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An expeditious entry to carbohydrate derived enynes and ene-diynes via Sonogashira coupling of halo-*exo*-glycals

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Abstract—Sonogashira coupling of bromo or iodo-*exo*-glycals, readily prepared from 1-*exo*-methylene furanoses and pyranoses, provides an efficient entry to furanose- and pyranose-derived enyne and ene-diyne moieties found in biologically relevant structures.

Enyne is an important structural unit for biologically active organic compounds, including anticancer antibiotics,[1] natural products,[2] and also for new functional materials.[3] In this context, tetrahydrofuran containing exocyclic enyne and ene-diyne moieties (e.g., **1**, Fig. 1) have been found as substructures in natural products (**2**,[4] **3**,[4a] **4**,[5] **5**,[6] **6**,[7]) or have been synthesized to evaluate their potential biological activities[8] (**7**, **8**). Our group has recently been interested in the synthesis of substituted furanosidic *exo*-glycals (2,5-anhydro-1-deoxy-hex-1-enitols),[9,10] and in this Letter, we wish to report (a) that Sonogashira coupling[11] of carbohydrate derived halo-*exo*-glycals, for example, **9**, with terminal alkynes can be successfully applied for the preparation of furanosidic and pyranosidic enynes, **10a** and **10b**, respectively, and (b) the preparation of furanose and pyranose derived ene-diynes (**10a**,**b** R=≡–Ph, Scheme 1).

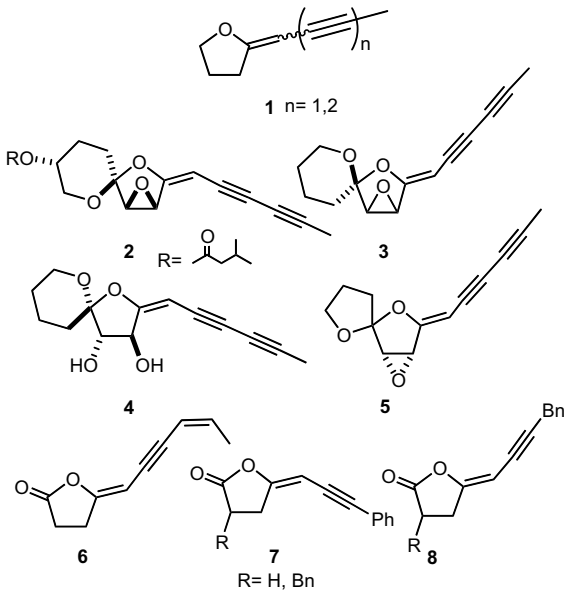
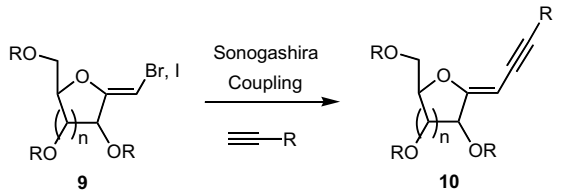


Figure 1. Enyne and ene-diyne derived tetrahydrofurans.

During the course of this work we have illustrated the potential of the method with the preparation of substituted *exo*-glycals **17**–**22** from D-glucofuranose (**11a**,[10] **11b**[10]) and D-galacto and D-glucopyranose-derived halo-*exo*-glycals (**12**,[12] **13**[12]) (See Table 1, Fig. 2).

The coupling reactions of halo-*exo*-glycals **11a**,**b**, **12**, and **13**, with trimethylsilyl acetylene (**14**), 1-dodecyne (**15**) and phenyl acetylene (**16**) took place smoothly to



Scheme 1. Synthesis of furanosidic enynes from halo-*exo*-glycals.

Keywords: *exo*-Glycals; Sonogashira; Enyne; Ene-diyne.
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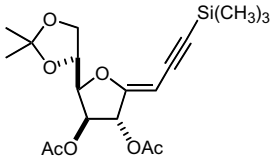
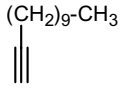
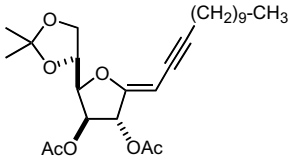
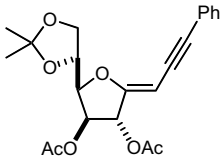
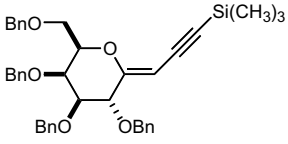
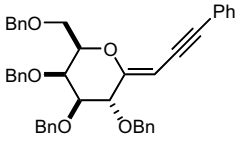
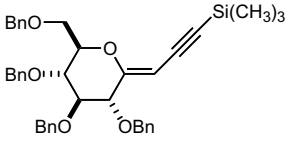
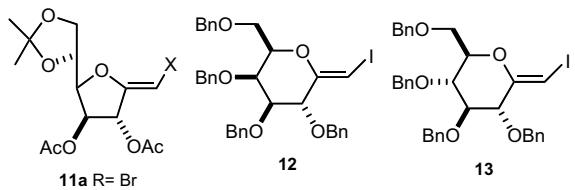
Table 1. Preparation of enynes by reaction of halo-*exo*-glycals **11–13** with terminal alkynes **14–16**

Entry	Glycal	Alkyne	Product	Yield (%)
i	**11a**	 **14**	 **17**	87[a]
ii	**11a**	 **15**	 **18**	93[a]
iii	**11a**	 **16**	 **19**	88[a]
iv	**11b**	**14**	**17**	90[a]
v	**11b**	**15**	**18**	96[a]
vi	**11b**	**16**	**19**	91[a]
viii	**12**	**14**	—	0[a]
ix	**12**	**14**	 **20**	84[b]
x	**12**	**16**	—	0[a]
xi	**12**	**16**	 **21**	92[b]
xii	**13**	**14**	 **22**	84[b]

[a] Et_2NH, CuI (5%), $Pd(PPh_3)_2Cl_2$ (10%).
[b] Et_2NH, CuI (10%), $Pd(PPh_3)_4$ (5%).

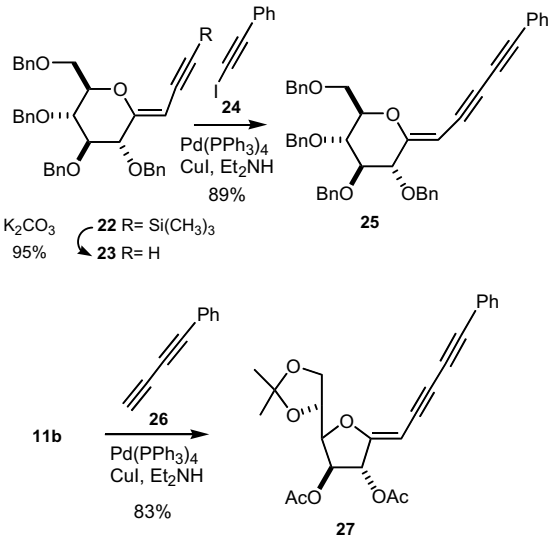


11a R= Br
11b R= I

12 **13**

Figure 2. Halo-*exo*-glycals starting materials.

give high yields of the corresponding substituted *exo*-glycals.[13,14] Several aspects of these reactions, however, deserve further comment: (a) the use of iodo-*exo*-glycals, compared with that of bromo-*exo*-glycals, resulted in slightly higher yields of substituted *exo*-glycals (Table 1, compare entries (i)–(iii) with (iv)–(vi)); (b) furanosidic halo-derivatives underwent coupling reactions under standard Sonogashira–Hagihara conditions ($Pd(PPh_3)_2Cl_2$, Et_2NH, CuI, THF);[15] (c) the corresponding pyranosidic iodo-derivatives, however, did



Scheme 2. Synthesis of pyrano- and furanosidic ene-diynes.

not undergo any coupling reaction under the above mentioned conditions and required the presence of Pd(0)[16,17] ($Pd(PPh_3)_4$, Et_2NH, CuI, THF), rather than Pd(II), as catalyst[18] (Table 1, compare entries (viii) and (x) with entries (ix), (xi)), (d) the coupling reactions, which are described to take place with retention of the configuration,[19] afforded one single stereoisomeric *exo*-glycal from the single starting halo-*exo*-glycal.

The synthesis of ene-diyne moieties was next studied. An approach based on, the sometimes unreliable,[16] sp–sp Sonogashira coupling[20] was first evaluated (Scheme 2). Accordingly, terminal alkyne **23** (readily prepared from enyne **22** by desilylation) was treated ($Pd(PPh_3)_4$, CuI, Et_2NH) with alkynyl iodide **24**[21] to yield ene-diyne **25**. In order to assure the feasibility of the synthesis of ene-diynes we decided to investigate an alternative approach for the synthesis of furanose ene-diynes. In this context we found that ene-diyne **27** could be obtained in excellent yield by Sonogashira coupling of iodo-*exo*-glycal **11** with diyne **26**.[22]

In summary, we have reported an efficient strategy for the preparation of synthetically useful carbohydrate derived ene-ynes by Sonogashira coupling of halo-*exo*-glycals and terminal alkynes. Furanose derivatives undergo the coupling reaction under standard Sonogashira–Hagihara conditions whereas pyranose derivatives required the use of Pd(0) as catalyst. Finally, two convergent approaches for the preparation of the ene-diyne moiety, present in several natural products, have been disclosed. The first approach involved Sonogashira coupling of halo-*exo*-glycals[23,24] with a terminal alkyne followed by sp–sp Sonogashira coupling of the ensuing enyne with a iodo-alkyne. The second, and more direct, strategy implied direct Sonogashira coupling of a iodo-*exo*-glycal with a terminal diyne. The use of these protocols for the preparation of naturally occurring natural products is underway in our laboratory and will be described in due course.

Acknowledgements

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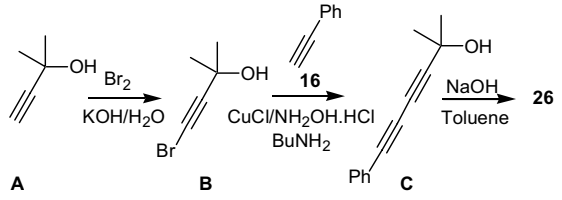
22. Diyne **26** was prepared, according to the synthetic Scheme shown below according to: Dabdoub, M. J.; Baroni, A. C. M.; Lenardão, E. J.; Gianeti, T. R.; Hurtado, G. R. *Tetrahedron* **2001**, *57*, 4271, Cadiot–Chodkiewicz coupling reaction of bromo alkyne **B** and phenyl acetylene **16** yielded diyne **C**, which upon deprotection furnished terminal alkyne **26**.



23. *General procedure for the Sonogashira coupling reaction*. *Method* (a): To a thoroughly degassed (argon, 10 min) solution of halo-*exo*-glycal (0.17 mmol) in Et_2NH, were added CuI (5%) and $Pd(PPh_3)_2Cl_2$ (10%). The reaction mixture was kept at room temperature with stirring for 5 min. The appropriate terminal alkyne (1 equiv) dissolved in Et_2NH (3 mL) was then added via cannula. The reaction was then stirred at room temperature until complete disappearance of the starting material. The solution was treated with H_2O and extracted with ethyl acetate (EtOAc). The organic layer was then dried (magnesium sulfate) and evaporated to furnish a residue, which was purified by flash chromatography using hexane–EtOAc mixtures as eluant. *Method* (b): To a thoroughly degassed (argon, 10 min) solution of iodo-*exo*-glycal (0.1 mmol) in Et_2NH (4 mL/mmol) were added successively $Pd(PPh_3)_4$ (5 μmol), CuI (0.01 mmol) and the corresponding alkyne (1.1 equiv, 0.11 mmol). The reaction was then stirred at room temperature until complete disappearance of the starting material (1–2 h). The solution was diluted with ethyl acetate and washed successively with saturated NH_4Cl and brine. The organic layer was dried (magnesium sulfate) and evaporated to furnish a residue, which was purified by flash chromatography using hexane–EtOAc mixtures as eluant.
24. *Data for selected compounds*: *Enyne* **17**: $[\alpha]_D^{21} + 21.0$ (*c* 0.15, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 5.48 (d, $J = 1.1$ Hz, 1H), 5.33 (dd, $J = 1.1$, 3.6 Hz, 1H), 4.98 (s, 1H), 4.57 (dd, $J = 3.6$, 7.6 Hz, 1H), 4.36 (ddd, $J = 5.3$, 5.8, 7.6 Hz, 1H), 4.15 (m, 2H), 2.12 (s, 3H), 2.09 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 0.20 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 169.3, 169.1, 162.5, 109.7, 98.9, 85.2, 83.2, 82.2, 75.1, 74.1, 72.3, 66.7, 26.8, 25.5, 20.9 (×2), 0.0. API-ES: 397 $[M^+ + 1]$, 419.0 $[M^+ + Na]$.
Enyne **18**: $[\alpha]_D^{21} + 23.4$ (*c* 0.83, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.45 (s, 1H), 5.29 (d, $J = 3.6$ Hz, 1H), 4.90 (s, 1H), 4.46 (dd, $J = 3.9$, 7.9 Hz, 1H), 4.32 (ddd, $J = 5.4$, 6.3, 7.9 Hz, 1H), 4.12 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.11 (m, 16H), 0.87 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.5, 169.3, 160.6, 109.8, 96.3, 86.0, 83.0, 75.1, 74.4, 74.3, 72.4, 67.2, 32.1, 29.8 (×2), 29.5, 29.4, 29.1, 28.9, 27.0, 25.5, 22.9, 21.1, 21.0, 20.0, 14.3. API-ES: 451.6 $[M^+ + 1]$.
Enyne **19** : $[\alpha]_D^{21} + 31.5$ (*c* 0.9, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32 (m, 5H), 5.54 (s, 1H), 5.37 (d, $J = 4.0$ Hz, 1H), 5.17 (s, 1H), 4.58 (dd, $J = 4.0$, 7.9 Hz, 1H), 4.37 (ddd, $J = 5.3$, 5.6, 7.8 Hz, 1H), 4.18 (m, 2H), 2.12 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.3, 169.2, 161.3, 131.4, 128.3, 128.1, 123.7, 109.8, 94.7, 85.4, 83.6, 83.3, 75.2, 74.2, 72.4, 67.0, 26.9, 25.4, 20.9, 20.8. API-ES: 401.2 $[M^+ + 1]$, 423.3 $[M^+ + Na]$.
Enyne **20**: $[\alpha]_D^{21} + 31.4$ (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41–7.25 (m, 20H), 5.24 (d, $J = 1.8$ Hz, 1H), 4.87 (d, $J = 11.4$ Hz, 1H), 4.71–4.42 (m, 7H), 4.35 (dd, $J = 9.0$, 1.8 Hz, 1H), 4.03 (t, $J = 2.1$ Hz, 1H), 3.92 (dt, $J = 6.3$, 2.1 Hz, 1H), 3.70 (d, $J = 6.3$ Hz, 2H), 3.62 (dd, $J = 9.0$, 2.1 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.1, 138.4, 138.1, 137.9, 137.7, 128.4, 128.3, 128.2, 127.9 (×2), 127.7, 127.6, 127.5 (×2), 99.9, 98.7, 90.2, 81.6, 78.7, 76.5, 74.3, 74.1, 74.0, 73.5, 72.7,68.3, 0.0 (×3); API-ES: m/e: 633.3 $[M+1]^+$.
Enyne **21**: $[\alpha]_D^{21} + 33.9$ (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44–7.23 (m, 25H), 5.42 (d, $J = 1.5$ Hz, 1H), 4.89 (d, $J = 11.7$ Hz, 1H), 4.71–4.55 (m, 6H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.41 (dd, $J = 9.0$, 1.0 Hz, 1H), 4.07 (t, $J = 2.0$ Hz, 1H), 3.99 (dt, $J = 6.0$, 2.0 Hz, 1H), 3.82–3.70 (m, 2H), 3.68 (dd, $J = 9.0$, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.7, 138.3, 138.1, 138.0, 137.8, 131.4, 128.4, 128.3 (×2), 128.1 (×2), 127.9, 127.8, 127.7, 127.6 (×2), 127.5, 123.9, 93.6, 90.7, 84.4, 81.6, 78.9, 76.7, 74.3, 74.1,74.0, 73.5, 72.8, 68.8; API-ES: m/e: 659.3 $[M+Na]^+$.
Enyne **22**: $[\alpha]_D^{21} + 33.6$ (*c* 1.2, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42–7.19 (m, 20H), 5.00 (s, 1H), 4.80–4.51 (m, 8H), 4.18 (ddd, $J = 9.7$, 3.1, 2.4 Hz, 1H), 3.91 (d, $J = 4.1$ Hz, 1H), 3.89–3.79 (m, 4H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.8, 138.3, 138.0, 137.8, 137.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 99.7, 98.7, 89.8, 83.6, 77.6 (×2), 77.5, 73.8 (×2), 73.0, 71.4, 68.4, 0.4 (×3); API-ES: m/e: 633.3 $[M+1]^+$, 655.3 $[M+Na]^+$.
Ene-diyne **25**: $[\alpha]_D^{21} + 3.0$ (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71–7.26 (m, 25H), 5.04 (d, $J = 0.7$ Hz, 1H), 4.80–4.53 (m, 8H), 4.24–4.18 (m, 1H), 3.95–3.80 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.7, 138.3, 137.9, 137.7, 137.2, 132.3, 128.8, 128.5, 128.4, 128.3 (×2), 128.0, 127.9, 127.8 (×2), 127.7 (×2), 127.6, 127.4, 122.2, 88.5, 83.4, 81.5, 77.8, 77.7, 77.4 (×2), 77.1, 74.6, 73.8, 73.5, 73.1, 71.6, 68.1; API-ES: m/e: 683.3 $[M+Na]^+$.
Ene-diyne **27**: $[\alpha]_D^{21} + 11.5$ (*c* 0.6, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 (m, 5H), 7.32 (m, 5H), 5.50 (s, 1H, $J = 0.98$ Hz), 5.34 (dd, 1H, $J = 0.98$ Hz, $J = 3.7$ Hz, H-3), 5.05 (s, 1H), 4.53 (dd, 1H, $J = 3.7$, 8.5 Hz), 4.34 (ddd, 1H, $J = 4.6$, 5.4, 8.3 Hz, H-5), 4.19 (dd, 1H, $J = 5.6$, 8.9 Hz), 4.13 (dd, 1H, $J = 4.6$, 8.8 Hz), 2.13 (s, 3H, Me),2.11 (s, 3H), 1.45 (s, 3H), 1.35 (s 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.5, 169.3, 164.9, 132.6, 129.3, 128.6, 122.2, 110.0, 84.3, 83.9, 82.4, 78.9, 76.3, 75.3, 74.4, 74.1, 72.3, 67.3, 27.1, 25.5, 21.1, 20.1. API-ES: 425.2 $[M^+ + 1]$.