Rhodium-Catalyzed Alkyne Cyclotrimerization Strategies for *C*-Arylglycoside Synthesis

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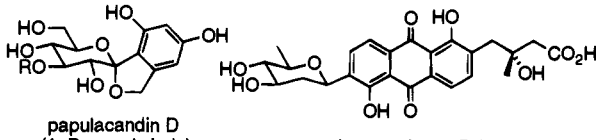
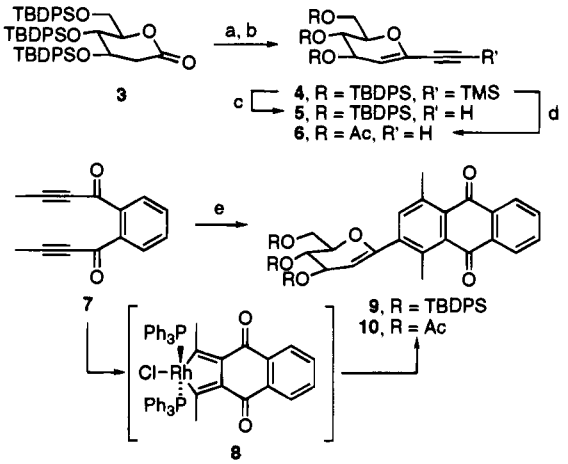
The *C*-arylglycosides are a large family of natural products which generally exhibit a wide variety of antibiotic, antitumor, and antifungal activities. For instance, the papulacandins are a group of spiroketal *C*-arylglycosides which exhibit selective antifungal activity against *Candida albicans*.[1] *C*-Anthracyclinone glycoside structures are found in antineoplastic natural products including vineomycin, urdamycin, and kidamycin.[2] Most synthetic routes reported to *C*-arylglycosides feature formation of the carbon–carbon bond between carbohydrate and aromatic precursors.[3] However, alternative approaches which feature postcoupling assemblage of carbohydrate[4] or aromatic components[5] have been reported. Herein we report a novel strategy for constructing the core skeletons of two families of *C*-arylglycosides represented by structures **1** and **2** by rhodium-catalyzed alkyne cyclotrimerization[6,7] with *C*-alkynylcarbohydrate substrates.



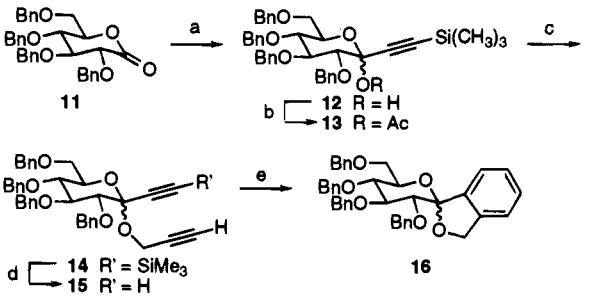
Our initial goal of assessing the viability of metal-catalyzed alkyne cyclotrimerization for *C*-arylglycoside synthesis required preparation of a *C*-alkynylcarbohydrate substrate[8] (Scheme 1). Addition of 2-(trimethylsilyl)ethynylmagnesium bromide to 2-deoxy-D-gluconolactone **3**[9] followed by dehydration of the cyclic lactol intermediate[10] afforded alkynylglycal **4**.[11] Straightforward protective group manipulations afforded substrates **5** and **6**. Our first experiments with a stoichiometric rhodium metallacycle **8** (derived from diketodiyne **7**)[12] proved encouraging, as the *C*-anthracyclinone glycoside **9** was obtained in 46% isolated yield from **5**. With protic solvents, a rhodium-*catalyzed* reaction[13] produced *C*-arylglycosides **9** and **10** in 35% and 58% yields, respectively.

Scheme 1. Synthesis of *C*-Anthracyclinone Glycosides[a]



[a] Reagents and conditions: (a) BrMg–C≡C–TMS, THF; (b) $POCl_3$, pyridine, CH_2Cl_2, 43% (two steps); (c) 50% aqueous NaOH, 10 mol % $BnNEt_3Cl$, MeCN, 90% (d) TBAF, THF; then Ac_2O, pyridine, 15 mol % DMAP, CH_2Cl_2, 92% (e) **5** or **6**, 20 mol % $ClRh(PPh_3)_3$, EtOH, 78 °C; 35% for **9**; 58% for **10**.

Scheme 2. Synthesis of *C*-Aryl Spiroglycoside[a]



[a] Reagents and conditions: (a) Li–C≡C–TMS, THF, 57%; (b) Ac_2O, pyridine, 20 mol % DMAP, CH_2Cl_2, 57% (2.6:1 mixture); (c) $TMSOCH_2C{\equiv}CH$, 10 mol % $SnCl_4$, 10 mol % $AgClO_4$, CH_2Cl_2; (d) 50% aqueous NaOH, 20 mol % $BnNEt_3Cl$, MeCN, 67% (two steps, 2.2:1 mixture); (e) saturated HC≡CH in EtOH, 10 mol % $ClRh(PPh_3)_3$, 0 °C, 89%.

We have also explored this strategy for synthesis of the spiroglycoside structure **16** from bisalkynylcarbohydrate derivatives (Scheme 2). Addition of 2-(trimethylsilyl)ethynyllithium to **11**[14] proceeds without elimination to give **12** as a mixture of anomers.[15] The *C*-alkynyl-*O*-propargyl substrate **15** is obtained

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(11) Alkynylglycal **4** was initially prepared from 3,4,6-tris-*O*-(*tert*-butyldiphenylsilyl)-1-(tributylstannyl)-D-glucal (Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944): (1) I_2, CH_2Cl_2 (in dark), 72%; (2) $ClZn–C{\equiv}C–TMS$, 10 mol % $Cl_2Pd(PPh_3)_2$, THF, 90%.

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(13) Grigg et al. have proposed that polar solvents promote a catalytic mechanism by facilitating ligand dissociation (ref 6d).

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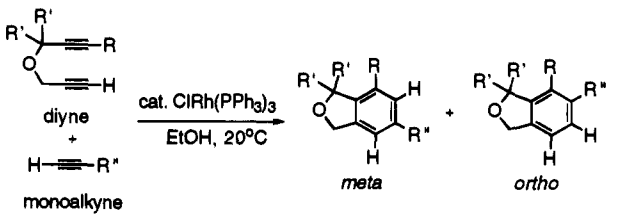
by Lewis acid-catalyzed glycosylation[16] of the anomeric acetates **13** with *O*-propargyl trimethylsilyl ether followed by alkaline desilylation of the synthetic intermediate **14**. Cyclotrimerization of each anomer of the bis-terminal diyne **15** with a saturated ethanolic solution of acetylene and Wilkinson's catalyst provides an excellent yield of the corresponding unfunctionalized spirocyclic *C*-arylglycosides **16**.

The regioselectivity of rhodium-catalyzed alkyne cyclotrimerization with differently substituted diyne substrates has not been previously reported. To this end, diyne substrates **17**–**19**[17] were evaluated in various combinations with the simple monosubstituted alkynes **20**–**22** to afford a variety of substituted dihydroisobenzofuran products (Table 1). These results indicate that the magnitude of *meta*-selectivity is highly dependent on the steric size of the alkyne substituents. Whereas the methyl-substituted diyne **17** does not show high regioselectivity except upon reaction with the hindered monosubstituted alkyne **21** (entries 1–3), the sterically bulky tertiary alcohol-substituted diyne **18** gives only the *meta*-substituted aromatic isomers upon reaction with all three monoalkynes **20**–**22** (entries 4–6). Rhodium-catalyzed cyclotrimerization is compatible with the acid-sensitive alkoxyacetylene substrate **19** (entries 7–9), but diynes capped with one or two trimethylsilyl groups are unreactive. In contrast to cobalt-mediated cyclotrimerizations,[18] the rhodium-catalyzed reaction is predominantly *meta*-regioselective. In addition, oligomerization or dimerization of terminal alkyne-containing diyne substrates **15**, **18**, and **19** is only a minor side reaction with rhodium catalysis and is further minimized by the use of an excess of inexpensive monoalkyne components.

Further studies are in progress to explore mechanistic factors responsible for *meta*-selectivity, as well as the application of cyclotrimerization strategies to the total synthesis of bioactive *C*-arylglycoside natural products.

Table 1. Regioselectivity of $ClRh(PPh_3)_3$-Catalyzed Cyclotrimerization



entry	diyne	monoalkyne	yield of aromatic products (isomer ratio)
1	R = CH_3, R' = H (**17**)	R" = *n*-Bu (**20**)	35% (*m*: *o* = 1.7 : 1)
2	**17**	R" = $C(CH_3)_2OH$ (**21**)	54% (*meta* only)
3	**17**	R" = CH_2OH (**22**)	53% (*m*: *o* = 1.8 : 1)[a]
4	R = $C(CH_3)_2OH$, R' = H (**18**)	**20**	36% (*meta* only)
5	**18**	**21**	60% (*meta* only)[b]
6	**18**	**22**	52% (*meta* only)[b, c]
7	R = OEt, R' = CH_3 (**19**)	**20**	61% (*m*: *o* = 4 : 1)
8	**19**	**21**	53% (*meta* only)
9	**19**	**22**	59% (*m*: *o* = 4 : 1)

[a] 2 mol % $ClRh(PPh_3)_3$ was used for this entry. [b] Analytically pure compounds were obtained by conversion of aromatic products to the corresponding bis-*O*-trimethylsilyl ethers (excess 1-(trimethylsilyl)imidazole, THF, 20 °C, 16 h) followed by flash chromatography. [c] The yield was 95% based on recovered diyne **18**.

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Supplementary Material Available: Experimental procedures and tabulated spectral data for compounds **4**–**6**, **9**, **10**, **12**–**16**, **18**, **19**, and aromatic products from Table 1 (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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