Carbohydrate to Carbocycle Conversions via Intramolecular Propargylation with $Et_2Zn/Pd(0)/Yb(OTf)_3$

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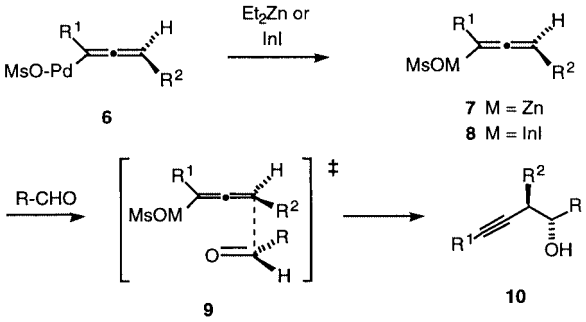
Abstract: Carbohydrate-derived propargylic esters react with Et_2Zn and catalytic Pd(0), in the presence of a Lewis acid, to generate nucleophilic allenyl metal species capable of intramolecular addition to a tethered carbonyl group. This results in the formation of enantiomerically pure functionalized cyclopentanes with high stereoselectivity and in preparatively useful yields. A high preference is observed for a *trans* relationship between the alkynyl and OH groups in the cyclopentane products, implying that the cyclization proceeds through open transition states.

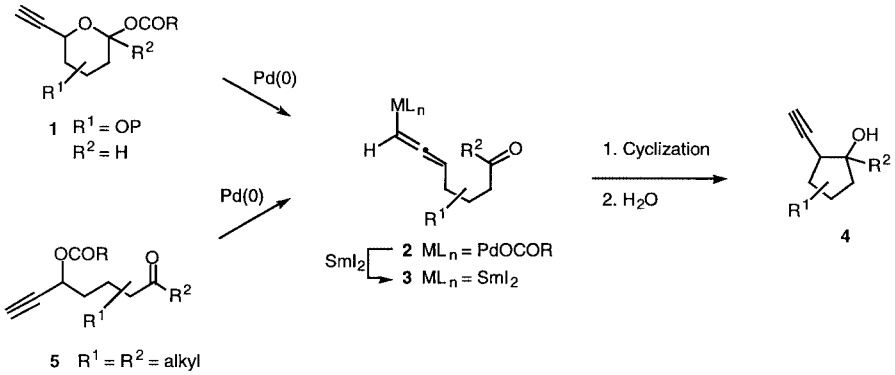
Key words: carbohydrates, carbocycles, cyclizations, palladium, zinc

The stereoselective synthesis of densely functionalized carbocycles from carbohydrate starting materials is a topic of current interest.[1] We have recently reported that treatment of modified carbohydrates **1** with the one-electron reducing agent SmI_2 and a catalytic amount of Pd(0) brings about the formation of homopropargyl cyclopentanols **4** (Scheme 1).[2] These transformations are thought to proceed through the intermediacy of Pd(II)-complexes **2** resulting from Pd(0)-promoted carbohydrate ring-opening. Intermediates **2** are then reduced in situ with two equivalents of SmI_2, presumably generating the cyclizing carbanionic species **3** and regenerating the Pd(0) catalyst. Access to intermediates analogous to **2** and **3** can also be gained, under similar treatment with SmI_2/Pd(0),[3] from non-carbohydrate open-chain propargylic esters **5** with a tethered carbonyl group. These two methods for preparation of carbocycles **4** are complementary in that the conversion **5** → **4** is only effective for ketone substrates ($R^2 \neq H$)[3] whereas substrates **1** ($R^2 = H$) function as aldehyde equivalents.[2] Therefore, the scope of this general strategy for conversion of carbohydrates into carbocycles would be significantly expanded with the use of substrates **5** derived from carbohydrates. In this manner, a more diverse array of enantiomerically pure cyclopentanes **4**, with $R^2 \neq H$, would become readily available.

In related work, the transmetalation of analogous allenyl-Pd(II) complexes **6** with Et_2Zn or InI has been utilized to generate the corresponding organometallic species **7** or **8**, respectively, capable of intermolecular addition to a carbonyl derivative to yield homopropargyl alcohols **10** with excellent stereocontrol (Scheme 2).[4] The intramolecular application of these processes to effect carbohydrate-to-carbocycle conversions of the type **1**, **5** → **4** through intermediates **3** (MLn = ZnX, InIX), would be also a valuable addition to the synthetic chemist repertoire. This paper reports our preliminary results in this area.

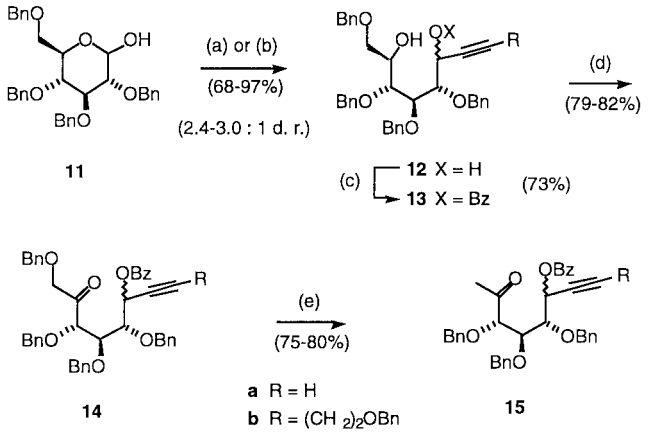


Scheme 2



Scheme 1

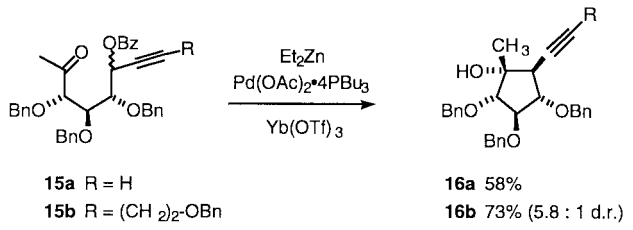
Appropriate model substrates for this study were prepared from commercial 2,3,4,6-tetra-*O*-benzylglucopyranose (**11**) in three steps as outlined in Scheme 3. Key to this straightforward synthesis was the chemoselective benzoylation[5] of propargylic alcohols **12**. Oxidation of the remaining secondary hydroxyl group in benzoates **13** afforded the corresponding ketones **14**.



Scheme 3 a) H-C≡C-MgBr; b) $BnO(CH_2)_2$-C≡C-Li; c) BzCl, Pyr.; d) PCC, NaOAc; e) SmI_2, *t*-BuOH

Treatment of **14a** with either SmI_2/Pd(0) or Et_2Zn/Pd(0), led to substantial degradation whereupon methyl ketone **15a** and benzyl alcohol were isolated in low yields. Ketones **15** were independently prepared in high yield by treatment of **14** with SmI_2/t-BuOH[6] and their reactivity with both SmI_2/Pd(0) and Et_2Zn/Pd(0) was tested.

The reactions of methyl ketones **15** with SmI_2/Pd(0) resulted again in degradation, with benzyl alcohol being the only identified product. On the other hand, the same substrates produced cyclopentanes **16** when treated with Et_2Zn/Pd(0) in the presence of an external Lewis acid (Scheme 4). In the absence of this no reaction was observed at room temperature and higher temperatures led to the degradation of **15**. The stereochemistry of cyclopentanes **16** was unambiguously determined with the aid of ^{1}H NMR NOE experiments.[7]



Scheme 4

A number of reaction conditions have been tested by changing solvent, Pd catalyst and Lewis acid. So far, $Yb(OTf)_3$ has been found to be the most effective Lewis acid to promote these reactions. $ZnCl_2$, $TiCl_4$ and TMSCl gave inferior results and TMSOTf led only to degradation. As for the Pd(0) catalyst, $Pd(PPh_3)_4$, $Pd(OAc)_2$•$4PBu_3$ and $Pd_2(dba)_3$•$4PBu_3$ were all found to give good yields of **16**. $Pd_2(dba)_3$•$4PPh_3$ and $Pd(OAc)_2$•$4PPh_3$ gave inferior results while $PdCl_2(dppf)_2$ and $Pd(OAc)_2$•PPh_3[8] were ineffective. Both THF and benzene are useful solvents for these reactions. CH_2Cl_2 has also been effective but its generalized use was not explored. For practical purposes, the combination of $Yb(OTf)_3$ as Lewis acid with a $Pd(OAc)_2$•$4PBu_3$ catalyst and benzene as solvent gave the best results in terms of combined yields and diastereoselectivities.[9] Under these conditions, one diastereoisomer was obtained as a single or very major product in preparatively useful yields (Scheme 4).

Interestingly, the stereochemical course of these reactions departs from that reported for the corresponding intermolecular additions of allenylzinc reagents to aldehydes.[8] In the latter cases the formation of a configurationally stable key allenylzinc intermediate **7** takes place with net inversion of configuration from precursor propargylic mesylates. Carbonyl addition then proceeds through a chelated cyclic transition state **9** (Scheme 2).[8] A similar arrangement, i.e **17**, in our cyclizations would lead to a product with a *cis* relationship between the alkynyl and OH groups. However, the major diastereoisomer formed displayed instead a *trans* relationship between those groups implying that open transition states **18** are probably involved in the formation of **16**. One reasonable explanation for this behavior is that coordination of the carbonyl group to the strong Lewis acid $Yb(OTf)_3$[10] is the stereocontrolling factor[11,12] in our reactions.

In conclusion, propargylic esters with a tethered carbonyl group are prepared in few steps from carbohydrate precursors. These esters react with Et_2Zn and catalytic Pd(0) in the presence of a Lewis acid to generate nucleophilic allenyl metal species that undergo intramolecular carbonyl addition to afford enantiomerically pure, densely functionalized cyclopentanes with high diastereoselectivity.

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(7) Under appropriate conditions all four isomers of **16** could be obtained and were readily separated by liquid chromatography. This facilitated the stereochemical assignments, as useful comparisons could be made between the observed NOE's of the individual isomers.

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(9) Experimental procedure: To a solution of $Pd(OAc)_2$•$4PBu_3$ (0.05 mmol) and **15** (1.0 mmol) in dry THF (10 mL) under Ar were successively added $Yb(OTf)_3$ (744 mg, 1.2 mmol) and Et_2Zn (1.0 M in hexanes, 3.0 mL, 3.0 mmol). The mixture was stirred at r.t. (**15a**) or 50 °C (bath temperature, **15b**) until consumption of the substrate (TLC). The mixture was diluted with EtOAc (40 mL) and washed successively with 1 M HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The crude product was purified by liquid chromatography on silica gel to afford cyclopentanes **16**. Data for **16a**: $[\alpha]_D^{20}$ -32.0° (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.38 (s, 3H), 2.31 (d, *J* = 2.4 Hz, 1H), 2.98-3.03 (m, 1H), 3.05 (s, 1H), 3.55 (d, *J* = 2.2 Hz, 1H), 3.91-3.95 (m, 2H), 4.51 (s, 2H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 7.30-7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.3, 45.5, 71.9, 72.1, 73.0, 77.1, 82.4, 85.6, 86.5, 86.6, 127.7, 127.9, 128.0, 128.3, 128.4, 128.5, 137.3, 137.7, 137.8; IR (neat) ν 3680-3400, 3360, 2215 cm^{-1}; HRMS calcd for $C_{29}H_{30}O_2$ 442.2144, found 442.2158. Data for **16b**: $[\alpha]_D^{20}$+21.9° (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.36 (s, 3H), 2.57 (td, *J* = 7.2, 2.4 Hz, 2H), 2.98 (m, 1H), 3.02 (s, 1H), 3.55 (d, *J* = 2.9 Hz, 1H), 3.62 (t, *J* = 7.1 Hz, 2H), 3.76-3.96 (m, 2H), 4.52-4.59 (m, 5H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 7.28-7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 20.3, 22.5, 45.7, 68.6, 71.7, 71.9, 72.0, 72.8, 77.5, 79.2, 81.5, 85.6, 86.5, 86.7, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 137.4, 137.8, 137.9, 138.0; IR (neat) ν 3600-3300, 3000-2850 cm^{-1}; HRMS calcd for $C_{38}H_{40}O_5$ 576.2876, found 576.2851.

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(12) It is important to note that substrates **15** were obtained and used as approximately 3:1 diastereomeric mixtures at the propargylic position. Therefore, from the results presented in Scheme 4, the conclussion could be drawn that the major product **16** originates in the major diastereoisomer of **15** and that this one has an (*S*) configuration at the propargylic center. The implicit assumption is that, under the reaction conditions, little stereochemical scrambling takes place at the allenyl metal moiety of species **2** and **3**.[13,14]

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