Preparation of Key Intermediates for the Synthesis of *C*-Nucleosides and other Derivatives of 1-Deoxyribose

Peter D. Kane and John Mann*

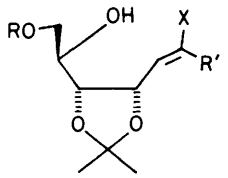
Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD, U.K.

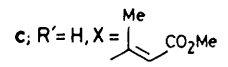
The reaction of D-ribose with stabilised ylides can be made to yield solely acyclic products, which may then be cyclised with high stereoselectivity using phenylselenenyl chloride to produce 1-β-substituted 1-deoxyribose derivatives.

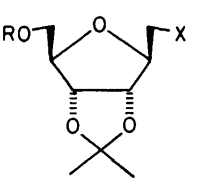
There are several reports in the literature concerning reactions of D-ribose with phosphorus ylides.[1] However, with the exception of Moffatt's work,[1a] the stereochemical outcome of these reactions has received scant attention, and acyclic products, if formed, have been cyclised with poor stereoselectivity. We wished to prepare acyclic Wittig products of general formula (**1**), and then to convert these, in a stereocontrolled manner, into 1-deoxyribose derivatives of type (**2**).

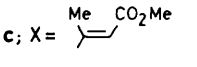
First, we confirmed the results obtained by Moffatt[1a] using methoxycarbonylmethylenetriphenylphosphorane and cyanomethylenetriphenylphosphorane. Reactions of 2,3-di-*O*-isopropylidene-D-ribose (**3b**) with these ylides provided good yields of the 1-deoxyribose derivatives (**2a**) and (**2b**) with excellent $\beta:\alpha$ anomer ratios (in the range 25 to 50:1), provided refluxing acetonitrile was employed as solvent. If dichloromethane was utilised (at room temp.), we were able to maximise the formation of acyclic products, for example (**1a**) and (**1b**). These we could cyclise in a variety of ways, and we give below two examples of the use of these processes in synthesis.

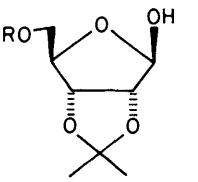
The unsaturated ester (**1b**) was obtained in 80—90% yield from (**3a**) and ethoxycarbonylethylidenetriphenylphosphorane, and upon treatment with phenylselenenyl chloride in di-



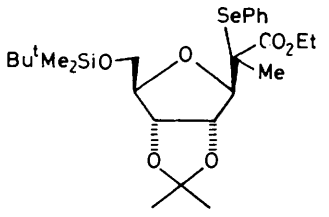
(1) R = H or $SiMe_2Bu^t$
a; R' = H, X = CO_2Me
b; R' = Me, X = CO_2Et
c; R' = H, X = 



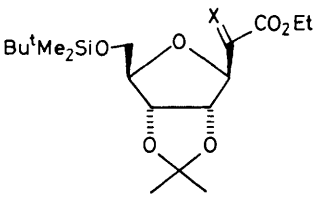
(2) R = H or $SiMe_2Bu^t$
a; X = CO_2Me
b; X = CN
c; X = 



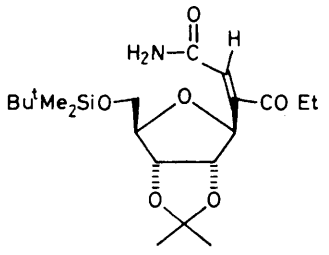
(3)
a; R = $SiMe_2Bu^t$
b; R = H



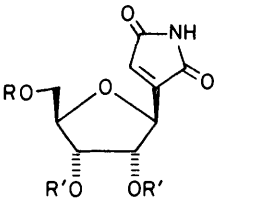
(4)



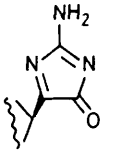
(5)
a; X = CH_2
b; X = O



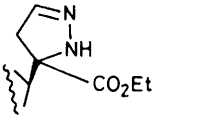
(6)



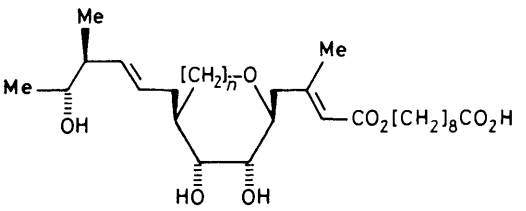
(7)
a; R = $SiMe_2Bu^t$, R' = isopropylidene
b; R = R' = H



(8) R = R' = H



(9) R = R' = H



(10)
a; $n = 1$
b; $n = 0$

chloromethane (−78 °C to room temp., 5 equiv. of $NaHCO_3$) yielded the selenenophenyl derivative (**4**) (40% after flash chromatography). None of the alternative α-isomer was obtained, but some (29%) unchanged starting material was recovered. The stereochemistry of the product was established by ^{13}C- and ^1H-n.m.r. spectroscopic studies on α-methylene ester (**5a**) (*vide infra*). Selenium compounds have been used to facilitate ring closure on numerous occasions,[2] but to our knowledge this is the first time a stereochemically defined ribose derivative has been prepared using these reagents. Similar stereoselectivity was observed when the 5-unprotected ribose derivative (**3b**) was employed, and it seems that the isopropylidene group provides enough steric hindrance by itself to ensure exclusive formation of the β-product. Reaction of (**4**) with hydrogen peroxide at 0 °C led to elimination of phenylselenenic acid and the key α-methylene ester (**5a**) was obtained in excellent yield (97%). The stereochemistry of this compound was assigned primarily through interpretation of its ^{13}C-n.m.r. spectrum (isopropylidene methyls at δ 25.462 and 27.574 p.p.m. and isopropylidene quaternary carbon at 114.15 p.p.m. are characteristic of the β-forms of ribose),[1a] of its ^1H-n.m.r. spectrum (isopropylidene methyls at δ 1.35 and 1.58 agree well with Moffatt's data),[1a] and by its conversion into the protected derivative of showdomycin (**7a**), previously prepared by Just and coworkers.[3a] This conversion was achieved by first ozonising (**5a**) to yield (**5b**), and then allowing (**5b**) to react with carbamoylmethylenetriphenylphosphorane to produce the (*E*)-ester, amide (**6**) [33% overall from (**5a**)]. Upon treatment with a catalytic amount of pyridinium toluene-*p*-sulphonate in refluxing benzene this cyclised to form the showdomycin derivative (**7a**).† Many syntheses of the *C*-nucleoside showdomycin (**7b**) have been attempted,[3] and our synthetic approach compares very favourably with all of them, owing, in particular, to its brevity and minimal use of protecting groups. In addition, several novel *C*-nucleosides have been prepared from the key intermediates (**5**), for example (**8**) (m.p. 190 °C), upon reaction of guanidine and (**5b**), and (**9**) (m.p. 54 °C) upon reaction of diazomethane and (**5a**), followed by deprotection.

Our second example concerns the synthesis of the unsaturated ester (**2c**). We required this for our programme which aims to determine the effect of ring size on the biological activity of pseudomonic acid C (**10a**),[4] and hoped to convert it into the analogue (**10b**). The diene ester (**1c**; R = H) was prepared from 2,3-di-*O*-isopropylidene-D-ribose (**3b**) and $Br^-PPh_3^+-CH_2C(Me)=CHCO_2Me$ (1.2 equiv. of the phosphonium salt and 1.2 equiv. of 1,2-epoxybutane in MeCN in a sealed tube at 95 °C for 20 h) in moderate yield [40% of a mixture of the 2-(*E*),4-(*E*)- and 2-(*E*), 4(*Z*)-isomers in a ratio of *ca.* 4 : 1]. In addition, *ca.* 35% of starting acetonide was recovered for recycling. Ring closure was effected this time by employing methoxycarbonylmethylenetriphenylphosphorane as base (1.5 equiv. in refluxing MeCN, 10—20 h). This provided (**2c**), contaminated with small amounts of the *cis*-ester, in yields of *ca.* 55%. Once again the products were exclusively 1-β-substituted, 1-deoxy-derivatives of ribose (^{13}C n.m.r. evidence).

Finally, the Wittig reaction on the 5-*O*-silyl derivative (**3a**) provided diene ester (**1c**; R = $SiMe_2Bu^t$) in an isolated yield of 65%. Treatment with tetrabutylammonium fluoride in tetrahydrofuran (0 °C, 1 h) removed the 5-*O*-silyl group and effected ring closure to an extent (*ca.* 30%) and the cyclisation was completed as described above [*ca.* 50% isolated yield of (**2c**)]. Although most of the yields remain to be optimised, these two-step sequences provide a simple and effective means of introducing a complex sidechain in a stereochemically defined fashion.

† The spectra obtained for (**7a**) were identical in every respect with those kindly supplied by Professor Just. All compounds gave satisfactory spectral and analytical results.

Our experience with these and other systems have shown that the two reagents, phenylselenenyl chloride and methoxycarbonylmethylenetriphenylphosphorane, have general utility as mediators of stereoselective cyclisations, and offer real advantages over such alternative reagents as sodium ethoxide,[1a,b] which tend to cause epimerisation with ribose derivatives.

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