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A facile synthesis of aryldihydropyrans using a Sonogashira–selenoetherification strategy

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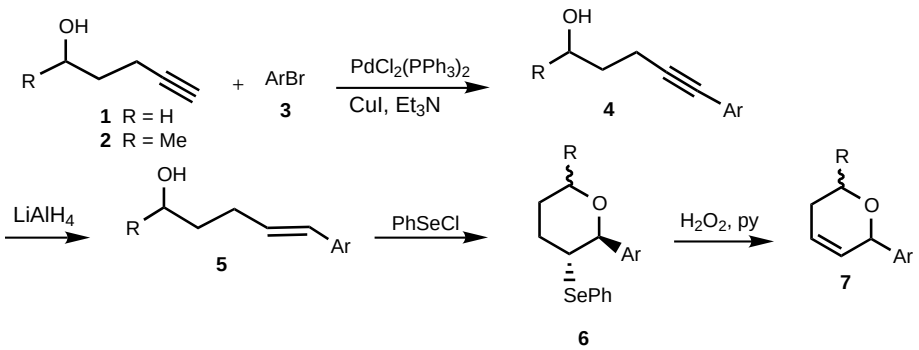
Abstract—A high yielding and convenient synthesis of 2-aryl-2,5-dihydro-2*H*-pyrans is reported. Sonogashira coupling of 4-pentyn-1-ol and 5-hexyn-2-ol with a range of phenyl and naphthyl bromides affords the appropriate aryl acetylenic alcohols which then undergo ready reduction to the corresponding (*E*)-1-aryl-5-hydroxyalkenes. Subsequent selenoetherification of the (*E*)-5-hydroxyalkenes proceeds via a 6-*endo*-trig pathway cleanly affording the *trans*-2-aryl-3-phenylselenyltetrahydropyrans. Finally oxidative elimination of the selenides afforded the 2-aryl-2,5-dihydro-2*H*-pyrans which are convenient intermediates for the synthesis of *C*-aryl glycosides in that they contain a double bond which is available for further oxygenation.

C-Aryl glycosides are a class of natural product which have attracted considerable interest due to their ability to form stable complexes with DNA.[1] Molecular recognition involving van der Waals and/or hydrogen bonding interactions between the sugar substituent and the DNA helix are implicated. Whereas the more common *O*-glycosides are susceptible to acidic or enzymatic hydrolysis, *C*-glycosides are largely inert towards these processes. The literature dealing with this subject is extensive[2] and methods available for the synthesis of aryl *C*-glycosides fall into two broad categories: (i) grafting an aryl group onto an appropriately functionalized carbohydrate or (ii) de novo synthesis of an aryl-containing carbohydrate.

Methods belonging to the first category dominate the field and include reactions between carbohydrate C-1 carbocation equivalents and aromatic nucleophiles,[3] addition of carbohydrate C-1 carbanions to aryl cation equivalents[4] and palladium-mediated coupling of C-1 substituted stannyl, borane and zinc glycals with aryl halides.[5] To date cycloaddition reactions between aromatic aldehydes and silyloxydienyl ethers have constituted the main approach for the de novo synthesis of *C*-aryl glycosides.[6] We therefore herein report a novel approach for the de novo synthesis of *C*-aryl glycosides whereby an aryl dihydropyran precursor is assembled via an electrophile-initiated etherification[7] of an aryl bishomoallylic alcohol. The aryl bishomoallylic alcohol



Scheme 1.

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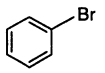
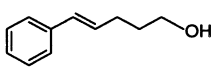
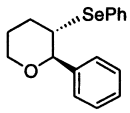
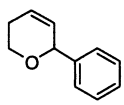
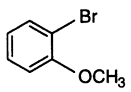
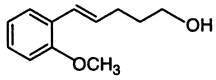
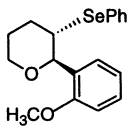
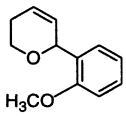
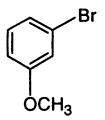
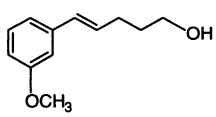
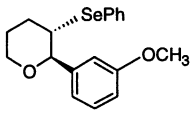
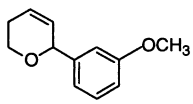
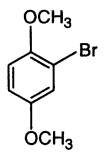
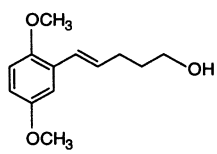
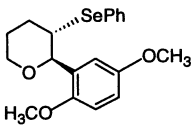
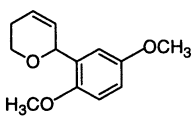
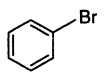
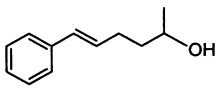
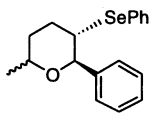
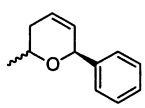
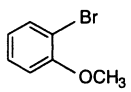
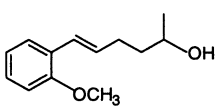
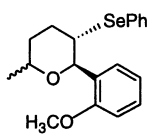
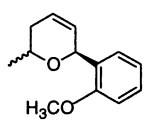
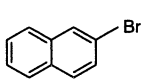
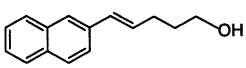
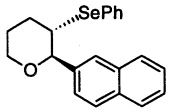
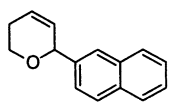
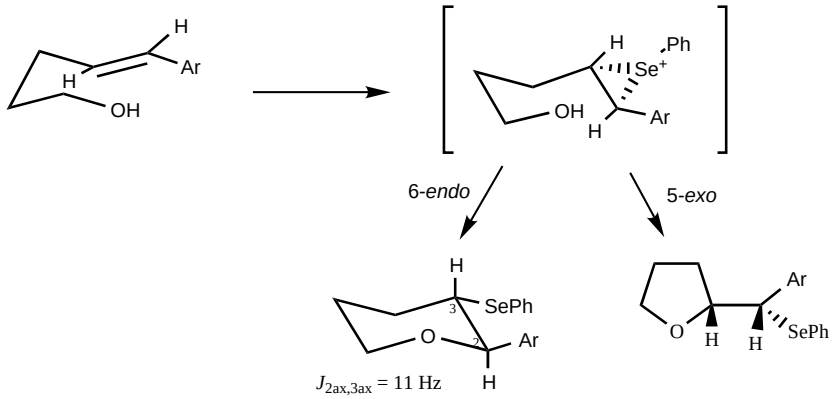
in turn is readily assembled via Sonogashira coupling of an acetylenic alcohol with an aromatic bromide followed by stereoselective partial reduction to an (*E*)-alkene (Scheme 1). Hart et al.[8] have reported an approach to *C*-aryl glycosides using an electrophile-initiated cyclization of an unsaturated alcohol, however, a limiting factor was the need to develop better methods for the preparation of the olefin cyclization precursors in order to advance this synthetic strategy. This issue is addressed in the present work by using a Sonogashira reaction in tandem with an electrophilic cyclization.

There has been considerable interest in the stereoselective synthesis of oxygenated heterocyclic rings via the intermediate formation of a seleniranium ion[9] hence, we opted for the use of selenium as the electrophilic reagent in the present work. We required that the key selenoetherification proceeded regioselectively following a 6-*endo*-trig mode of cyclization. Although 6-*endo*-trig cyclizations are not favored by Baldwin's rules[10] similar 5-*endo*-trig iodo- and seleno-cyclizations of homoallylic alcohols have been reported.[11] These cyclizations do not contravene Baldwin's rules as they are electrophile-

Table 1. The synthesis of aryldihydropyrans using a Sonogashira–selenoetherification strategy

Bromide	Alkyne	Yield % [a]	Yield % [b]	Yield % [c]	Yield % [d]
	1	**4a** (94 %)			
3a			**5a** (86 %)	**6a** (89 %)	**7a** (76 %)
	1	**4b** (64 %)			
3b			**5b** (82 %)	**6b** (87 %)	**7b** (81 %)
	1	**4c** (82 %)			
3c			**5c** (85 %)	**6c** (92 %)	**7c** (83 %)
	1	**4d** (84 %)			
3d			**5d** (93 %)	**6d** (81 %)	**7d** (79 %)
	2	**4e** (81 %)			
3e			**5e** (81 %)	**6e** (90 %)[e]	**7e** (81 %)[e]
	2	**4f** (85 %)			
3f			**5f** (89 %)	**6f** (89 %)[e]	**7f** (86 %)[e]
	1	**4g** (91 %)			
3g			**5g** (94 %)	**6g** (86 %)	**7g** (82 %)

[a] *Reaction conditions:* **3** (1.0 equiv), **1** (R=H), **2** (R=CH_3) (1.5 equiv.), PPh_3 (0.02 equiv.), $PdCl_2(PPh_3)_2$ (0.01 equiv.) in Et_3N at 40 °C for 15 min. CuI (0.02 equiv.) was then added and the reaction heated to 80 °C for 24-48 h. [b] *Reaction conditions:* **4** (1.0 equiv.), $LiAlH_4$ (5.0 equiv.) in THF at reflux for 48-68 h. [c] *Reaction conditions:* **5** (1.0 equiv.), PhSeCl (2.0 equiv.) in CH_2Cl_2 at -78 °C for 2-4 h. [d] *Reaction conditions:* **6** (1.0 equiv.), 30% H_2O_2 (10.0 equiv.), pyridine (2.0 equiv.) at 25 °C for 24-36 h. [e] Denotes a mixture of diastereoisomers arising from the presence of the methyl group residing at the C-6 position.



Scheme 2.

rather than nucleophile-driven and proceed via a late transition state. In our case it was reasoned that the ability of the aryl group to stabilize an electron deficient benzylic centre should promote cyclization proceeding via the 6-*endo*-trig mode leading to the formation of the tetrahydropyran at the expense of the competing 5-*exo*-trig etherification which leads to the undesired tetrahydrofuran.

Early work by Mihailovic et al.[12] on the electrochemical phenylselenoetherification of simple unsaturated alcohols suggested that the geometry of the double bond has a pronounced influence on the regioselectivity of the ring closure. In particular, electrolysis of (*Z*)-4-hexen-1-ol in the presence of diphenyl diselenide afforded five-membered cyclic ethers whereas in the case of (*E*)-4-hexen-1-ol the corresponding six-membered cyclic ethers were produced. These experimental results suggested that in our case the use of (*E*)-alkenols in the key selenocyclization would also lead to more of the desired tetrahydropyran product. These postulations required experimental evidence to support their claims and are addressed in the work reported herein.

Sonogashira coupling[13] of homopropargylic alcohols with aryl bromides provides an efficient method for the synthesis of the (*E*)-arylhydroxyalkene cyclization precursors. A series of aryl bromides **3** underwent smooth Sonogashira reactions with 4-pentyn-1-ol **1** or 5-hexyn-2-ol **2** using $PdCl_2(PPh_3)_2$ and CuI as catalysts in triethylamine (Table 1).[14] An excess of the acetylene (1.5 equiv.) was required to effect complete reaction and the products were readily purified by flash chromatography. The resultant substituted acetylenes **4** then underwent smooth and clean reduction to the (*E*)-alkenols **5** using $LiAlH_4$ in THF. No trace of the corresponding (*Z*)-alkenol was observed.

With the (*E*)-alkenols **5** in hand, smooth and clean cyclization to the *trans* 2,3-disubstituted tetrahydropyrans **6** was effected in good yield using phenylselenenyl chloride in dichloromethane.[15] None of the regioisomeric tetrahydrofuran products were observed. The excellent levels of regio- and stereoselection observed can be explained by assuming the intermediacy of a partial chair-like transition state (Scheme 2) arising from addition of selenium across the double bond, followed by attack of the oxygen of the hydroxyl group from the opposite side. The ^1H NMR spectra (including 2D) of the selenide-tetrahydropyrans **6**[16] thus obtained, confirmed that the phenylselenenyl and aryl groups occupied equatorial positions ($J_{2ax,3ax} = 11$ Hz). In contrast to these results, use of the isomeric (*Z*)-alkenes gave a complex mixture of products. Finally, oxidative–elimination of the selenides **6** proceeded regioselectively using 30% hydrogen peroxide and pyridine in THF providing the 2-aryl-2,5-dihydro-2*H*-pyrans **7** in good yield.

In conclusion, we have developed a practical, high yielding synthesis of 2-aryl-2,5-dihydro-2*H*-pyrans by union of an acetylenic alcohol with an aromatic bromide by means of a Sonogashira coupling. Subsequent selenoetherification and oxidative elimination of the (*E*)-alkene derived from the initial coupled product proceeded stereo- and regioselectively forming the 2-aryl-2,5-dihydro-2*H*-pyran product cleanly. The key reactions proceed under mild conditions and offer a practical method for the synthesis of *C*-aryl glycosides by carrying out further oxygenation of these aryl dihydropyrans or by using a more functionalized acetylenic alcohol as a coupling partner in the initial Sonogashira reaction.

Acknowledgements

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14. All new compounds gave satisfactory ^{1}H, ^{13}C NMR, IR and HRMS data.
15. A representative example of the experimental procedure—*tetrahydro-2-naphthyl-3-(phenylselenenyl)-2H-pyran* **6g**: Phenylselenenyl chloride (0.18 g, 0.94 mmol) was added to a cooled solution (−78°C) of *trans*-5-naphthylpent-4-en-1-ol **5g** (0.10 g, 0.47 mmol) in dichloromethane (3 mL) under nitrogen. After 4 h, the reaction was diluted using dichloromethane (7 mL) and sequentially washed with two portions of saturated sodium bicarbonate (7 mL). The aqueous fraction was then further extracted using three portions of dichloromethane (10 mL). The organic fractions were combined, washed with brine and dried over $MgSO_4$. The organic fraction was reduced under vacuum to yield a white solid. Recrystallization of the crude product from ethyl acetate:hexane (1:19) afforded the title compound **6g** as opaque crystals (86%).
16. Spectroscopic data for **6g**: δ_H (300 MHz, $CDCl_3$) 1.62–1.67 (1H, m, H-5_A), 1.70–1.84 (2H, m, H-4_A, H-5_B), 2.22–2.27 (1H, m, H-4_B), 3.42 (1H, ddd, $J_{2ax,3ax}$ 11.0, $J_{3ax,4ax}$ 11.0, $J_{3ax,4eq}$ 3.9 MHz, H-3_{ax}), 3.57 (1H, ddd, $J_{6ax,6eq}$ 11.6, $J_{6ax,5ax}$ 11.6, $J_{6ax,5eq}$ 2.2, H-6_{ax}), 4.03–4.09 (1H, m, H-6_{eq}), 4.38 (1H, d, $J_{2ax,3ax}$ 10.4 Hz, H-2_{ax}), 6.90–7.70 (12H, m, ArH). δ_C (300 MHz) 27.9 (CH_2, C-4), 32.6 (CH_2, C-5), 46.1 (CH, C-3), 68.7 (CH_2, C-6), 85.7 (CH, C-2), 125.0 (CH, Ar), 125.7 (CH, Ar), 127.0 (CH, Ar), 127.4 (CH, Ar), 127.5 (CH, Ar), 127.9 (CH, Ar), 128.0 (CH, Ar), 128.4 (CH, Ar), 133.0 (quat., Ar), 133.3 (quat., Ar), 135.5 (CH, Ar), 137.5 (quat., Ar).