Synthesis of (±)-2′,3′-Didehydro-2′,3′-dideoxy Nucleosides *via* a Modified Prins Reaction and Palladium(0) Catalysed Coupling

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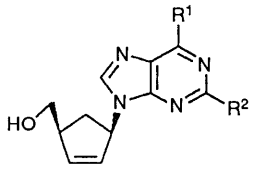
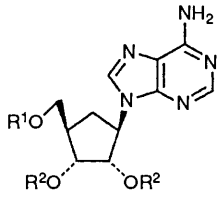
Cyclopentenyl allylic acetates have been prepared in diastereoisomerically enriched form by modification of the Prins reaction. Palladium(0) catalysed coupling between these allylic acetates and a heteroaromatic base provides a highly convergent and direct route for synthesising carbocyclic 2′,3′-didehydro-2′,3′-dideoxy nucleosides. The method is exemplified by the coupling reaction with adenine which yields (±)-2′,3′-didehydro-2′,3′-dideoxyaristeromycin 5′-*O*-acetate **22** in 50% yield. This has been converted in two steps into (±)-aristeromycin triacetate **5**.

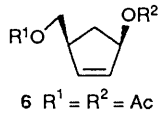
Nucleosides exhibit a wide range of biological properties of both agrochemical and pharmaceutical interest.[1] Amongst the many structural types, carbocyclic nucleosides are of special interest, since they are not susceptible to degradation *in vivo* by nucleosidases and phosphorylases.[2] For example carbovir **1** and its adenine analogue **2** exhibit antiviral activity.[3] Current syntheses of carbocyclic 2′,3′-didehydro-2′,3′-dideoxy nucleosides such as **1** or **2** are based either on elaboration of the natural product aristeromycin **3**,[4] or on a linear multi-step sequence from cyclopentadiene.[5] In principle, a very simple and highly convergent route to such molecules would result from the palladium(0) catalysed coupling between a heteroaromatic base and the allylic acetate **6**.[6] For example, coupling between adenine and **6** would give directly the 5′-*O*-acetyl derivative of **2**. Here we present our investigation into this synthetic approach, which we have found provides a simple and versatile route to the title compounds.



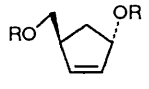
1 R^1 = OH, R^2 = NH_2
2 R^1 = NH_2, R^2 = H



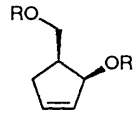
3 R^1 = R^2 = H
4 R^1 = Ac, R^2 = H
5 R^1 = R^2 = Ac



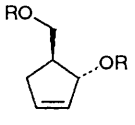
6 R^1 = R^2 = Ac
7 R^1 = R^2 = H
8 R^1 = ^{t}BuMe$_2$Si, R^2 = H
9 R^1 = ^{t}BuMe$_2$Si, R^2 = Ac



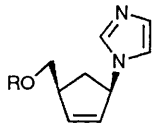
10 R = Ac
11 R = H



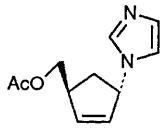
12 R = Ac
13 R = H



14 R = Ac
15 R = H



16 R = ^{t}BuMe$_2$Si
17 R = Ac



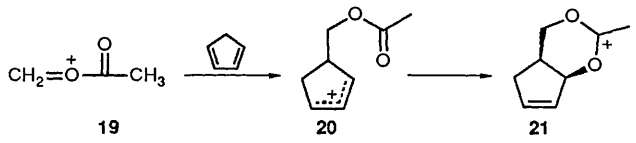
18

The *cis*-diacetate **6** is readily available *via* a Prins reaction between cyclopentadiene and paraformaldehyde, albeit as a mixture with the three other possible stereo- and regio-isomers **10**, **12** and **14**.[7] Although we were unable to separate these diacetates, the *cis*-diols **7** and **13** can be separated from the *trans*-diols **11** and **15** by careful chromatography.[7] Monosilylation of this *cis*-diol mixture [Bu^{t}Me$_2$SiCl (1 equiv.), imidazole, THF], followed by careful column chromatography yielded the alcohol **8**, which was acetylated to give the allylic acetate **9**. In a simple model reaction designed to test our synthesis strategy, imidazole coupled with **9** under palladium(0) catalysis [$Pd(PPh_3)_4$ (0.15 equiv.), Et_3N (1.5 equiv.), THF, reflux, 21 h] as would be predicted,[6] to yield the *N*-alkylated imidazole **16** in 51% yield. We next sought a method for preparing the *cis*-substituted allylic acetate which avoided the need for difficult and tedious chromatography, and which would be amenable to larger scale syntheses.

Because of the extreme ease with which the Prins reaction provides the basic carbocyclic framework we chose to study this reaction in more detail. We believe that the reported [7] ratio of the diols **7**:**11**:**13**:**15** of 38:37:12:13, obtained after hydrolysis of the Prins products, results from equilibration of the initially formed reaction products. Thus, the ratio of the diacetates **6**:**10**:**12**:**14**, obtained after acylation of the Prins products, is changed to 31:13:47:9 (GC) by conducting the Prins reaction under milder conditions (1 mol dm^{-3} cyclopentadiene, 3 mol dm^{-3} paraformaldehyde, 0.4 mmol dm^{-3} tosic acid in AcOH, 10 °C, 23 h; cyclopentadiene added neat to a cooled solution of the other reagents).† After a single distillation through a short Vigreux column a 10% yield of material of ratio 26:10:56:8 can be easily and routinely obtained. We postulate that the major

† It is noted that while reagent concentrations and temperature are important in determining the outcome of the Prins reaction, the ratio of products is especially sensitive to small changes in the concentration of tosic acid.

product of our reaction, the *cis*-diacetate **12**, is a kinetic product which undergoes a *syn*-S_N2' solvolysis to give the second most abundant product, the *cis*-diacetate **6**. A possible explanation for formation of **12** is shown in Scheme 1. Electrophilic reaction



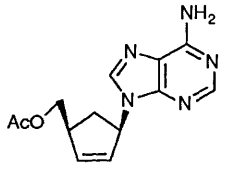
19 **20** **21**

Scheme 1

between cyclopentadiene and an acetylmethyleneoxonium species **19** (generated under acid catalysis from AcOH and paraformaldehyde) to give the allylic cation **20**, followed by intramolecular cyclisation would give the stabilised cation **21**. Ring opening with water and subsequent acetylation then yields the *cis*-acetate **12**.

The change in the ratio of the Prins reaction products is important because the ratio of *cis*-diacetates **6** and **12** to *trans*-diacetates **10** and **14** has been increased from 50:50 to 82:18. Since both **6** and **12** should give the same π-allylpalladium complex, we hoped it might now be possible to use this very easily obtained diacetate mixture directly in the coupling reaction. The diacetate mixture was found to couple very smoothly with imidazole (1 equiv.) under palladium(0) catalysis [$Pd(PPh_3)_4$ (0.05 equiv.), Et_3N (1.5 equiv.), THF, reflux, 1.5 h]. Following column chromatography an 88:12 mixture (^1H NMR and GC) of the coupling products **17**:**18** was isolated in 62% yield.

In extending the methodology from imidazole to adenine it was found best to first form the sodium salt with sodium hydride in DMF, and then add the allylic acetate (1 equiv.) and palladium catalyst [$Pd(PPh_3)_4$ (0.03 equiv.)]. The coupling reaction is easily conducted on a reasonably large scale (0.22 mol) and following column chromatography the coupling product **22** was isolated in 79% yield as an 82:18 mixture of



22

cis:*trans* isomers. A simple trituration of **22** with ethyl acetate–diisopropyl ether (1:1) removed the undesired *trans* product to yield the pure *cis* product in 50% overall yield. Removal of the acetate protecting group (Et_3N, MeOH, reflux) gave the target molecule, (±)-2′,3′-didehydro-2′,3′-dideoxyaristeromycin **2**, in 97% yield.

The stereo- and regio-chemistry of the coupling reaction was confirmed by converting compound **22** into (±)-aristeromycin triacetate as follows. *cis*-Hydroxylation with catalytic osmium tetroxide [OsO_4 (0.05 equiv.), NMO (1.3 equiv.), aqueous acetone] proceeded smoothly (59% yield), but contrary to expectation gave a 1:1 mixture of the desired diol **4** and its all-*cis*-isomer. Unfortunately, we were unable to separate this mixture, but acylation to the triacetate followed by fractional crystallisation (CH_2Cl_2–Et_2O) did give a low yield (5%) of pure (±)-aristeromycin triacetate **5**. This was identical (m.p.; IR, ^1H NMR, TLC) with an authentic sample prepared from natural (−)-aristeromycin.*

Finally, we note that the palladium(0)-catalysed coupling reaction can be generalised to include a variety of different N-heteroaromatic bases (*e.g.* benzimidazoles and indazoles),[8] so that the present method provides a general route for synthesising 2′,3′-didehydro-2′,3′-dideoxynucleosides. The methodology was designed for multigramme scale reactions, but on a smaller scale the chromatographic separation of the minor *trans*-Prins diols from the major *cis*-Prins diols becomes more practical, and should render the coupling process totally stereoselective.[9]

Experimental

Preparation of 9-(4-*Acetoxymethylcyclopent*-2-*en*-1-*yl*)*adenine*.—Sodium hydride (80% dispersion in oil; 6.7 g, 0.22 mol) was added over 15 min to a stirred suspension of adenine (30.0 g, 0.22 mol) in dry DMF (430 cm^3) at 21 °C. The mixture was heated at 60 °C for 30 min and then cooled back to 21 °C. A mixture of the diacetates **6**, **10**, **12** and **14** (43.5 g, 0.22 mmol; 70:30 mixture of *cis*:*trans* isomers†) in DMF (30 cm^3) was added, followed by tetrakis(triphenylphosphine)palladium(0) (7.7 g, 6.7 mmol). The resulting mixture was heated and stirred at 60 °C for 18 h and then cooled and poured into diethyl ether. The precipitate was filtered off and the filtrate was concentrated under high vacuum. Flash chromatography yielded 9-(4-acetoxymethylcyclopent-2-enyl)adenine **22** (48.2 g, 0.18 mol, 79%) as an 82:18 mixture of *cis*:*trans* isomers.

Acknowledgements

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References

1 K. Isono, *J. Antibiot*, 1988, **41**, 1711.
2 S. M. Roberts, K. Biggadike, A. D. Borthwick and B. E. Kirk, in *Topics in Medicinal Chemistry*, ed. P. R. Leeming, RSC Special Publ. No. 65, 1988, 172.
3 R. Vince, M. Hua, J. Brownell, S. Daluge, F. Lee, W. M. Shannon, G. C. Lavelle, J. Qualls, O. S. Weislow, R. Kiser, P. G. Canonico, R. H. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Shoemaker and M. R. Boyd, *Biochem. Biophys. Res. Commun.*, 1988, **156**, 1046.
4 C. Williamson, A. M. Exall, M. F. Jones, C. L. Mo, P. L. Meyers, I. L. Paternoster and R. Storer, Poster presented at the 5th SCI-RSC Medicinal Chemistry Symposium, 10–13th Sept. 1989, Churchill College, Cambridge. M. F. Jones, C. L. Mo, P. L. Meyers, I. L. Paternoster, R. Storer, G. G. Weingarten and C. Williamson, Poster presented at the 2nd International Conference on Drug Research in Immunologic and Infectious Disease: AIDS, 6–9th Nov. 1989, Arlington, Virginia, USA.
5 R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17; S. J. C. Taylor, A. G. S. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120.
6 R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, London, 1985; see also B. M. Trost, G-H. Kuo and T. Benneche, *J. Am. Chem. Soc.*, 1988, **110**, 621.
7 H. Paulsen and U. Maaß, *Chem. Ber.*, 1981, **114**, 346.
8 S. D. Lindell, E. A. Saville-Stones, N. S. Jennings and D. S. Carver, unpublished results.
9 All compounds described in this communication had ^1H NMR and IR spectra entirely consistent with the assigned structures. Satisfactory elemental analyses were obtained on all new compounds.

* We thank Glaxo Group Research, Greenford for supplying us with a sample of natural (−)-aristeromycin. The triacetate was made by adapting the method of V. Nair and S. D. Chamberlain, *Synthesis*, 1984, 401.

† This experiment was performed using a diacetate mixture obtained prior to full optimisation of the Prins reaction conditions.

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