Radical cyclisation of carbohydrate alkynes: synthesis of highly functionalised cyclohexanes and carbasugars

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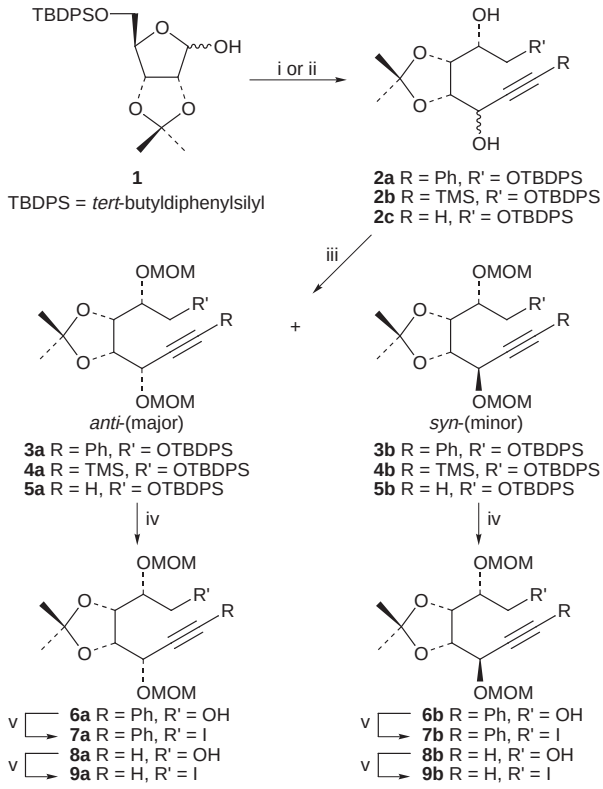
Carbohydrate alkynes undergo 6-*exo* radical cyclisation to afford cyclohexanes resulting in the synthesis of carbasugars.

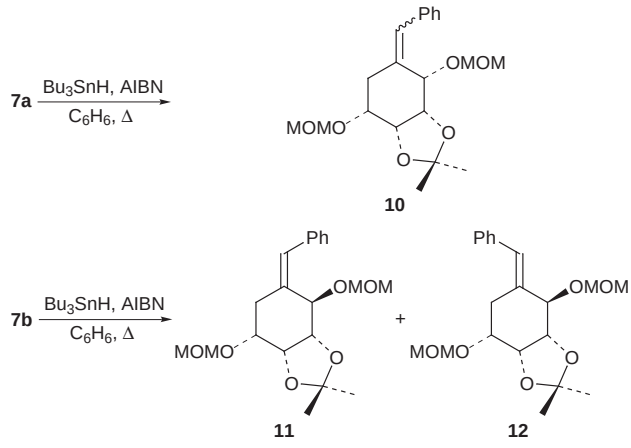
The use of carbohydrates as synthetic precursors of many functionalised carbocyclic compounds is widespread.[1] The first conversion of a sugar to a cyclohexane ring involved the preparation of nitroinositols from 6-deoxy-6-nitrohexose.[2] In the intervening years there have been numerous examples of the use of radical chemistry for the synthesis of cyclopentane derivatives,[3] with notable work in the carbohydrate area coming from the Fraser-Reid group.[4] It is thus surprising that there are few examples of the preparation of six-membered aliphatic rings employing radical cyclisation onto an alkyne.[5] Some reasons for this can be inferred from work on cyclisations of ω-alkenyl radicals. The formation of six-membered rings by radical chain reactions involving 6-*exo* cyclisation is some 40 times slower than that of the hex-5-enyl cyclisation.[6] The consequence of this is that chain transfer by attack of the acyclic radical on the stannane usually present is a much more effective process than with the hex-5-enyl radical. The second problem is that 1,5-hydrogen abstraction leading to a resonance stabilised allyl radical is favourable and in fact this can become synthetically useful.[3b]

We have been interested in the development of 6-*exo* cyclisations of alk-6-ynyl radicals as these would allow the preparation of heavily substituted hydroxycyclohexanes and of carbasugars. In this regard we chose to prepare alkynes derived from D-ribose[7] and to investigate their chemistry. Treatment of the protected silyl-D-ribose derivative **1** with lithium phenylacetylide afforded an inseparable diastereomeric mixture of the diols **2a** in 90% yield (Scheme 1). The protection of both the hydroxy groups as methoxymethyl (MOM) ethers[8] proceeded in a yield of 89% and allowed chromatographic separation of the diastereomers **3a** and **3b** with an *anti*:*syn* ratio of 3 : 2. Alternatively the *syn* isomer **3b** could be prepared almost exclusively using D-ribonolactone as the starting material.[9] Desilylation of **3a** was effected with TBAF in THF in 92% yield and afforded the primary alcohol **6a** which was converted to the corresponding iodide **7a** in 76% yield with triphenylphosphine, imidazole and iodine.[10] Similar chemistry with the isomer **3b** gave the alcohol **6b** and subsequently the iodide **7b** in comparable yields. With both the iodides **7a** and **7b** in hand we investigated their radical cyclisation reactions. Treatment of the iodide **7a** with tri-*n*-butyltin hydride in refluxing benzene in the presence of AIBN effected the 6-*exo* cyclisation affording only the substituted cyclohexanes **10** in 93% yield (Scheme 2) as an inseparable mixture of *E* and *Z* geometric isomers in a ratio of 1 : 1 as determined by ^{1}H NMR analysis. Analogous reaction of the diastereomer **7b** afforded the corresponding cyclohexanes **11** and **12** in 70% yield. In this case we were able to separate the *E* and *Z* stereoisomers by chromatography, in a ratio of 2 : 3. The major isomer **11** was assigned the *Z* geometry about the double bond on the basis of NOE experiments.

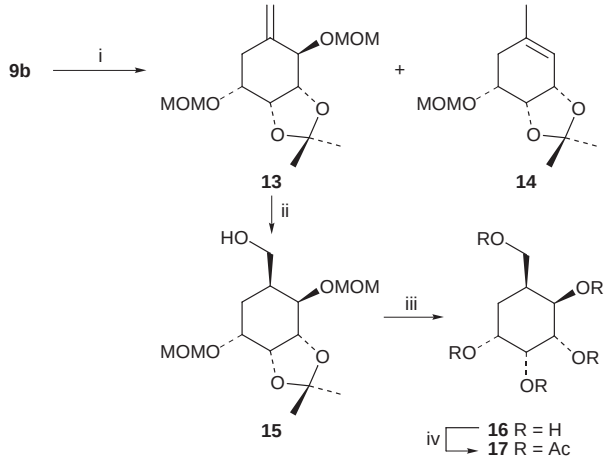
Having been successful in our initial goal we turned our attention to the syntheses of compounds with an unsubstituted *exo*-methylene group. Thus the protected ribose **1** was treated with lithium trimethylsilylacetylide in THF and afforded the diols **2b**, in a combined yield of 45% along with the alkynes **2c**, in 28% yield. The diastereomeric mixture **2b** was converted to



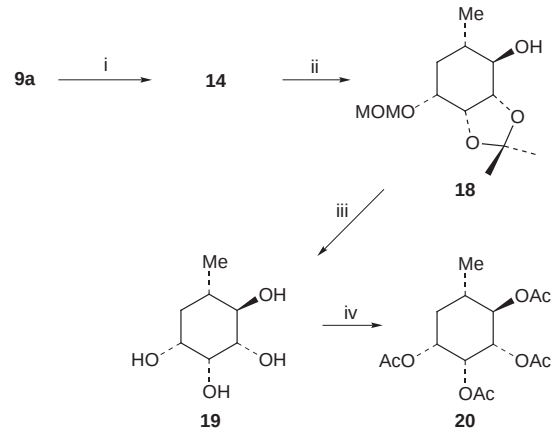
Scheme 1 *Reagents and conditions:* i, LiC≡CPh, THF, −78 °C; ii, LiC≡CTMS, THF, −78 °C; iii, MOMCl, NEt_2Pr^i, CH_2Cl_2, RT; iv, Bu_4NF, THF, RT; v, I_2, PPh_3, Im, PhMe, Δ



Scheme 2



Scheme 3 *Reagents and conditions:* i, Bu_3SnH, AIBN, PhH, Δ; ii, BH_3–Me_2S, THF; 0 °C, H_2O_2, NaOH; iii, 6 M HCl, MeOH; iv, Ac_2O, Py, RT



Scheme 4 *Reagents and conditions:* i, Bu_3SnH, PhH, AIBN, Δ; ii, BH_3–Me_2S, THF; 0 °C, H_2O_2, NaOH; iii, 6 M HCl, MeOH; iv, Ac_2O, Py, RT

the MOM ethers **4a** and **4b** that could be separated in a combined yield of 71% with an *anti*:*syn* ratio of 3.5 : 1. Both of these diastereomers were processed separately. Desilylation of **4a** and **4b** gave the corresponding primary alcohols **8a** and **8b** in 91 and 96% yields respectively. These compounds were identical to those obtained from **2c** after the diastereoisomers had been subjected to protection by MOM chloride to afford **5a**, **5b** and desilylation, the *anti*:*syn* ratio being 3 : 1. The *syn*-product was correlated with material prepared from the pure *syn*-isomer **2c**, which we have described in our earlier report.[9] The alcohols **8a** and **8b** were converted smoothly to the corresponding iodides **9a** and **9b** in 71 and 78% yields respectively. At this juncture we were in a position to study the 6-*exo* radical cyclisation of these iodides. Thus (Scheme 3) the *syn* isomer **9b** was treated with tri-*n*-butyltin hydride and AIBN in refluxing benzene and afforded the expected *exo*-methylenecyclohexane **13** in 49% yield along with the cyclohexene **14** in 39% yield where the MOM group had been lost. The structure of **14** was clearly evident from the ^{1}H NMR spectrum which had resonances due to only one MOM group and in addition there was a resonance at δ 5.33 due to the vinylic proton and a resonance at δ 1.75 due to a methyl group. We next subjected the iodide **9a** to these conditions (Scheme 4) and we observed that in this case the cyclisation reaction was appreciably slower, taking 24 h to reach completion, but much cleaner in that only **14** was obtained in 99% yield. The formation of **14** can be rationalised by cyclisation of a primary radical in a 6-*exo* mode onto the alkyne, resulting in the formation of a vinyl radical which then abstracts a hydrogen from the methylene carbon of the MOM group followed by β-scission[11] resulting in an allylic radical which subsequently affords the observed product. The formation of **14** is a reflection of the geometry of the vinyl radical in that these are bent with a bond angle of *ca*. 135° whilst the α-phenyl substituted vinyl radical is linear.[12]

The *exo*-methylenecyclohexane **13** (Scheme 3) was hydroborated and gave after oxidation the primary alcohol **15** in 94% yield. Removal of the protecting groups of **15** with 6 M HCl gave carba-α-L-gulopyranose **16** whose spectral properties were in accord with those reported in the literature.[13] Additional structural proof was obtained by acetylation of **16** with excess acetic anhydride and pyridine which afforded the pentaacetate **17** in 100% yield. The cyclohexene **14** underwent hydroboration/oxidation (Scheme 4) with BH_3–Me_2S and afforded the protected carba-β-D-rhamnose derivative **18** in 77% yield. The stereochemistry of the newly formed chiral centres was *anti* with the C-4 hydroxy group β as a result of hydroboration occurring from the opposite face from the *O*-isopropylidene group, and this was confirmed by NOE experiments. Removal of the MOM and isopropylidene protection proceeded uneventfully with 6 M HCl and afforded the fully deprotected carba-β-D-rhamnose **19** in 99% yield. Further structural integrity of **19** was established by acetylation with excess acetic anhydride and pyridine which resulted in formation of the tetraacetate **20** in 99% yield.

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Notes and References

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