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Carbocyclic nucleoside precursors by intramolecular cyclopropanation of sugar-derived diazo compounds

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Abstract—Bicyclo[3.1.0]hexane derivatives, selectively prepared by intramolecular cyclopropanation of sugar-derived unsaturated diazo compounds, are common precursors for the sugar moiety of cyclopentane, cyclopropane and bicyclo[3.1.0]hexane nucleosides, such as aristeromycin, the carbocyclic analogue of neplanocin C and the nucleoside A-5021.

Carbocyclic nucleosides—usually with a cyclopentane ring as the sugar moiety—have been widely studied as potential antiviral and antitumour agents.[1] Amongst these, nucleosides with a cyclopropane ring or a bicyclo[3.1.0]hexane ring system, have attracted considerable attention because of their significant antiviral activity[2] (Fig. 1).

Bicyclo[3.1.0]hexane derivatives **3** and **4** (Scheme 1) could be excellent precursors for the synthesis of nucleosides like those shown in Fig. 1, because of the highly versatile functional groups present. Their synthesis, therefore, in enantiomerically pure form is strongly desirable and the intramolecular cyclopropanation of sugar-derived chiral diazo compounds is an attractive approach. Some time ago,[3] we reported the intramolecular cyclopropanation of diazo compound **2** and the corresponding iodonium ylide to give the enantiopure bicyclo[3.1.0]hexane derivatives **3** and **4**. Compound **2** in turn was prepared from D-ribose via the pentenal **1**. Although the CuI catalysed decomposition of **2** is a good method to prepare compound **3** (4.5:1 diastereomeric ratio, 81% combined yield after optimisation), compound **4** was not accessible in acceptable yield and selectivity: the CuI catalysed decomposition of the respective iodonium ylide[3] favoured the formation of **4**, but in moderate yield and poor diastereoselection (1:1.5). Looking for a better way to prepare compound **4**, we found that the $Rh_2(OAc)_4$ catalysed decomposition of **2**, afforded compound **4** as the major

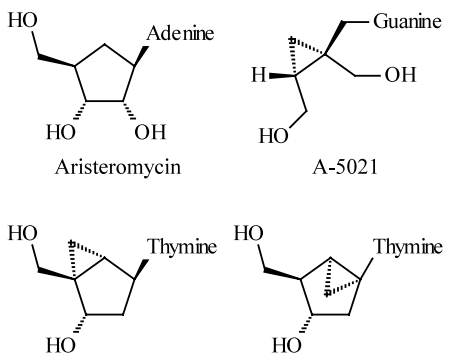
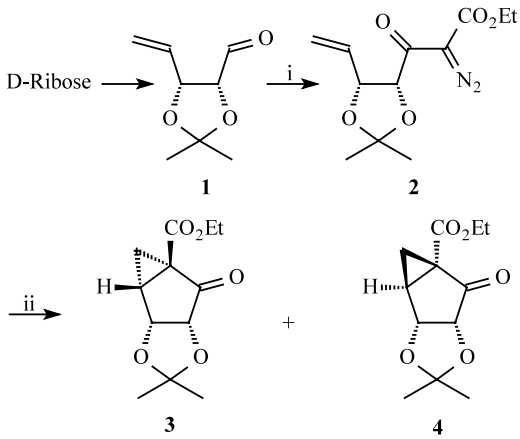


Figure 1.



Scheme 1. *Reagents and conditions*: (i) (a) N_2CHCO_2Et, $SnCl_2$ (anhydrous), CH_2Cl_2, 0°C, 76%; (b) TsN_3, Et_3N, EtOH, 20°C, 92% optimised yield; (ii) CuI, toluene, reflux, 3 h, 81% optimised yield (**3**:**4** ratio 4.5:1) or $Rh_2(OAc)_4$, toluene, reflux, 1.5 h, 74% (**3**:**4** ratio 1:3).

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product, in 74% combined yield and 1:3 diastereoselectivity. Interestingly, the enantiomers of **3** and **4** could also be obtained, since the enantiomer of aldehyde **1** is easily accessible.[4]

The observed different diastereoselectivity in these reactions should originate in the nature of their transition states. It is generally accepted that the metal catalysed decomposition of diazo compounds proceeds via metallo–carbenoid intermediates,[5] which preserve their structural integrity during the addition to the double bond. Thus, in the $Rh_2(OAc)_4$ catalysed cyclopropanation of **2**, the transition state **TS-1** (Fig. 2) leading to the formation of **3**, is more strongly destabilised as a result of the interactions of the bulky Rh(II) species with the acetonide group, compared to those of the ethoxycarbonyl group in **TS-2**. In the case of CuI, the interactions of the ethoxycarbonyl group in **TS-2** with the acetonide group predominate over those of the smaller atom of Cu with the acetonide in **TS-1**.

Having established satisfactory preparative methods for compounds **3** and **4**, a number of further transformations demonstrated their synthetic interest. $LiAlH_4$ reduction of both compounds (Scheme 2) afforded the respective protected tetraols **5** and **6**, as the only products in good yield,[6] compounds which constitute the sugar part of carbocyclic nucleosides with a bicyclo[3.1.0]hexane ring system.[2] The deprotected *ent*-**5**, in particular, which could be prepared by the same way from *ent*-**1**, is the sugar moiety of the carbocyclic analog of neplanocin C and related nucleosides.[2d] Treatment of compounds **3** and **4** with thiophenol in *t*-BuOH/*t*-BuOK caused cyclopropane ring opening[7] and the resulting ketoesters were decarboxylated at 160°C with NaCl/DMSO/H_2O[8] to give the enantiopure hydroxylated cyclopentanoids **9** and **10**. Since it is well known[7] that the thiophenyl group could be easily transformed to a hydroxyl group via a Pummerer oxidation, compound **10** is directly related to the aristeromycin and analogous nucleosides.

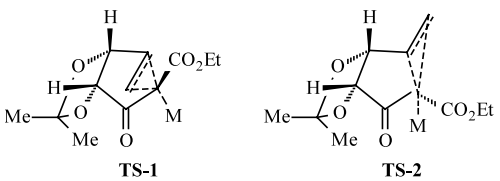
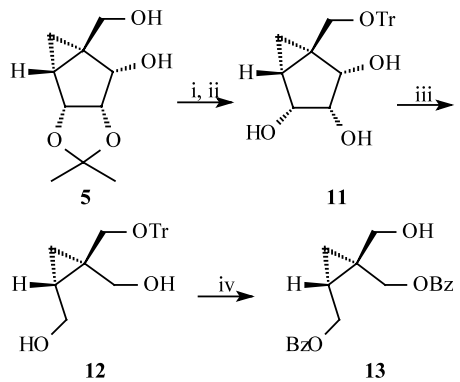


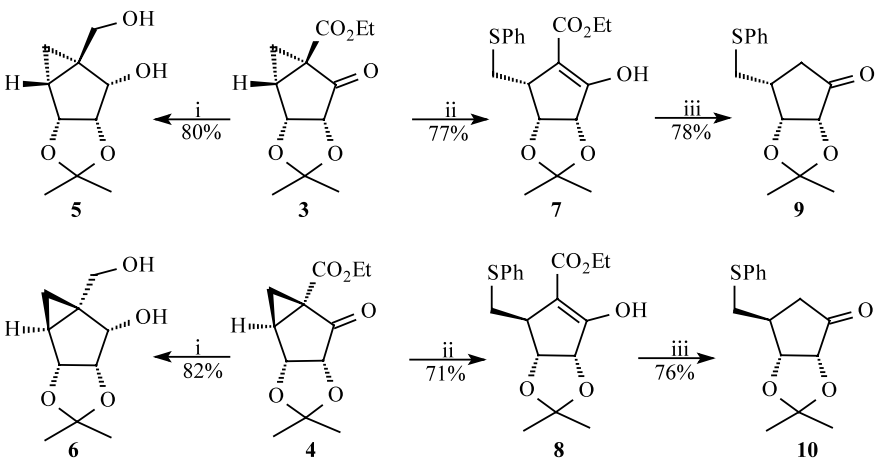
Figure 2.

The synthesis of the antiviral cyclopropane nucleoside A-5021[9] is another example of the synthetic potential of the intramolecular cyclopropanation reactions in sugar derivatives. Tsuji et al. recently reported[9] that A-5021 exhibits extraordinary activity against HSV-1 and VZV, being superior and more selective than acyclovir. It becomes evident when comparing the structure of A-5021 as those of **5** and **6** that the two chiral centres of the cyclopropane ring of A-5021 have the same absolute configuration as those of **5**, from which the sugar moiety of A-5021 could be prepared by standard deprotection and glycolic cleavage reactions.

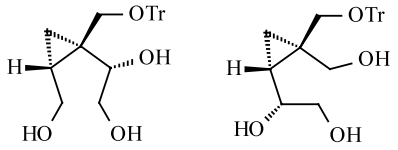
To this end, compound **5** was deprotected and the primary hydroxyl group tritylated (Scheme 3). Further



Scheme 3. *Reagents and conditions*: (i) HCl, THF, H_2O, 20°C, 30 min; (ii) Ph_3CCl, DMAP, Et_3N, DMF, 20°C, 24 h, 65%; (iii) $NaIO_4$, THF, H_2O, 45 min then $NaBH_4$, MeOH, 30 min, (twice), 55% overall; (iv) PhCOCl, pyridine, 0°C, 1 h, then HCO_2H, Et_2O, 20 min, 60%.



Scheme 2. *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, −10°C, 30 min; (ii) PhSH, *t*-KOBu, 20°C, 3–7 h; (iii) DMSO, H_2O, NaCl, 160°C, 5 h.



14 **15**

Figure 3.

glycolic cleavage required prolonged stirring with an excess of $NaIO_4$ and yielded compound **12** upon $NaBH_4$ reduction, as a mixture with polyols **14** and **15** (Fig. 3), evidently because the initially formed hydroxy-bis-aldehydes exist predominantly as lactols, resisting the action of $NaIO_4$. To overcome this problem, **11** was subjected to two consecutive short-time glycolic cleavage/$NaBH_4$ reduction treatments, to give the desired compound **12**, in good overall yield. Conventional benzoylation of the two free hydroxyl groups and detritylation gave the known compound **13**, which can be readily converted to the nucleoside A-5021, according to the literature procedure.[9a]

In short, we have established preparative methods for the directed intramolecular cyclopropanation of diazo compound **2** to give bicyclo[3.1.0]hexane derivatives **3** or **4**. Furthermore, we have demonstrated their synthetic potential, by converting them into the sugar part of cyclopentane, cyclopropane and bicyclo[3.1.0]hexane nucleosides. Of particular interest is the synthesis of the suger part of the antiviral cyclopropane nucleoside A-5021, in enantiomerically pure form.

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6. The absolute configuration of the newly formed stereocentre in **5** and **6** was deduced by NOE experiments. All new compounds gave spectroscopic and analytical data consistent with the proposed structures. NMR data for selected compounds are listed. Compound **5**: ^{1}H NMR ($CDCl_3$): δ 0.66 (dd, 1 H, $J=7.8$, 5.9 Hz), 1.20 (dd, 1 H, $J=5.9$, 4.5 Hz), 1.30 (s, 3 H), 1.55 (s, 3 H), 1.6 (ddd, 1 H, $J=7.8$, 5.9, 4.0 Hz), 3.05 (br s, 2 H), 3.45 (d, 1 H, $J=11.7$ Hz), 3.79 (d, 1 H, $J=11.7$ Hz), 4.55 (dd as t, 1 H, $J=6.8$ Hz), 4.61 (d, 1 H, $J=6.8$ Hz), 4.88 (dd, 1 H, $J=6.8$, 4.0 Hz); ^{13}C NMR ($CDCl_3$): δ 10.9, 24.5, 26.1, 41.1, 65.1, 72.0, 79.2, 80.0, 112.3. Compound **10**: ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3 H), 1.42 (s, 3 H), 2.27 (d 1 H, $J=18.0$ Hz), 2.67 (m, 1 H), 2.79 (dd, 1 H, $J=18.0$, 8.7 Hz), 2.91 (dd, 1 H, $J=13.3$, 6.3 Hz), 3.01 (dd, 1 H, $J=13.3$, 6.8 Hz), 4.32 (d, 1 H, $J=5.0$ Hz), 4.67 (d, 1 H, $J=5.0$ Hz), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 24.8, 26.8, 37.0, 38.0, 39.5, 78.3, 81.1, 112.2, 127.0, 129.2, 130.3, 134.9, 212.9. Compound **12**: ^{1}H NMR ($CDCl_3$): δ 0.35 (dd as t, 1 H, $J=5.4$ Hz), 0.56 (dd, 1 H, $J=8.3$, 5.4 Hz), 1.30 (m, 1 H), 3.02 (d, 1 H, $J=9.8$ Hz), 3.19 (d, 1 H, $J=9.8$ Hz), 3.28 (d, 1 H, $J=11.7$ Hz), 3.32 (dd, 1 H, $J=12.2$, 5.4 Hz), 4.05 (dd, 1 H, $J=12.2$, 5.4 Hz), 4.15 (d, 1 H, $J=11.7$ Hz), 7.30 (m, 9 H), 7.45 (m, 6 H); ^{13}C NMR ($CDCl_3$): δ 13.7, 24.8, 26.7, 63.6, 65.7, 70.9, 87.0, 127.2, 128.0, 128.6, 143.6.
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