Regio- and Stereocontrolled 6-*Endo-Trig* Radical Cyclization of Vinyl Radicals: A Novel Entry to Carbasugars from Carbohydrates

Ana M. Gómez,* Gerardo O. Danelón, Serafín Valverde, and J. Cristóbal López*

Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

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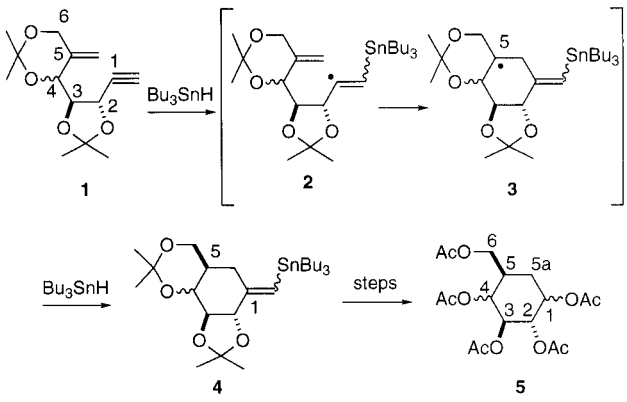
The term "carbasugar" is currently used to describe monosaccharide analogues having a methylene group instead of the ring oxygen atom.[1] Carbasugars have received considerable attention recently due to their close structural resemblance to carbohydrates and to the interesting range of biological activities which they have shown.[2] This interest has resulted in the development of a plethora of synthetic methods, and all 16 racemic carbapyranoses and most of the 32 enantiopure carbapyranoses have already been prepared.[3,4] There are, however, only two reports involving a radical cyclization[5] as the key step in the formation of the carbasugar cyclohexane ring.[6,7] Both methods utilize a 6-*exo* radical cyclization although they differ on the nature of the unsaturated radical acceptor (6-*exo*-*trig*[6] and 6-*exo*-*dig*[7]). As part of an ongoing program in our laboratory aimed at the synthesis of carbocycles from carbohydrates,[8,9] we report in this paper on a novel entry to carbasugars from monosaccharides which features the radical cyclization of a vinyl radical[10] as the key step. We have successfully applied this method for the preparation of carbasugar analogues of D-glucose and D-galactose.

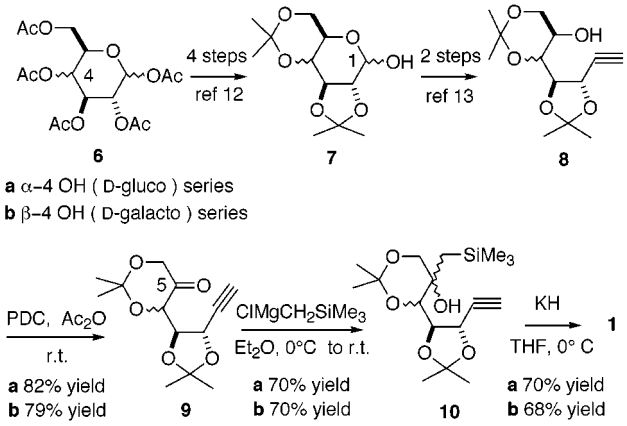
Our approach for the synthesis of carbasugars from monosaccharides is illustrated in Scheme 1. It involves the 6-(*π*-*exo*)-*endo*-*trig*[11] radical cyclization of an intermediate vinyl radical (**2**), generated by tri-*n*-butyltin hydride (Bu_3SnH) addition to a carbohydrate enyne **1**, to produce a cyclohexenyl radical, **3**, that after hydrogen transfer will lead to **4**. Standard manipulations on alkenyl stannane **4** will then pave the way to carbasugar **5**.

Scheme 1



The synthetic pathway (Scheme 2) started with commercially available D-glucose or D-galactose pentaacetates (**6a** and **6b**, respectively) which were transformed in four steps into 2,3:4,6-di-*O*-isopropylidene-D-gluco and D-galacto pyranoses (**7a** and **7b**, respectively).[12,13] Known alkynes **8a**,**b** were then prepared by Wittig reaction of hemiacetals **7a**,**b** with chloromethylenetriphenylphosphorane followed by dehydrohalogenation according to Toma and co-workers.[13] Oxidation at C-5 was carried out with PDC/Ac_2O,[14] to yield ketones **9a**,**b**, and was followed by Peterson olefination[15] to generate enynes **1a**,**b**. Enyne **1b** underwent radical cyclization (Scheme 3) by treatment with Bu_3SnH and AIBN (syringe pump addition, 12 h, toluene reflux, 0.02 M) to give alkenyl stannane **4b**[16] as the sole isolated product. On the other hand, reaction of **1a** under similar conditions also afforded **4a**[16] as the major compound although accompanied

Scheme 2



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(16) Only one isomeric alkenyl stannane was observed, although the stereochemistry had not been assigned.

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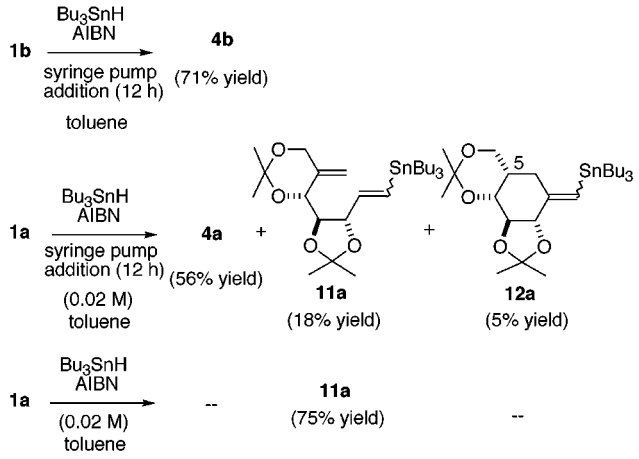
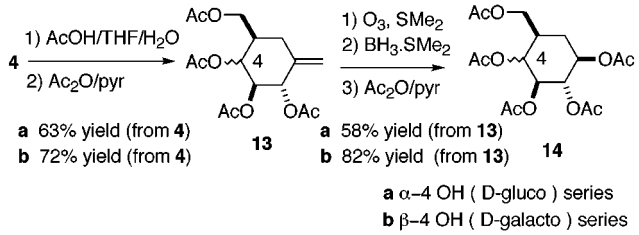
Scheme 3



by reduced **11a** and the epimer at C-5 **12a**.[16,17] Rapid addition of Bu_3SnH and AIBN to a refluxing solution of **1a** resulted in the exclusive formation of **11a** (75% yield). The final correlation between stannanes **4a**,**b** and carbasugars was carried out uneventfully (Scheme 4): acid hydrolysis

Scheme 4



followed by acetylation led to alkene **13**, ozonolysis followed by stereoselective reduction ($BH_3{\cdot}SMe_2$)[18] and acetylation produced penta-*O*-acetyl carba-*β*-D-gluco and galacto pyranoses **14a**[19,20] and **14b**[21] ($[\alpha]^{21}_D = -3.4$ (*c* 0.4, $CHCl_3$), mp = 143−145 °C), respectively.

Several aspects of the synthetic scheme deserve further comment: (a) In vinyl radical cyclizations[10] the 5-*exo* cyclization was found to be largely favored over 6-*endo* ring closure.[22,23] This *exo* versus *endo* preference, which has normally been inverted by inducing reversibility under low stannane concentration,[22,23] has occasionally been directed to the *endo* mode by substituting the internal position of the alkene.[10a,24] In our enyne system (**1a**,**b**) we have included two elements of regiocontrol to induce the 6-*endo* ring closure, the above-mentioned substitution and the strain associated with the presence of the *trans*-2,3-*O*-isopropylidene ring;[25,26] (b) hydrogen atom transfer to the cyclohexenyl radical **3** takes place stereoselectively from the α-face of the molecule, thus generating the stereochemistry at C-5 associated with sugars of the D-series; (c) the judicious choice of a 2,3:4,6 di-*O*-isopropylidene derivative has reduced the protecting group manipulations in the synthetic scheme to a minimum; (d) unlike other approaches to carbasugars from carbohydrates,[6,7] in this protocol a hexose (i.e., D-glucose) is correlated with its corresponding carbapyranoside (i.e., carba-D-glucose); (e) the alkenyl stannane intermediates **4a**,**b** are valuable precursors for the preparation of carbasugar derivatives.

In summary, we have described a new procedure for the preparation of highly functionalized cyclohexane derivatives from carbohydrates which features the 6-*endo*-*trig* radical ring closure of a vinyl radical. This protocol has been successfully applied to the synthesis of 5a-carba-*β*-D-glucose and 5a-carba-*β*-D-galactose pentaacetates. The application of this method for the preparation of other carbasugars as well as synthetic transformations of alkenyl stannanes **4a**,**b**, aimed at the preparation of carba-*C*-glycosides and carba-*C*-disaccharides[27] are underway in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds (6 pages).

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(17) Compound **12a** afforded upon destannylation alkene **A** which is the epimer at C-5 of the corresponding alkene **B** prepared by destannylation of **4a**.

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