Tetrahedron Letters, Vol. 33, No. 8, pp. 1085-1088, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Pd(0)-Catalyzed Allylic Alkylation in the Synthesis of (±)*Carbovir*.

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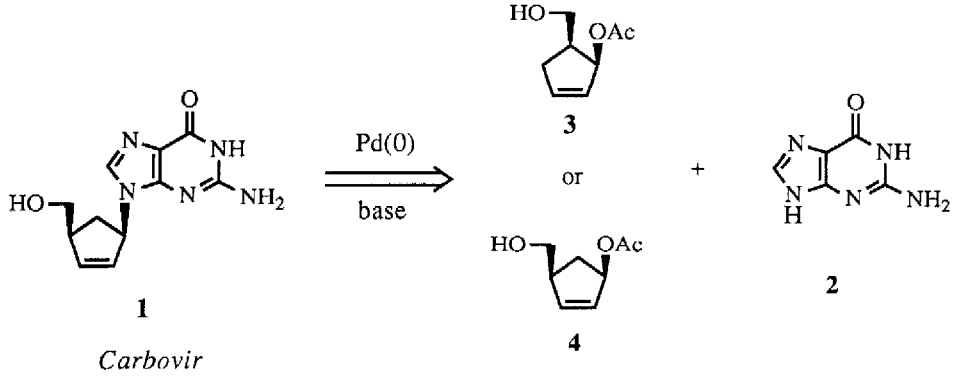
Abstract: Racemic *carbovir* **1** has been synthesized in 6 steps from the cyclopentanone **8** with a Pd(0)-catalyzed allylation as a key reaction.

The carbocyclic nucleoside *carbovir* **1** is a highly selective inhibitor of human immunodeficiency virus (HIV) *in vitro*.[1] *Carbovir* is one of several biologically active carbocyclic nucleosides which has a cyclopentene ring with a heterocyclic moiety in an allylic position.[2] This structural feature suggests that carbovir and related carbocyclic nucleosides might be prepared by Pd(0)-catalyzed allylic alkylation of the nucleoside base with an appropriately substituted cyclopentenyl acetate, e.g. **3** or **4**.

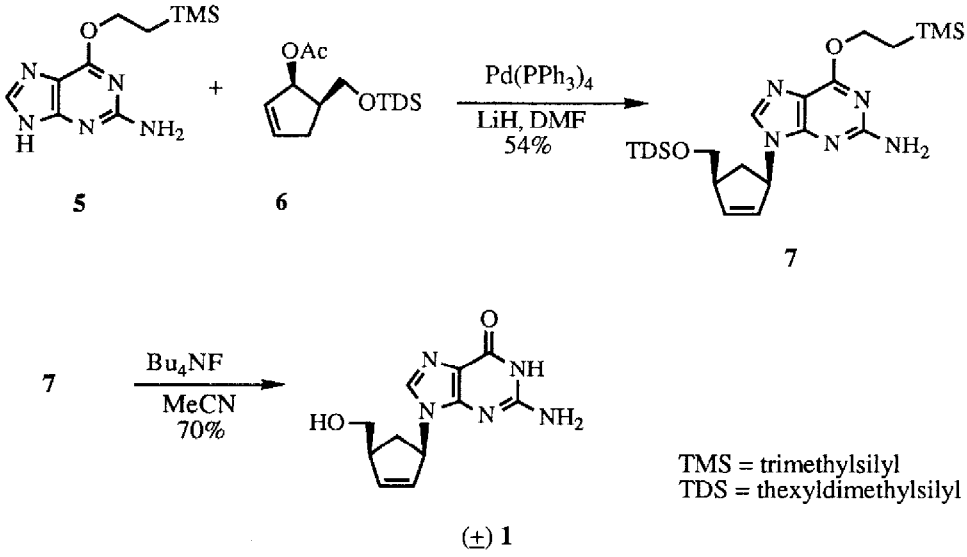


Scheme 1

In Pd(0)-catalyzed allylic alkylations the positional identity is lost once the leaving group (i.e. OAc in **4**) has departed.[3] Therefore either of the allylic acetates **3** or **4** should give the same intermediate palladium complex in the

alkylation reaction, and the regioselectivity for the nucleophilic attack by the base would be controlled by the non-bonded interaction from the substituent in the cyclopentene ring. Furthermore, the diastereoselectivity in the allylic alkylation would be controlled by the stereochemistry of the Pd(0)-template; retention of the acetate configuration prevails.[3]

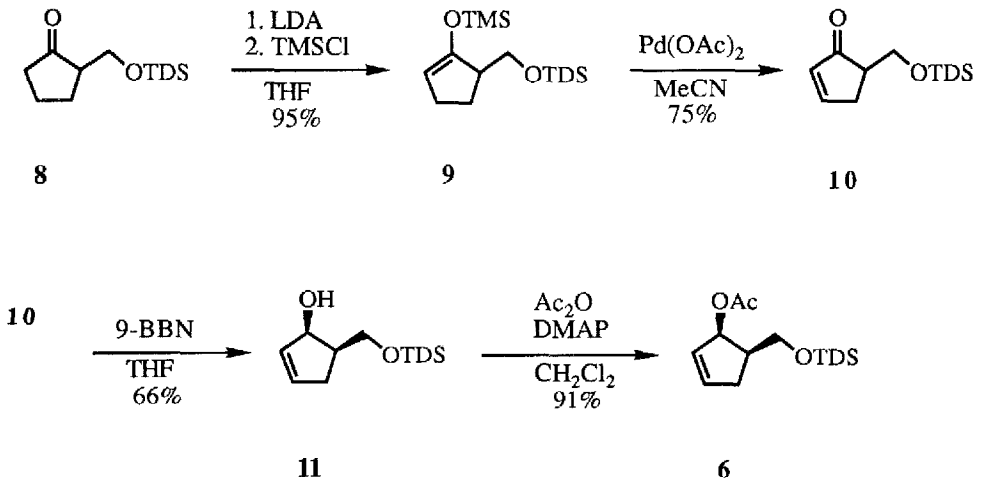
The reaction was run using the O-silylated allylic acetate **6** with tetrakis(triphenylphosphine)palladium as the catalyst. The anionic form of O6-protected guanine **5** was generated by lithium hydride in DMF. Under



Scheme 2

these reaction conditions exclusive formation of the desired N-9 alkylated isomer **7** was obtained.[4,5] The regio- and stereochemical assignments in the cyclopentene ring of **7** are based upon the characteristic ^{1}H NMR absorption of the methylene protons in disubsituted *cis*-1,4-cyclopent-2-enes.[6] Removal of the protecting groups of the guanine and cyclopentene moities was a one-pot reaction using tetrabutylammonium fluoride in acetonitrile. The product was identified as racemic *carbovir* **1**.[7]

The starting material for the allylic acetate **6** was the cyclopentanone **8** which was prepared as we have described previously.[8] The dimethyl-thexylsilyl protected cyclopentanone **8** was converted to its trimethylsilyl



Scheme 3

enol ether **9** and oxidized to the α,β-unsaturated ketone **10** by palladium acetate. The use of Pd(II) with cooxidants such as benzoquinone or DDQ was less satisfactory. Almost exclusive formation of the *cis*-alcohol **11** was achieved in the reduction of the enone **10** by 9-BBN (9-borabicyclo[3.3.1]-nonane) in THF at °C. Cerium catalyzed sodium borohydride reduction[9] of the enone was less satisfactory; the product contained the desired *cis*-allylic alcohol **11** admixed with significant amounts of fully saturated alcohols and the *trans*-isomer of **11**. Acetylation of **11** using acetic anhydride and DMAP (4-*N*,*N*-dimethylaminopyridine) furnished the allylic acetate **6**.

References and notes.

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5. ^{1}H , ^{13}C NMR and MS data for compound **7**: ^{1}H NMR ($CDCl_3$): δ 0.02 ($SiMe_2$), 0.03 ($SiMe_3$), 0.79 (Me in thexyl), 0.82 (d, *J* 6.8 Hz, Me in thexyl), 1.18 (t, *J* 8.4 Hz, CH_2Si), 1.5--1.6 (2H, m, CH in thexyl and H in CH_2 *trans* to H-1′/H-4′), 2.68 (1H, dt, *J* 13.6 and 8.5 Hz, H in CH_2 *cis* to H-1′/H-4′), 2.91 (m, H-4′), 3.59 (1H, dd, *J* 9.9 and 4.7 Hz, H_A, CH_2O), 3.61 (1H, dd, *J* 9.9 and 5.7 Hz, H_B, CH_2O), 4.53 (t, *J* 8.4 Hz, CH_2O), 5.05 (br s, NH_2), 5.51 (m, H-1′), 5.78 (dt, *J* 5.6 and 2.0 Hz, H-2′), 6.07 (dt, *J* 5.6 and 2.0 Hz, H-3′), 7.61 (H-8). ^{13}C NMR ($CDCl_3$): δ -3.0 and -0.9 (SiMe), 18.1 (CH_2Si), 19.0 and 20.8 (Me in thexyl), 25.7 (C in thexyl), 34.6 (CH in thexyl), 36.5 (CH_2), 48.3 (C-4′), 59.4 (C-1′), 65.2 and 66.1 (CH_2O), 116.3 (C-5), 129.1 (C-2′), 137.7 (C-3′), 139.1 (C-8), 154.0 (C-4), 159.8 (C-6) 161.9 (C-2). MS (CI - CH_4): 490 (88, M+1), 474 (18), 462 (11), 446 (12), 404 (15), 376 (41), 298 (25), 224 (21), 208 (25), 73 (100).
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(Received in UK 21 November 1991)