An Efficacious Synthesis of Aryl and Heteroaryl *C*-Glycosides

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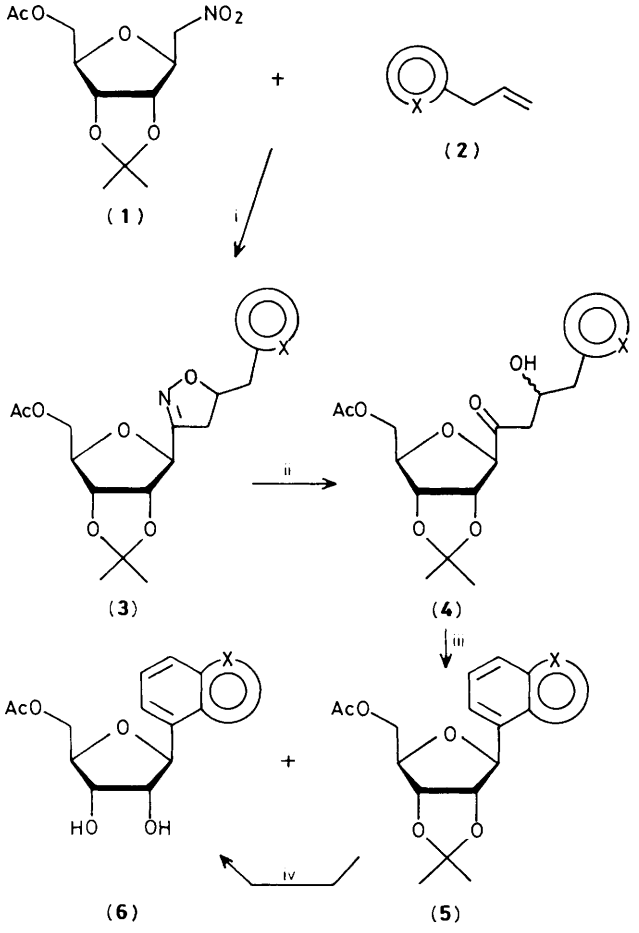
A new scheme for the preparation of aryl and heteroaryl *C*-glycosides through the dipolar cycloaddition reaction of nitrile oxides to allyl substituted aromatics is described.

As a consequence of our interest in exploring the structure–activity relationships of the gilvocarcins[1] and their analogues *vis-à-vis* their antitumour activity, we have been led to devise a new synthesis of aryl and heteroaryl *C*-glycosides. A number of methods have been devised over the years for acquiring access to both the natural and unnatural members of this family of compounds as a result of their significant biological activity. The methods currently available include *inter alia* the modification of naturally occurring *C*-glycosides, the use of C-1 functionalized carbohydrate precursors, the coupling of metallated heterocycles with protected carbohydrate derivatives, the palladium catalysed reaction of aryl and heterocyclic

Table 1. Preparation of *C*-glycosides.

Entry	Nitrile oxide	Dipolarophile	% Yield [3 + 2] step	% Yield Hydrogenation	Lewis acid[a]	*C*-Glycoside, % yield
1	(7)	(8)	73	83	A or B	(9), 36; (10), 47
2	(11)	(8)	50	80	A	(12), tr.; (13), 80
3	(7)	(14)	71[b]	—		(15), 15
4	(7)	(16)	69	58	A	(17), 44; (18), 41
5	(7)	(19)	44 overall		B	(20), tr.; (21), 46
6	(7)	(22)	41 overall		B	(23), 24; (24), 36
7	(7)	(25)	70	64	B	(26) → (27), 71[c]
8	(11)	(25)	62	73	B	(28), 74
9	(29)	(8)	65	80	A	(30), 24;[d] (31), 47[d]

[a] In CH_2Cl_2; A = $Zn(OSO_2CF_3)_2$; B = $Me_3SiOSO_2CF_3$. [b] Desilylation (Bu^n_4NF, tetrahydrofuran, 89%) of the isoxazoline intermediate was carried out prior to cyclization; cyclization occurs during hydrogenation (HOAc). [c] The yield of (27) was determined after treatment of the mixture of (26) and (27) with CF_3CO_2H–H_2O to cleave the isopropylidene group. [d] The two isomers were separated by silica gel chromatography after the cyclization.



Scheme 1. *Reagents and conditions:* i, PhNCO, Et_3N, C_6H_6, 60 °C; ii, H_2, Raney-Ni, HOAc, MeOH–H_2O (4 : 1), iii, Lewis acid, CH_2Cl_2; iv, CF_3CO_2H–H_2O, (4 : 1).

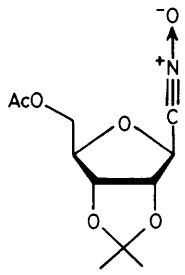
mercurials with glycals, and the use of Diels–Alder cycloaddition chemistry generally in the construction of the carbohydrate moiety.[2]

Our new method for *C*-glycoside synthesis is versatile in scope and simple to execute. It represents a logical extension of a new indole synthesis reported earlier by us.[3] One begins with the reaction of a C-1 nitromethyl substituted carbohydrate derivative (**1**), prepared from the appropriate carbohydrate precursor, with the desired allylated benzenoid or allylated heterocyclic derivative (**2**). In this first reaction, phenyl isocyanate is used to transform the nitro compound into its nitrile oxide which reacts with the allylated aromatic to provide an isoxazoline (dihydro-isoxazole) (**3**). The isoxazoline is hydrogenated in turn using Raney nickel to provide an intermediate β-ketol (**4**). The β-ketol is then readily cyclized using either zinc trifluoromethanesulphonate (triflate) or trimethylsilyl triflate as the Lewis acid catalyst to produce aryl *C*-glycosides (**5**) and (**6**). In a few cases, the benzannulation reaction was found to occur during the hydrogenation reaction itself. The generalized sequence is outlined in Scheme 1.

This generalized strategy was tested by the reaction of D-ribose with nitromethane to furnish the corresponding β-ribofuranosylnitromethane as the major product.[4] The *cis*-diol unit of this intermediate was then protected as its acetonide, and the remaining hydroxy group was acetylated to provide (**7**). Next, this nitro compound was treated with *N*-phenylsulphonyl-2-allylindole (**8**)[5] in the presence of phenyl isocyanate and triethylamine to furnish the isoxazoline in 73% yield. Hydrogenation delivered the β-ketol in 83% yield as a 1 : 1 mixture of diastereoisomers. Lastly, on exposing this β-ketol to zinc triflate[6] or trimethylsilyl triflate,[7] cyclization ensued to provide a mixture of the ribofuranosylcarbazoles (**9**) and (**10**), in which one of the products had suffered loss of its acetonide protecting group. The products were separated by silica gel chromatography, and the purified acetonide (**10**) was treated with CF_3CO_2H–H_2O[8] to provide additional amounts of the deprotected carbazole (**9**) (Table 1).

By using the minor isomer produced in the condensation reaction of nitromethane with ribose,[4] it was also possible to assemble the (α-D-ribofuranosyl)carbazole derivative (**13**). The sequence of operations proceeded in similar yield with the exception of the [3 + 2] cycloaddition step. In this case, the reaction proceeded at a much slower rate owing presumably to the greater steric hindrance of the α-oriented nitrile oxide group of (**11**). The isolated yield of isoxazoline was 50%.

As summarized in Table 1, this reaction scheme was also applied to both *N*-tri-isopropylsilyl-3-allylpyrrole (**14**)[9] and to



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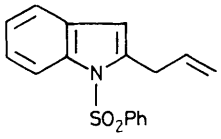

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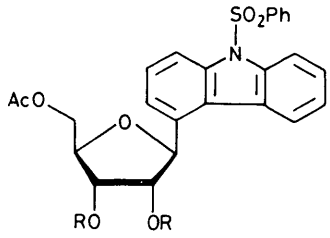
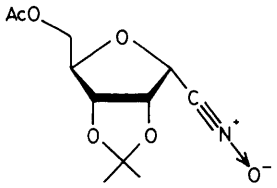
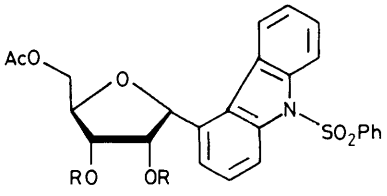


(9) R = H

(10) RR = $>CMe_2$



(11)



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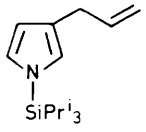

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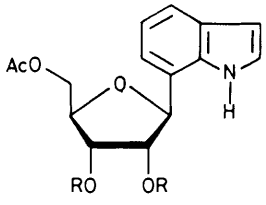

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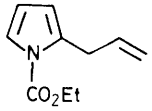

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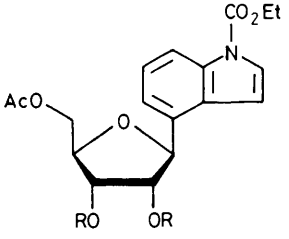

(17) R = H

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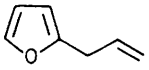

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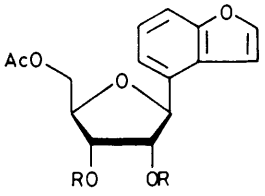

(20) R = H

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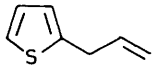

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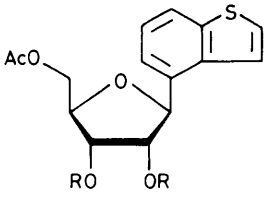

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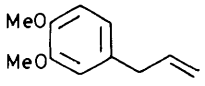

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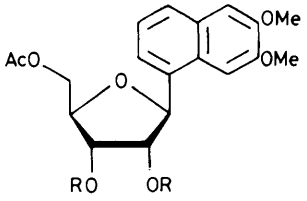

(26) RR = $>CMe_2$

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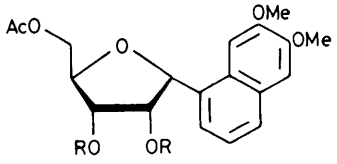
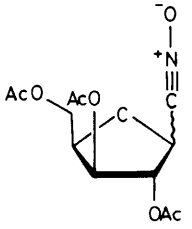


(28) RR = $>CMe_2$



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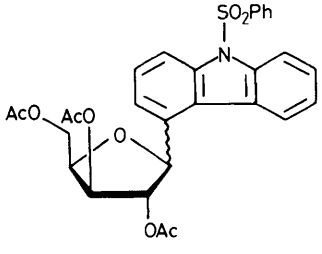

(30), α-isomer

(31), β-isomer

N-ethoxycarbonyl-2-allylpyrrole (**16**)[10] to provide the 7- and 4-carbohydrate substituted indole derivatives (**15**) and (**17**), (**18**), respectively. For reasons as yet unclear to us, the yield of cyclization product obtained in the former case was low.

Use of 2-allylfuran (**19**)[11] and 2-allylthiophene (**22**)[12] in this *C*-glycoside forming strategy worked equally well to provide the expected benzofuran and benzothiophene analogues (**20**), (**21**) and (**23**), (**24**).

As an example of the application of this chemistry to the synthesis of a structure more closely related to that of the gilvocarcins, we have examined the conversion of 4-allyl-1,2-dimethoxybenzene (**25**) into a *C*-naphthylglycoside. As indicated in Table 1, entry 7, the cyclization process again proceeded with partial cleavage of the acetonide group. Treatment of this mixture with CF_3CO_2H–H_2O provided the deprotected naphthalene derivative (**27**) in good overall yield. Similarly, the α-isomer (**28**) could be prepared by employing the nitrile oxide (**11**).

Lastly, as shown in entry 9, nitrile oxides derived from carbohydrates other than ribose can be employed in this scheme. The C-1 nitromethyl derivative of xylose prepared in the same fashion as described above for ribose was used to procure the xylofuranosylcarbazoles (**30**)/(**31**).†

In summary, the methodology disclosed herein provides a simple and efficient means for gaining access to a variety of *C*-aryl and *C*-heteroaryl glycosides. The structures available through this chemistry may provide new leads in the design of chemotherapeutic agents for use in combating viral related diseases.[13]

A patent (Serial no. 892 040) is pending on this condensed ring aromatic synthesis.

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† Satisfactory ^{1}H n.m.r., i.r., and high resolution mass spectra were obtained for all new compounds.

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