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# A New Versatile Strategy for C-Aryl Glycosides†

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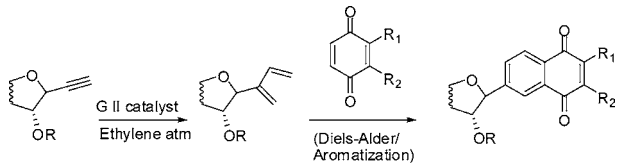
## ABSTRACT




**A versatile strategy involving a sequential intermolecular enyne metathesis of C-alkynyl glycosides with ethylene, Diels–Alder, and aromatization reactions is successfully developed to provide a range of C-aryl glycosides.**

The C-aryl glycosides[1] are a class of C-glycosides wherein carbohydrates are directly attached to an aromatic moiety through a C−C bond rather than the usual C−O bond. Due to this small change in the connectivity, these compounds are known to be quite stable to both enzymatic and acid hydrolysis. It is also believed that they bind to DNA to form stable complexes and may have interesting biological properties. Furthermore, C-aryl glycoside frameworks are an integral part of many natural products. Two such materials are gilvocarcin M (**1**) and vineomycinone B2 methyl ester (**2**) that have useful pharmacological activities. As a consequence, this class of natural products has attracted synthetic chemists' attention[2] for quite some time. Several strategies have been developed in response to the challenges posed by these natural products. Most of the existing strategies that lead to simple C-aryl glycosides concentrate on construction of the key C−C bond between the carbohydrates and aromatic components.[3]

However, there are many naturally occurring C-aryl glycosides having anthraquinones as their structural subunit which need further functionalization of the aromatic unit. To circumvent these difficulties, a few elegant benzannulation[4] strategies have been conceived for the direct construction of the polysubstituted aryl component from a simpler preformed C-glycoside. Martin and co-workers cleverly utilized benzyne precursors as quinone equivalents in their synthesis of C-aryl glycosides via furan−benzyne cycloaddition.[5] Nevertheless, given the availability of quinones from commercial sources, direct use of quinones in the Diels−Alder reaction/aromatization to generate the anthraquinone functionality of C-aryl glycosides is an attractive and efficient strategy. However, this route has seldom been explored,

† Dedicated with respect to Professor G. Mehta, Indian Institute of Science, Bangalore, India.

(1) For general reviews on aryl glycosides, see: (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier Science: Tarrytown, NY, 1995. (b) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83. (c) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−195. (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959. (e) Postema, M. H. D.; Liu, L.; McKee, M. *Curr. Org. Chem.* **2001**, *5*, 1133−1167.

(2) (a) Parker, K. A. *Pure Appl. Chem.* **1994**, *66*, 2135−2138. (b) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (c) Martin, S. F. *Pure Appl. Chem.* **2003**, *75*, 63−70.

(3) For selected approaches to C-aryl glycosides, see: (a) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201−206. (b) Parker, K. A.; Koh, Y. H. *J. Am. Chem. Soc.* **1994**, *116*, 11149−11150. (c) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004−1015. (d) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061−11068. (e) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307−2313. (f) Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2*, 497−499. (g) Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2001**, *3*, 1547−1550. (h) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013−2015. (i) Hauser, F. M.; Hu, X. *Org. Lett.* **2002**, *4*, 977−978. (j) Vijayasaradhi, S.; Aidhen, I. S. *Org. Lett.* **2002**, *4*, 1739−1742. (k) Rousseau, C.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3763−3766. (l) Vu, N. Q.; Leconte, S.; Brown, E.; Grée, D.; Grée, R.; Dujardin, G. *J. Org. Chem.* **2005**, *70*, 2641−2650.

(4) (a) Pully, S. R.; Carey, J. P. *J. Org. Chem.* **1998**, *63*, 5275−5279. (b) Janes, E.; Nieger, M.; Saarenketo, P.; Doetz, K. H. *Eur. J. Org. Chem.* **2003**, 2276−2285. (c) Yamamoto, Y.; Saigoku, T.; Ohgai, T.; Nishiyama, H.; Itoh, K. *Chem. Commun.* **2004**, 2702−2703.

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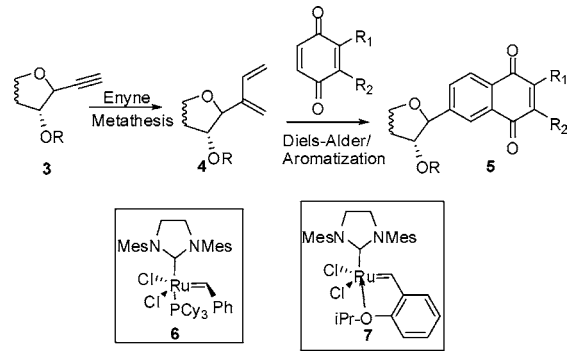
presumably due to (i) difficulties associated with elaboration of a suitable diene moiety from the sugar and (ii) the drastic conditions required for the cycloaddition between furan and quinones.[6] We envisioned the possibility of introducing the diene indirectly via alkyne enyne metathesis[7] and carrying out the Diels−Alder reaction with quinones followed by subsequent aromatization[8] to provide a direct access to C-aryl glycosides. Herein, we disclose our initial results on the application of this simple diversity-oriented strategy, which is also atom-economical, to a range of new quinone-based C-aryl glycosides.

Our proposed general strategy is delineated in Scheme 1. In the recent past, intermolecular catalytic enyne metathesis

**Scheme 1.** General Strategy for C-Aryl Glycosides




between ethylene and alkynes, producing conjugated dienes,[9] has received significant attention due to its broad utility in synthesis. Several catalysts have been developed for such metatheses, and it is worth mentioning the high success of the Grubbs's second generation catalyst **6**[10] and Hoveyda's phosphine-free catalyst **7**[11] in cross-metathesis reactions. According to our strategy, the requisite 1,3-dienes would be generated from the cross enyne metathesis between alkyne **3** and ethylene. These dienes **4** can undergo cycloaddition reaction with a variety of quinones followed by aromatization reaction to provide C-aryl glycosides having naphthaquinone/anthraquinone subunits.

To study the feasibility of this approach, we began with the C-alkynyl glycoside **12**,[12] which was easily prepared from the commercially available D-glucose in seven straightforward steps in approximately 50% overall yield. While the initial study with 3 mol % of Grubbs's second generation catalyst **6** under ethylene atmosphere gave disappointingly low yields of diene, further studies revealed that 5 mol % of the catalyst was extremely effective for this intermolecular cross enyne metathesis, providing the diene **17** in good yield. With diene **17** in hand, the stage was now set for the versatile Diels−Alder reaction with different quinones (Table 1) as a

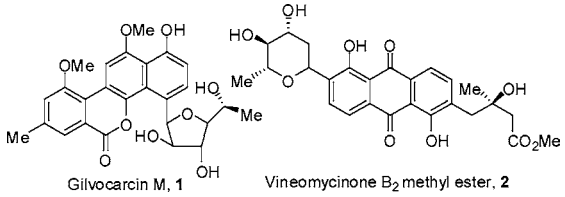



**Figure 1.** C-aryl glycoside natural products.

means of installing the required aromatic moiety. As planned, it underwent a smooth cycloaddition reaction with 1,4-naphthaquinone **8**, affording the corresponding cycloadduct in good yield. On the basis of our earlier experience,[8g] we decided to treat the crude cycloaddition product immediately with triethylamine and silica gel without further purification, and as expected, this protocol worked well to allow us to directly isolate the respective aromatized/oxidized cycloadduct **22**.

The success of the Diels−Alder/aromatization sequence provided the foundation for synthesizing a variety of C-aryl glycosides, starting from various C-alkynyl glycosides. Toward this end, C-alkynyl glycosides **13**−**16**, derived from D-mannose, D-ribose, and D-galactose, respectively, were converted to the corresponding 1,3-dienes (Table 1) and were later treated with dienophiles 1,4-naphthaquinone **8**, benzoquinone **9**, and 5-hydroxy-1,4-naphthaquinone **10** individually to afford a range of new C-aryl glycosides in good yield (Table 1).

Our strategy has also been successfully extended to simple trisubstituted C-aryl glycosides, with DMAD **11** as dieno-

(5) (a) Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937−6938. (b) Kaelin, D. E., Jr.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994−12995. (c) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075−1077. (d) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696−13697.

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(7) For recent reviews on enyne metathesis and/or cross metathesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056. (b) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−378. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (f) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. (g) Connon, C. S.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (h) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (i) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382.

(8) For sequential enyne metathesis and Diels−Alder reaction with quinones as well as other dienophiles, see: (a) Bentz, D.; Laschat, S. *Synthesis* **2000**, 1766−1773. (b) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, *4*, 787−792. (c) Moreno-Manas, M.; Pleixats, R.; Santamaria, A. *Synlett* **2001**, 1784−1786. (d) Guo, H.; Madhushaw, R.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, *58*, 5627−5637. (e) Yang, Y.-K.; Tae, J. *Synlett* **2003**, 2017−2020. (f) Dolhem, F.; Lievre, C.; Demailly, G. *Eur. J. Org. Chem.* **2003**, 2336−2342. (g) Kaliappan, K. P.; Ravikumar, V. *Org. Biomol. Chem.* **2005**, *3*, 848−851.

(9) Ethylene cross enyne metathesis: (a) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788−1792. (b) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. (c) Tonagaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235−2238. (d) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793−1796.

(10) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(11) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23.

(12) This preparation of starting material compares favorably with that for the Martin glycosyl furans which require two steps from a sugar lactone with approximately 50% yield.

**Table 1.** Synthesis of C-Aryl Glycosides

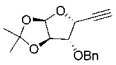
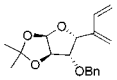
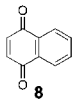
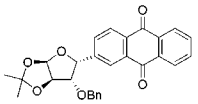
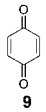
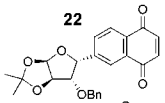
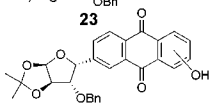
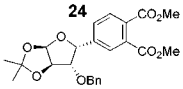
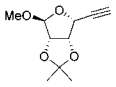
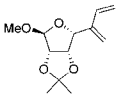
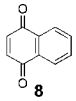
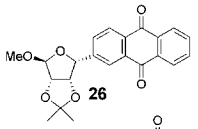
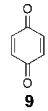
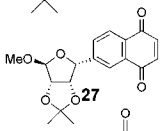
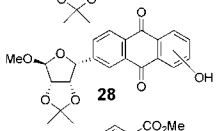
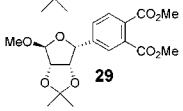
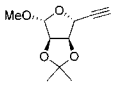
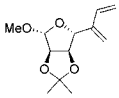
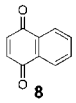
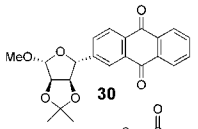
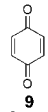
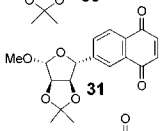
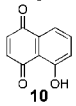
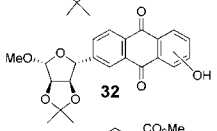
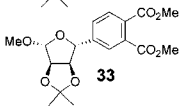
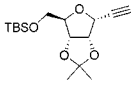
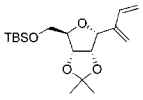
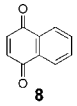
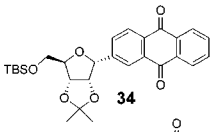
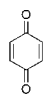
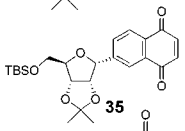
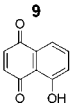
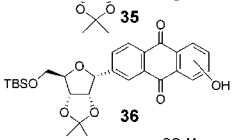
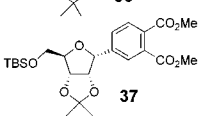
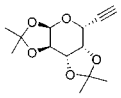
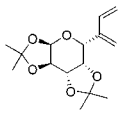
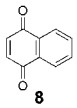
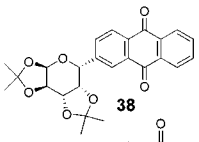
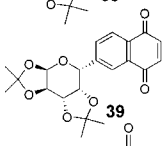
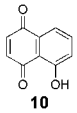
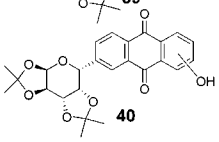
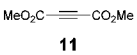
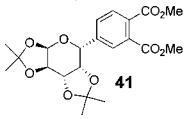
| serial no. | alkyne | 1,3-diene[a] | dienophile | C-aryl glycoside[b] | yield[c] |
|---|---|---|---|---|---|
| 1 |  **12** |  **17** (89%) |  **8** |  **22** | 60% |
| | | |  **9** |  **23** | 59% |
| | | |  **10** |  **24** | 56%[d] |
| | | |  **11** |  **25** | 82% |
| 2 |  **13** |  **18** (89%) |  **8** |  **26** | 59% |
| | | |  **9** |  **27** | 61% |
| | | |  **10** |  **28** | 53%[d] |
| | | |  **11** |  **29** | 81% |
| 3 |  **14** |  **19** (98%) |  **8** |  **30** | 51% |
| | | |  **9** |  **31** | 54% |
| | | |  **10** |  **32** | 57%[d] |
| | | |  **11** |  **33** | 85% |
| 4 |  **15** |  **20** (98%) |  **8** |  **34** | 62% |
| | | |  **9** |  **35** | 72% |
| | | |  **10** |  **36** | 57%[d] |
| | | |  **11** |  **37** | 83% |

Table 1 (Continued)

| serial no. | alkyne | 1,3-diene[a] | dienophile | C-aryl glycoside[b] | yield[c] |
|---|---|---|---|---|---|
| 5 |  16 |  21 (98%) |  8 |  38 | 61% |
| | | |  9 |  39 | 58% |
| | | |  10 |  40 | 51%[d] |
| | | |  11 |  41 | 89% |

[a] The dienes were synthesized from the respective C-alkynyl glycosides using Grubbs's second generation catalyst (5 mol %) under ethylene atmosphere in toluene at 80 °C. [b] All Diels−Alder reactions were carried out in toluene at 80 °C. [c] Overall yield for two steps. [d] Mixture of regioisomers was obtained.

phile, and in this case, the subsequent aromatization required $MnO_2$ oxidation (see Supporting Information).[13]

Furthermore, we probed a sequential one-pot tandem metathesis−cycloaddition−aromatization reaction[14] on C-alkynyl glycoside to obtain the C-aryl glycoside directly. Though it was heartening to realize this single-pot reaction provided the required C-aryl glycoside, yields were lower (30−35%) than the combined yield (more than 50%) over the two individual steps (intermolecular enyne metathesis and cycloaddition).

In summary, we have designed and executed an expedient synthetic strategy for C-aryl glycosides. Our methodology should be easily extendable to the synthesis of a much greater variety of C-aryl glycosides by using appropriate sugar-derived alkynes and dienophiles, thereby increasing the opportunities for diversity generation. This synthetic access to C-aryl glycosides should pave the way for the construction of several anthraquinone C-glycosides.[15] Having secured initial access to the C-aryl glycosides via cross enyne metathesis under ethylene atmosphere, we also carried out enyne cross metathesis[16] of C-alkynyl glycosides with vinyl acetate and ethyl vinyl ether for the generation of further diversity on the aromatic moiety, and this work will form a part of the full paper in due course. This process has important strategic implications for the design and implementation of future synthetic strategies toward C-aryl glycosides and related natural products.

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**Supporting Information Available:** Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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