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Enantioselective synthesis of carba-L-furanose precursors of carbanucleosides, using ring-closing metathesis

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Abstract—Carba-L-sugars were synthesized in seven steps from known tetra-*O*-benzyl-D-galactopyranose (**3**). The synthesis of cyclopentene ring has been accomplished via a ring-closing metathesis step. Schrock's catalyst was employed on the unique diene, key intermediate (**5**), to provide the cyclopentene derivative (**7**), a versatile intermediate for the synthesis of carbocyclic nucleosides.

Carbocyclic analogues of nucleosides where the furanose moiety is replaced with a cyclopentane or cyclopentene have furnished several active antiviral agents.[1] The (−)-neplanocin A (**1**) (Fig. 1) has, for instance, significant anti-leukemia activity,[2] meanwhile the cytosine analogue **2** has anti-tumor and anti-viral activity.[3] Those compounds have been mainly synthesized[4] from bicyclic systems,[5] by an asymmetric Diels–Alder,[6] or more recently by a chromium–carbene complex-derived optically active butenolide.[7]

Other approaches to the carbocyclic moiety utilize the 2-cyclopenten-1-one, prepared from (+)-γ-lactone-D-ribonic acid,[8] followed by a stereoselective reduction to an allylic alcohol. This involves an intramolecular Wittig reaction from a 1,4-diketo derivative prepared from chiral aldonolactones; nevertheless, it is well reported than 1,4-chiral diketo derivatives could undergo racemization, not only under basic media but also on standing.[9] This of course limits their use as optically pure starting materials. In fact, there is still a need for synthetic methods allowing a ready access to enantiomerically pure carbocyclic rings as found in neplanocin and analogues.

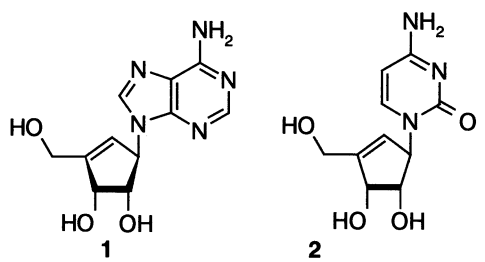

Figure 1.

As part of our drug discovery program, we have developed and report here an alternate route to obtain enantiomerically pure cyclopentene **6**. The synthetic sequence involves the conversion of the known tetra-*O*-benzyl-D-galactopyranoside **3** to diene **5** (Scheme 1), which is cyclized via a ring-closing metathesis (RCM) reaction. Subsequent steps of deprotection and protections afforded the desired cyclopentene framework **9**,[10] on which the heterocyclic base could be coupled either under Mitsunobu conditions[11] or via (π-allyl)palladium chemistry[12] (Tsuji–Trost conditions).

Starting from known tetra-*O*-benzyl-D-galactopyranoside (**3**) easily obtained from commercial methyl-α-D-galactopyranoside, the introduction of the first olefin was achieved via a Wittig reaction according to the procedure originally reported by Lancelin et al.[13] in order to prevent elimination during this step. Oxidation of the intermediate with PCC in the presence of AcONa[14] gave the optically pure L-tagatose (L-*lyxo*-hexulose) derivative **4**. Subsequent introduction of the second olefin via a Wittig reaction afforded the diene **5**.

The key step of this reaction, the ring-closing metathesis,[15] was accomplished by exposure of diene **5** to 12 mol% of Schrock's molybdenum catalyst[16] **10** (Fig. 2) to yield the optically pure highly hydroxylated cyclopentene derivative **6**[17] in 85% yield.[18] The use of Grubbs' ruthenium-based catalyst **11** provided the desired product in low yield (<10%). This is in agree-

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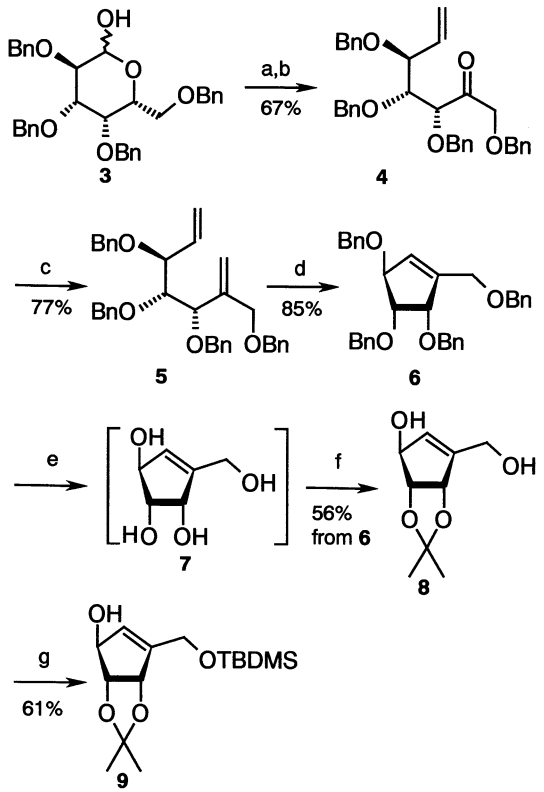


Scheme 1. *Reagents and conditions*: (a) Ph_3PCH_3Br, *n*-BuLi, THF, −78°C to rt; (b) PCC, AcONa, MS 4 Å, CH_2Cl_2; (c) Ph_3PCH_3Br, *n*-BuLi, THF, −78°C to rt; (d) Schrock's catalyst (12 mol%), benzene, 80°C, drybox; (e) 1 M BCl_3 in CH_2Cl_2, −78°C to rt; (f) acetone, cat. *p*TsOH, rt; (g) TBDMSCl, pyridine, 0°C; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C.

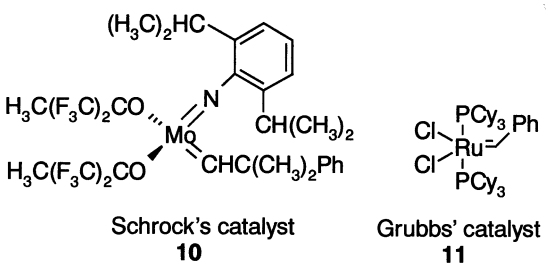
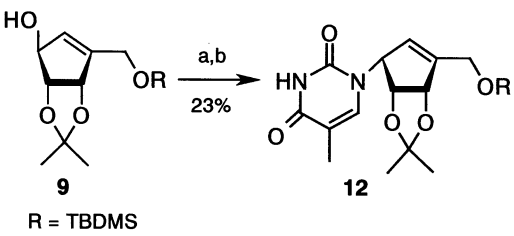


Figure 2.



Scheme 2. *Reagents and conditions*: (a) N^3-benzoyl-thymine, PPh_3, DEAD, THF, rt; (b) NH_3/MeOH, rt.

ment with literature; in fact, even if Grubb's ruthenium complex **11** has found the widest application, its general ineffectiveness for producing trisubstituted alkenes is generally recognized.[15b,19] At the opposite, the oxygen and moisture sensitive molybdenum complex **10** has proved to be more effective in the RCM of sterically congested olefins.[10c,d]

Subsequent selective debenzylation of **6** by the treatment with 1 M BCl_3 in CH_2Cl_2 afforded the tetraol **7**, which was directly converted to the acetonide **8** in 56% yield from **6**. Compound **8** is considered as a valuable intermediate for the syntheses of carbocyclic nucleosides.

The selective silylation of **8** afforded the derivative **9**,[20] which has been fully characterized. Its physico–chemical data and especially optical rotation {$[\alpha]_D^{20}$ +13.3 (*c* 0.4), $CHCl_3$)} have been compared with those reported for its D-enantiomer {Ref. 21; $[\alpha]_D^{29}$ −12.8 (*c* 1.84, $CHCl_3$)}. To explore the conversion of allylic alcohol **9** to a carbanucleoside, preliminary condensation of a nucleoside base was tried. Thus, thymidine analogue **12** was successfully obtained under the Mitsunobu conditions [triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF] by reaction of **9** with N^3-benzoylthymine[22] and subsequent deprotection (Scheme 2). This not-optimized result is in agreement with reported syntheses of carbanucleosides from allylic alcohol by the Mitsunobu reaction.[23]

In summary, we report herein the first enantioselective and total synthesis of **9** from methyl-α-D-galactopyranose by exploiting a ring-closing metathesis step.[24] Allylic substitution with suitable nucleophiles on **9** should afford L-neplanocins. Synthesis of other optically pure L-cyclopentenyl carbocyclic pyrimidine and purine nucleosides are in progress in our laboratory.

Acknowledgements

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17. **Representative procedure**: To a freshly distilled benzene (30 mL) solution of diene **5** (1.15 g; 2.14 mmol), in a drybox, was added Schrock's catalyst **12** (0.2 g; 0.262 mmol; 0.12 equiv.) in one portion, and the resulting mixture was refluxed for 10 h. The resulting solution was taken out of the box and concentrated in vacuo. Flash chromatography of the residue over silica using hexanes–EtOAc (9:1, v/v) gave **6** (0.92 g, 85%) as a pure yellowish oil.
18. **Physico–chemical data for compound 6**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.35–7.15 (m, 20H), 5.99 (s, 1H), 4.83 (m, 1H), 4.65 (m, 2H), 4.55–4.54 (m, 5H), 4.34 (d, $J=12.2$ Hz, 1H), 4.31 (d, $J=12.2$ Hz, 1H), 4.02 (t, $J=5$ Hz, 1H), 3.95 (m, 2H). ^{13}C NMR (62.5 MHz, C_6D_6) δ 142.3, 138.6, 138.4, 138.3, 138.1, 130.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.75, 127.7, 127.6, 86.4, 84.4, 78.8, 72.7, 72.3, 71.9, 71.5, 67.2. MS m/z 529 (M+Na). FTIR ν_{max} 3030, 2860, 1495, 1455, 1350, 1205, 1080, 735, 700. $[\alpha]_D$ +82.2 (c 0.6, $CHCl_3$).
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20. **Physico–chemical data for compound 9**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.15 (d, $J=5.4$ Hz, 1H), 4.84–4.81 (m, 2H), 4.38–4.24 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 0.92 (s, 9H), 0.09 (m, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.1, 126.2, 112.8, 87.2, 83.6, 65.1, 60.5, 27.8, 26.7, 26.2, 18.7. MS m/z 301 (M+H). FTIR ν_{max} 3415, 2930, 2850, 2360, 1600, 1380, 780. $[\alpha]_D$ +13.3 (c 0.4, $CHCl_3$).
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24. All new compounds **3**–**9** were purified by column chromatography and product structures were determined by MS, 250 MHz ^{1}H and ^{13}C NMR.