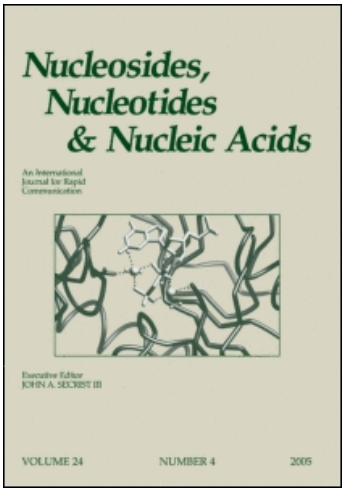

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Synthesis of a Novel Carbocyclic Nucleoside

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NUCLEOSIDES & NUCLEOTIDES, 16(10&11), 1961-1965 (1997)

SYNTHESIS OF A NOVEL CARBOCYCLIC NUCLEOSIDE

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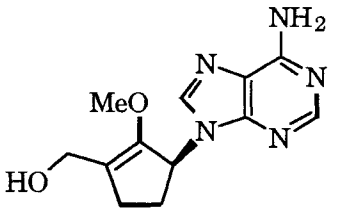
ABSTRACT: Carbocyclic nucleoside **1** was prepared from carbomethoxy cyclopentanone in eight steps.

The isolation and synthesis of novel antiviral agents has undergone explosive growth in the past decade. Although the impetus for this growth has, in large part, been the emergence of HIV which leads to the onset of acquired immune deficiency syndrome (AIDS), an increasing number of diseases have been shown to be the result of viral infections.[1] Carbocyclic analogs of nucleosides have been recognized as valuable sources of useful antiviral agents.[2] Biologically active carbocyclic nucleosides include neplanocin A,[3] aristeromycin,[4] and carbovir.[5]

As part of a program to develop effective antiviral agents,[6,7] we have prepared vinyl ether analog **1** and herein report the details of its synthesis. Our rationale is that an electron-donating vinyl ether in the γ-position will enable **1** to be a suicide inhibitor of certain kinases. Phosphorylation of the hydroxyl group in **1** would be expected to generate an excellent leaving group in the active site, leading to inactivation.



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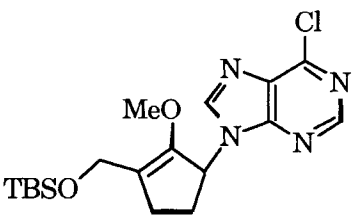
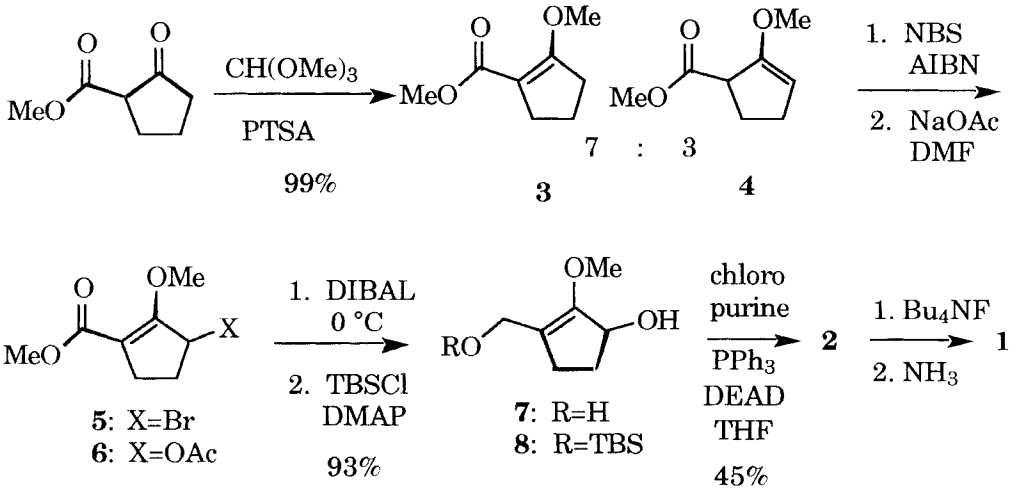


2

The synthesis of **1** began with commercially available 2-carbomethoxy cyclopentanone. Enol ether formation using trimethylorthoformate and a catalytic amount of p-toluenesulfonic acid afforded a mixture of esters **3** and **4** in a 7:3 ratio.[8] Although these compounds were inseparable by TLC, both compounds could be converted into bromide **5** by reaction with N-bromosuccinimide (NBS) and a catalytic amount of AIBN in carbon tetrachloride at 65 °C. Substitution with 10 equivalents of sodium acetate in DMF at 25 °C provided ester **6** in 76% yield. Reduction of both esters with diisobutylaluminum hydride (DIBAL) in methylene chloride at 0 °C afforded diol **7** in 93% yield. Selective protection of the primary alcohol in **7** using tert-butyldimethylchlorosilane (TBSCl) and 4-dimethylaminopyridine (DMAP) in methylene chloride at 25 °C produced alcohol **8** in 95% yield.[9] Substitution of the alcohol using conditions developed by Mitsunobu[10] furnished **2** in 45% yield. Interestingly, several attempts to convert bromide **5** directly into the ester corresponding to **2** were unsuccessful. Compound **2** was readily deprotected and aminated to generate **1** in 75% yield.[11]



A synthesis of **1** in eight steps in 25% overall yield has been achieved. The synthesis is flexible and direct. Alcohol **8** represents an advanced intermediate from which a number of related compounds could easily be prepared.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate

solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR.

*Methyl 3-bromo-2-methoxy-1-cyclopentene carboxylate (**5**)*

A mixture of esters **3** and **4** (1.00g, 6.41mmol), NBS (1.05g, 6.41mmol), and AIBN (0.097g, 0.641mmol) in 10 mL CCl_4 was warmed to 65° C and was stirred for 1 h. The reaction was cooled to 0° C, filtered, and the solvent was removed in vacuo to give 1.24g of **5** as a yellow oil. This material was used in the next reaction.

5: NMR ($CDCl_3$) δ 2.2–2.45 (m, 2H), 2.5-2.6 (m, 1H), 2.70-2.85, (m, 1H), 3.74 (s, 3H), 4.00 (s, 3H), 5.05 (d, J=6.6 Hz, 1H) IR ($CHCl_3$) cm^{-1} 2990, 2940, 2850, 1695, 1625, 1435, 1348, 1250, 1135, 1060. TLC (5:1 H:EA) R_f = 0.36

*Methyl 3-acetoxy-2-methoxy-1-cyclopentene carboxylate (**6**)*

A mixture of **5** (0.750g, 3.19mmol) and sodium acetate (2.46g, 31.9mmol) in 15mL DMF was stirred for 12 h at 25° C. The reaction was poured into cold water (60 mL) and was extracted with chloroform (4x60 mL). The combined organic extracts were washed with water (4x60mL) and dried over sodium sulfate. The solvent was removed in vacuo to give 0.705g of a dark brown oil. The residue was purified by sgc (5:1 H:EA) to give 0.618g of **6** (76% from **3** and **4**) as a light yellow oil.

6: NMR ($CDCl_3$) δ 1.73-1.78 (m, IH), 2.10 (s, 3H), 2.24-2.32, (m, 1H), 2.45-2.55 (m, 1H), 2.65-2.75 (m, 1H), 3.74 (s, 3H), 3.84 (s, 3H), 5.88 (d, J=7.8 Hz, 1H). IR $CHCl_3$) cm^{-1} 2990, 2950, 2865, 1738, 1690, 1640, 1440, 1387, 1226, 1148, 962. TLC (5:1 H:EA) R_f = 0.24

*3-Hydroxy-1-hydroxymethyl-2-methoxy-1-cyclopentene (**7**)*

A solution of **6** (0.400g, 1.75mmol, 15mL dry CH_2Cl_2) was cooled to 0° C. A 1.0 M solution of DIBAL (7.35mL) was added over a period of 10 min. The reaction mixture was then stirred for an additional 2 h with slow warming to rt. The reaction mixture was poured into a saturated aqueous solution of Rochelle salt (30mL), and the solvents were removed in vacuo. The product was extracted with ethyl acetate (4x20 mL), and was dried over sodium sulfate. Removal of the solvent in vacuo gave 0.250g (93%) of **7** as a yellow oil which was used without purification.

7: NMR ($CDCl_3$) δ 1.25 (s, IH), 1.69-1.80 (m, 2H), 2.22-2.32, (m, 3H), 2.4-2.5 (m, 1H), 3.77 (s, 3H), 4.24 (dd, J=15 Hz, 2H), 4.83-4.85 (m, 1H), IR (Neat)

cm^{-1} 3440, 3360, 3020, 2960, 2930, 2860, 1650, 1470, 1260, 1215 TLC (H:EA 1:2) R_f = 0.20

*3-Hydroxy-2-methoxy-1-tertbutyldimethylsiloxymethyl cyclopentene (**8**)*

A mixture of **7** (0.200g, 1.39 mmol), t-butyldimethylsilylchloride (0.226g, 1.50 mmol), triethylamine (0.233, 1.67mmol), and N,N-dimethylaminopyridine (0.0068g, 0.0556mmol) in 10mL CH_2Cl_2 was stirred at 25° C for 4 h under nitrogen. The reaction was washed with water, saturated NH_4Cl, and dried over sodium sulfate. The residue was purified by sgc (3:1 H:EA) to give 0.340g (95%) of **8** as a yellow oil.

8: NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.90 (s, 9H), 1.67-1.77 (m, 1H), 2.20-2.32 (m, 2H), 2.38-2.48 (m, 1H), 3.74 (s, 3H), 4.26 (dd, J=12.6Hz, 2H), 4.82 (d, J=7.2Hz, 1H). IR (Neat) cm^{-1} 3370, 2950, 2850, 1680, 1460, 1250, 1050, 840, 775. TLC (2:1 H:EA) R_f = 0.60.

*3-(6-Chloropurinyl)-2-methoxy-1-tertbutyldimethylsiloxymethyl cyclopentene (**2**)*

To a suspension of 6-chloropurine (0.179g, 1.16mmol) and triphenylphosphine (0.302g, 1.16mmol) in 6mL dry THF was added diethylazodicarboxylate (0.253mL, 1.45mmol). A solution of **8** (0.250g, 0.969 mmol) in 4mL THF was added dropwise at 25° C with stirring. Stirring was continued for an additional 24 h. The solvent was removed in vacuo to give a thick, dark yellow syrup. The residue was purified by sgc (2:1 H:EA) to give 0.173g (45%) of **2** as a light yellow oil.

2: NMR (CDCl3) δ 0.11 (s, 3 H), 0.93 (s, 9 H), 1.9-2.0 (m, 1 H), 2.50-2.75 (m, 3 H), 3.51 (s, 3 H), 4.39 (dd, J=12.6 Hz, 2 H), 5.82-5.85 (m, 1 H), 8.09 (s, 1 H), 8.76 (s, 1 H). IR ($CHCl_3$) 3020, 2930, 2860, 1680, 1590, 1560, 1260, 1220, 1105, 1060 cm^{-1}. TLC (2:1 H:EA) R_f = 0.50.

*3-(6-aminopurinyl)-2-methoxy-1-hydroxymethyl cyclopentene (**1**)*

To a solution of **2** (0.100g, 0.254 mmol) in 2mL THF was added a 1M solution of tetrabutylammonium fluoride in THF (0.305 mL). The mixture was stirred for 20 min at 25° C. The reaction was poured into brine (20 mL) and extracted with CH_2Cl_2 (6x10 mL). The solvent was dried over Na_2SO_4 and was removed in vacuo. The residue was purified by sgc (8:1 EA:H, the silica gel was treated with 1% Et_3N in hexane before sgc). to give 58.3mg (82%) of **1** as a thick, colorless syrup (NMR ($CDCl_3$) δ 1.97-2.05 (m, lH), 2.5-2.75 (m, 3H), 3.54, (s, 3H), 4.41 (dd, J=15Hz, 2H), 5.85 (d, J=7.8Hz, 1H), 8.12 (s, 1H), 8.76 (s, 1H).

IR ($CHCl_3$) cm^{-1} 3390, 3005, 2940, 2860, 1685, 1590, 1560, 1400, 1340, 1215, 1005, 950. MS: m/e 127, 281, 283, 298. TLC (8:1 EA:H) R_f = 0.25).

A solution of chloride (10 mg, 0.0035 mmole) in methanol (3 mL) was cooled to -20 °C. Into this solution in a sealable tube was bubbled with NH_3 gas for 10 min. The tube was sealed and the reaction was warmed to 45 °C for 2 days. The reaction was concentrated to give **1** (8.3 mg, 90.8% yield).
1: NMR ($CDCl_3$) δ 1.97-2.05 (m, 1 H), 2.50-2.64 (m, 3 H), 3.48 (s, 3 H), 4.36 (AB q J=13.2 Hz, 56.2 Hz, 2 H), 5.76 (d, J=8.4 Hz, 1 H), 5.90 (br s, 2 H), 7.80 (s, 1 H), 8.34 (s, 1 H). CMR ($CDCl_3$) δ 28.1, 29.5, 56.0, 57.6, 57.8, 119.6, 123.0, 138.7, 139.4, 149.1, 153.1, 155.5. IR ($CHCl_3$) cm^{-1} 3470, 3298, 3291. MS (EI): m/z 136, 151, 228, 246, 261. HRMS: m/z for $C_{12}H_{15}N_5O_2$ calcd. 261.1226; measured 261.1220. TLC (8:1 EA:H) R_f = 0.07.

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REFERENCES

1. Bean, B. Clin. Microbiol. Rev., 1992, 146-182.
2. Huryn, D. M.; Okabe, M. Chem. Rev. 1992, 92, 1745.
3. Hayashi, M.; Yaginuma, S.; Yoshioka, H.; Nakatsu, K. J. Antibiot., 1981, 34, 675.
4. Quinkert, G., Ed. Synform, 1989, 7, 192.
5. Vince, R.; Hua, M. J. Med. Chem., 1990, 33, 17.
6. Carpenter, S.; Kraus, G. A. *Photochem. and Photobiol.*, **1991**, 169.
7. Carpenter, S.; Fehr, M.J.; Kraus, G. A.; Petrich, J. W. Proc. Natl. Acad. Sci. USA, 1994, 91, 12273.
8. Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. J. Org. Chem., 1992, 57, 2585.
9. Chaudhary, S. K.; Hernandez, O. Tetrahedron Lett, 1979, 99.
10. Mitsunobu, O. Synthesis, 1981, 1.
11. Deprotection: Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc., 1972, 94, 6190. Amination: Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H.; Sakai, K. J. Org. Chem., 1996, 61, 6952.

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