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A new access to *C*-arylglycosides related to the gilvocarcins

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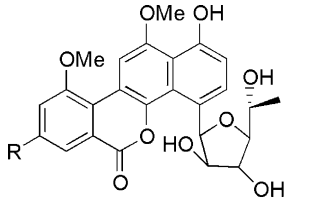
Abstract—A new strategy has been developed for the synthesis of *C*-aryl glycosides based on a xanthate-mediated free radical addition–cyclization sequence of an acetophenone xanthate to a vinylic carbohydrate followed by aromatization.

C-Aryl glycosides or glycosylarenes represent an important class of natural products in which carbohydrates are directly bound to an aromatic moiety through a C–C bond and which have been shown to be specially resistant to enzymatic hydrolysis.[1] These compounds constitute interesting synthetic targets in the light of their biological activities and unique structures. The anticancer gilvocarcins (**1a** and **1b**) belong to one of four classes of naturally occurring *C*-arylglycosides, in which the sugar is located *para* to a phenolic hydroxyl group (Fig. 1).[2]



Gilvocarcin M, R = CH_3 (**1a**)
Gilvocarcin V, R = $CH{=}CH_2$ (**1b**)

Figure 1.

Over the past few years, several methods for the construction of these compounds have been developed. The $O \rightarrow C$-glycoside rearrangement reported by Suzuki and co-workers[3] is probably the most useful because it has several advantages in terms of regio- and stereoselectivity. This method was successfully applied for the total synthesis of the gilvocarcins and their analogues.[2] However, because this is a Lewis acid promoted process, the aromatic moieties that take part in the reaction are required to be electron-rich and the carbohydrate unit solidly protected.

It is known that α-tetralones can be converted into the corresponding naphthols by different means.[4] Although this transformation is very effective, the main problem lies in the preparation of appropriately substituted tetralones. A few years ago, we reported a new method for the preparation of α-tetralones using a xanthate-mediated free radical addition–cyclization sequence.[5,6] This process allows the synthesis of a wide variety of substituted tetralones under mild and neutral conditions. We have now found that this approach can indeed be extended to the synthesis of group I *C*-aryl glycosides (in which the sugar is located *para* to a phenolic hydroxyl group) by combining the radical sequence with an efficient aromatization protocol. This opens a potentially short route to the gilvocarcins.

As shown in Scheme 1, we initially chose starting materials bearing electron withdrawing groups in order to show the applicability of our method. Thus, our path to the *C*-aryl glycosides initially involved the radical addition of xanthates **2a**–**b**[5,7] onto known olefin **3**[8] using dilauroyl peroxide (DLP) as initiator in 1,2-dichloroethane (DCE) as solvent, yielding **4a** and **4b** in 93% and 84% yields, respectively.[9] When a refluxing solution of **4a** and **4b** in DCE was treated with 1.4 equiv of DLP (added portionwise), tetralones **5a** (57%), and **5b** (53%) were obtained,[10] together with a small amount of the corresponding reduced products **6a** (15%) and **6b** (21%), respectively.

Keywords: *C*-Arylglycosides; Gilvocarcins; Xanthate; Addition; Cyclization; Aromatisation.
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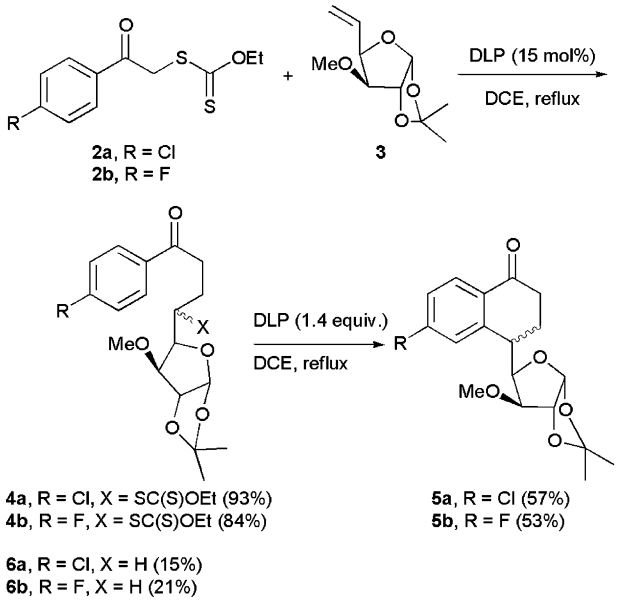
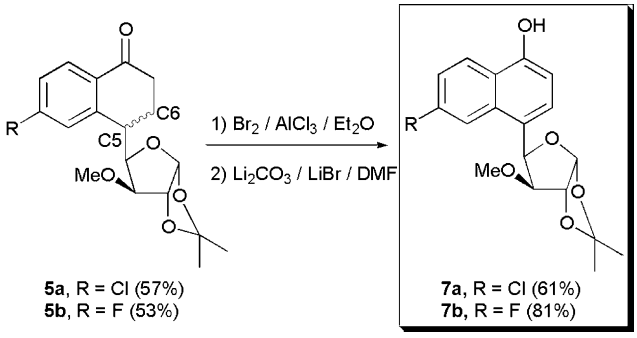


Scheme 1.

With tetralones **5a**–**b** in hand, completion of the synthesis required only the aromatization step. It was anticipated that oxidation of the C5–C6 bond would induce enolization of the ketone moiety yielding the completely aromatized product possessing an appropriately located phenolic hydroxyl. After some experimentation, we found that treatment of **5a**–**b** with Br_2 and a catalytic amount of $AlCl_3$ in Et_2O followed by elimination under basic conditions furnished *C*-aryl glycosides **7a** and **7b** in good yields[11] (Scheme 2).

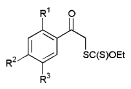
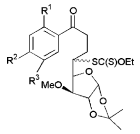
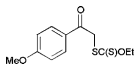
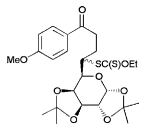
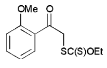
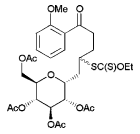
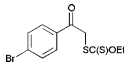
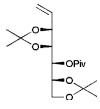
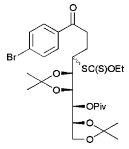


Scheme 2.

We have thus been able to assemble in a few steps complex structures, which would otherwise be only tediously accessible by conventional routes.

Having developed an effective and regioselective strategy for preparing group I *C*-aryl glycosides, it remained to extend this approach to different starting xanthates and carbohydrates. Thus, acetophenone xanthates **8**–**12** were subjected to the same reaction conditions depicted below in the presence of known olefins **3**,[8] **13**,[12] **14**,[13] and **15**[14] to afford the corresponding adducts **16**–**20** in good to excellent yields (Table 1).

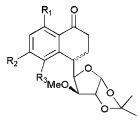
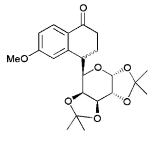
Table 1. Addition products

Starting xanthate	Olefin	Product (yield %)
		
8, R^1 = OMe, R^2 = H, R^3 = OMe **9**, R^1 = OPiv, R^2 = OMe, R^3 = H	**3**	**16**, R^1 = OMe, R^2 = H, R^3 = OMe (77%) **17**, R^1 = OPiv, R^2 = OMe, R^3 = H (95%)
		
10	**13**	**18** (64%)
		
11	**14**	**19** (58%)[a]
		
12	**15**	**20** (42%)[b]

[a] Along with 27% recovered starting material.
[b] 44% recovered starting material.

Adducts **16**–**20** were then treated with a stoichiometric amount of DLP in DCE to give the corresponding tetralones **21**–**23** in variable yields (Table 2). Compounds **19** and **20** did not afford the expected tetralones, producing a complex mixture of products instead. The reasons for the failures with these two compounds are still unclear. It is possible that intramolecular hydrogen abstraction followed by an uncontrolled sequence competed successfully with the desired ring-closure to the tetralone.

Table 2. Cyclization products

Adduct	Tetralone (yield %)
	
16, R^1 = OMe, R^2 = H, R^3 = OMe **17**, R^1 = OPiv, R^2 = OMe, R^3 = H	**21**, R^1 = OMe, R^2 = H, R^3 = OMe (41%) **22**, R^1 = OPiv, R^2 = OMe, R^3 = H (26%)
	
18	**23** (65%)
19	Degradation
20	Degradation

These preliminary studies indicate that this approach could indeed be used to construct the gilvocarcins (**1a**–**b**). The conditions are mild and many substituents are tolerated. The successful synthesis of differentially protected dihydroxy derivatives **21** and **22** is particularly relevant in this context. Furthermore, because this approach allows the use of a great variety of substituents (including electron withdrawing groups) on the aromatic ring and on the sugar moiety, it should be useful for the expedient preparation of a broad variety of analogues of the natural products.

Acknowledgements

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Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.009. This contains detailed description of experimental procedures and spectral information and analyses for new compounds.

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9. Synthesis of (±)-*S*-[4-(4-chlorophenyl)-1-(1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranosyl)-4-oxobutyl] *O*-ethyldithiocarbonate **4a**. A solution of **2a** (0.5 g, 1.81 mmol) and **3** (0.73 g, 3.63 mmol) in 1,2-dichloroethane (1.8 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added (5 mol%) to the refluxing solution, followed by additional portions (2 mol% every 90 min). When starting material was completely consumed (after addition of 17 mol% of DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9:1) to give adduct **4a** (0.801 g, 93%) as a separable mixture of diastereoisomers (ratio 2:1). *Diastereoisomer I* (white crystals, recrystallized from petroleum ether, mp = 95–96 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, C*H* arom, J = 8.0 Hz), 7.42 (d, 2H, C*H* arom, J = 8.8 Hz), 5.92 (d, 1H, O–C*H*–O, J = 4.0 Hz), 4.6 (q, 2H, OCH_2, J = 7.1 Hz), 4.55 (d, 1H, O_2CH–C*H*, J = 4.4 Hz), 4.34 (dd, 1H, S–CH–C*H*, J = 9.4, 3 Hz), 4.18 (dt, 1H, C*H*–S, J = 9.4, 4.3 Hz), 3.79 (d, 1H, C*H*–OMe, J = 2.8 Hz), 3.36 (s, 3H, OCH_3), 3.10–3.24 (m, 2H, CO–CH_2), 2.46–2.53 (m, 1H, CO–CH_2–CH_2), 2.05–2.14 (m, 1H, CO–CH_2–CH_2), 1.50 (s, 3H, C–CH_3), 1.39 (t, 3H, CH_2–CH_3, J = 7.0 Hz), 1.32 (s, 3H, C–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1 (*C*=S), 198.1 (*C*O), 139.4 (*C*–CO), 135.2 (*C*–Cl), 129.5 (*C*H arom), 128.9 (*C*H arom), 111.8 (O–*C*–O), 105.3 (O–*C*H–O), 84.1 (O_2CH–*C*H), 81.2 (S–CH–*C*H), 81.1 (*C*H–S), 70.3 (OCH_2), 57.9 (OCH_3), 48.4 (*C*H–OMe), 35.8 (CO–CH_2), 27.0 (CO–CH_2–CH_2), 26.9 (C–CH_3), 26.3 (C–CH_3), 13.8 (CH_2–CH_3); IR (CCl_4) 1691 (C=O), 1217 (C=S), 1052 (S–C) cm^{-1}; MS (CI+NH_3) *m/z* 494 (MH^++NH_3), 492 (MH^++NH_3), 477 (MH^+), 475 (MH^+); $[\alpha]_D^{25}$ +15.4 (*c* 1, $CHCl_3$). *Diastereoisomer II* (colorless oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, C*H* arom, J = 8.8 Hz), 7.47 (d, 2H, C*H* arom, J = 8.8 Hz), 5.91 (d, 1H, O–C*H*–O, J = 3.6 Hz), 4.58–4.65 (m, 3H, OCH_2 and O_2CH–C*H*),4.34 (dd, 1H, S–CH–C*H*, J = 8.8, 2.8 Hz), 4.24 (dt, 1H, C*H*–S, J = 9.4, 3.4 Hz), 3.78 (d, 1H, C*H*–OMe, J = 3.6 Hz), 3.42 (s, 3H, OCH_3), 3.16 (t, 2H, CO–CH_2, J = 7.6 Hz), 2.33 (dddd, 1H, CO–CH_2–CH_2, J = 15.0, 7.6, 7.4, 3.5 Hz), 1.98–2.07 (m, 1H, CO–CH_2–CH_2), 1.48 (s, 3H, C–CH_3), 1.39 (t, 3H, CH_2–CH_3, J = 7.4 Hz), 1.32 (s, 3H, C–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.8 (*C*=S), 198.2 (*C*O), 139.5 (*C*–CO), 135.1 (*C*–Cl), 129.6 (*C*H arom), 128.9 (*C*H arom), 111.7 (O–*C*–O), 104.9 (O–*C*H–O), 84.5 (O_2CH–*C*H), 81.3 (S–CH–*C*H), 80.6 (*C*H–S), 70.3 (OCH_2), 57.7 (OCH_3), 49.8 (*C*H–OMe), 36.0 (CO–CH_2), 26.9 (C–CH_3), 26.3 (C–CH_3), 25.1 (CO–CH_2–CH_2), 13.8 (CH_2–CH_3); IR (CCl_4) 1690 (C=O), 1217 (C=S), 1052 (S–C) cm^{-1}; MS (CI+NH_3) *m/z* 494 (MH^++NH_3), 492 (MH^++NH_3), 477 (MH^+), 475 (MH^+); $[\alpha]_D^{25}$ −35.1 (*c* 1, $CHCl_3$).
10. Synthesis of (±)-6-chloro-4-(1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranosyl)-3,4-dihydro-2*H*-naphthalen-1-one **5a**. A solution of **4a** (0.67 g, 1.43 mmol) in 1,2-dichloroethane (14 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added portionwise (20 mol% per hour) to the refluxing solution. When starting material was completely consumed (after addition of 1.4 equiv of DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure, and purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9:1 to 2:1) to give tetralone **5a** (0.283 g in 57%) as a separable mixture of diastereoisomers. *Diastereoisomer I* (white needles, recrystallized from petroleum ether, mp = 129–132 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0 (d, 1H, C*H* arom, J = 8.8 Hz), 7.35 (d, 1H, C*H* arom, J = 8.8 Hz), 7.35 (s, 1H, C*H* arom),

5.93 (d, 1H, O–C*H*–O, J = 4.0 Hz), 4.62 (d, 1H, O_2CH–C*H*, J = 4.0 Hz), 4.17 (dd, 1H, Ar–CH–C*H*, J = 10.8, 2.8 Hz), 3.51 (s, 3H, OCH_3), 3.45–3.56 (m, 1H, Ar–C*H*), 3.36 (d, 1H, C*H*–OMe, J = 2.8 Hz), 2.78 (ddd, 1H, CO–CH_2, J = 19.2, 14.2, 5.2 Hz), 2.64 (ddd, 1H, CO–CH_2–CH_2, J = 18.6, 4.8, 2.0 Hz), 2.51 (dddd, 1H, CO–CH_2–CH_2, J = 14.4, 5.2, 2.4, 2.4 Hz), 2.18 (tt, 1H, CO–CH_2, J = 14.0, 4.8 Hz), 1.40 (s, 3H, C–CH_3), 1.30 (s, 3H, C–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1 (*C*O), 145.5 (*C*–CO), 139.8 (*C*–Cl), 131.2 (*C*–CH), 129.4 (*C*H arom), 129.2 (*C*H arom), 128.1 (*C*H arom), 111.7 (O–*C*–O), 104.9 (O–*C*H–O), 83.0 (O_2CH–*C*H), 80.8 (Ar–CH–*C*H), 79.9 (*C*H–OMe), 56.8 (OCH_3), 35.7 (Ar–*C*H), 33.6 (CO–CH_2), 26.9 (C–CH_3), 26.2 (C–CH_3), 24.2 (CO–CH_2–CH_2); IR (CCl_4) 1691 (C=O) cm^{-1}; MS (CI+NH_3) *m*/*z* 372 (MH^++NH_3), 370 (MH^++NH_3), 355 (MH^+), 353 (MH^+); $[\alpha]_D^{25}$ −53.9 (*c* 1, $CHCl_3$). *Diastereoisomer II* (white powder, recrystallized from petroleum ether, mp = 108–110 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, 1H, C*H* arom, J = 8.4 Hz), 7.58 (d, 1H, C*H* arom, J = 1.6 Hz), 7.29 (dd, 1H, C*H* arom, J = 8.0, 1.6 Hz), 5.96 (d, 1H, O–C*H*–O, J = 4 Hz), 4.63 (d, 1H, O_2CH–C*H*, J = 4.0 Hz), 4.25 (dd, 1H, Ar–CH–C*H*, J = 10.0, 2.8 Hz), 3.75 (d, 1H, C*H*–OMe, J = 2.8 Hz), 3.48 (s, 3H, OCH_3), 3.30 (ddd, 1H, Ar–C*H*, J = 10.0, 5.0, 4.8 Hz), 2.60–2.75 (m, 2H, CO–CH_2), 2.20–2.29 (m, 1H, CO–CH_2–CH_2), 1.96–2.02 (m, 1H, CO–CH_2–CH_2), 1.40 (s, 3H, C–CH_3), 1.31 (s, 3H, C–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8 (*C*O), 146.8 (*C*–CO), 139.8 (*C*–Cl), 130.6 (*C*H arom), 130.5 (*C*–CH), 128.8 (*C*H arom), 127.8 (*C*H arom), 111.5 (O–*C*–O), 104.9 (O–*C*H–O), 84.1 (O_2CH–*C*H), 81.1 (Ar–CH–*C*H), 80.7 (*C*H–OMe), 57.6 (OCH_3), 37.2 (Ar–*C*H), 35.4 (CO–CH_2), 26.6 (C–CH_3), 26.1 (C–CH_3), 25.1 (CO–CH_2–CH_2); IR (CCl_4) 1690 (C=O) cm^{-1}; MS (CI+NH_3) *m*/*z* 372 (MH^++NH_3), 370 (MH^++NH_3), 355 (MH^+), 353 (MH^+); $[\alpha]_D^{25}$ −23.15 (*c* 1, $CHCl_3$).

11. Synthesis of 6-chloro-4-(1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranosyl)-naphthalen-1-ol **6a**. To a stirred solution of **5a** (0.06 g, 0.17 mmol) and $AlCl_3$ (0.002 g, 0.017 mmol) in Et_2O (1.7 mL) at 0 °C was added dropwise Br_2 (0.027 g, 0.008 mL, 0.17 mmol). The cooling bath was then removed and the mixture was stirred at room temperature for a further 1 h. When starting material was completely consumed, the solvent was removed under reduced pressure and the resulting mass decolorized with a 1:1 mixture of CH_2Cl_2/water and extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated and the residue was then dissolved in 1 mL of DMF and 0.025 g (3.4 mmol) of Li_2CO_3 and 0.03 g (3.4 mmol) of LiBr were added to the reaction mixture. The solution was heated for 30 min at 140 °C, cooled to room temperature, extracted with diethyl ether, and the combined organic extracts were dried and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 8:2) and recrystallized with CH_2Cl_2/petroleum ether to give *C*-aryl glycoside **7a** (0.037 g, 61% overall yield from **5a**) as pale-brown crystals (mp = 184–187 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, 1H, C*H* arom, J = 8.8 Hz), 7.83 (d, 1H, C*H* arom, J = 2.0 Hz), 7.63 (d, 1H, C*H* arom, J = 7.6 Hz), 7.43 (dd, 1H, C*H* arom, J = 9.0, 7.6 Hz), 6.79 (d, 1H, C*H* arom, J = 8.0 Hz), 6.15 (d, 1H, O–C*H*–O, J = 4.0 Hz), 5.79 (d, 1H, Ar–C*H*, J = 2.8 Hz), 4.75 (d, 1H, O_2CH–C*H*, J = 3.6 Hz), 4.05 (d, 1H, C*H*–OMe, J = 3.2 Hz), 2.89 (s, 3H, OCH_3), 1.67 (s, 3H, C–CH_3), 1.43 (s, 3H, C–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4 (*C*–OH), 132.9 (*C*–Cl), 132.2 (*C*–COH), 126.8 (*C*H arom), 125.6 (*C*H arom), 124.8 (*C*H arom), 122.6 (*C*–CH), 122.3 (*C*–CCH), 121.2 (*C*H arom), 111.9 (O–*C*–O), 108.7 (*C*H arom), 104.1 (O–*C*H–O), 84.9 (O_2CH–*C*H), 83.2 (Ar–*C*H), 78.5 (*C*H–OMe), 58.6 (OCH_3), 27.0 (C–CH_3), 26.4 (C–CH_3); IR (CCl_4) 3603 (OH) cm^{-1}; MS (CI+NH_3) *m*/*z* 370 (MH^++NH_3), 368 (MH^++NH_3), (MH^+), 353 (MH^+), 351 (MH^+); $[\alpha]_D^{25}$ −67.83 (*c* , $CHCl_3$); Anal. Calcd for $C_{18}H_{19}ClO_5$: C, 61.63; H, 5.46. Found: C, 61.92; H, 5.63.

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