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