with those of authentic samples. They were also treated with bis(trimethylsilyl)trifluoroacetamide at 150 °C for 5 min to give trimethylsilyl derivatives, which were analyzed by GC–mass spectroscopy.[16] The mass spectra were consistent with those of authentic samples. The conditions of the gas chromatography are as follows: column, glass, 3 mm × 1 m, 2% Silicone OV-1 on Gas Chrom Q (60–80 mesh); column temperature, 80–240 °C (10 °C min^{-1}); injection temperature, 240 °C; carrier gas, He (30 mL min^{-1}). The physical and spectral data of the products follow.

2-Amino-4,6-dihydroxy-1,3,5-triazine:[17] mp > 300 °C; ^1H NMR (DMSO-d_6) δ 5.77 (s, 2 H, exchanges with D_2O), 10.43 (s, 2 H, exchanges with D_2O); EIMS (70 eV) m/z (rel intensity) 128 (M^+, 51), 43 (100); HRMS m/z calcd for $C_3H_4N_4O_2$ 128.0348, found 128.0334; EIMS of trimethylsilyl derivative of **5** (20 eV) m/z (rel intensity) 344 (M^+ + 3TMS, 100).

Parabanic acid (6): mp 236–240 °C (lit.[18] mp 238–244 °C); ^1H NMR (DMSO-d_6) δ 11.75 (br, 2 H, exchanges with D_2O); EIMS (70 eV) m/z (rel intensity) 114 (M^+, 72), 43 (100); EIMS of trimethylsilyl derivative of **6** (20 eV) m/z (rel intensity) 258 (M^+ + 2TMS, 12), 243 (53), 100 (100).

X-ray Measurement of 4-Amino-1-formyl-5-hydroxy-1*H*-imidazol-2(5*H*)-one (2a). All data were collected at 23 °C on a Rigaku AFC-6R diffractometer with graphite-monochromated Mo-K_α radiation in the range $2\theta < 55°$ of the ω–2θ scan mode. A total of 1460 reflections having $|F| > 3\sigma|F|$ were used in the structure refinement. Crystal data for **2a**: monoclinic, $P2_1/c$, a = 11.919 (2) Å, b = 6.969 (2) Å, c = 6.919 (10) Å, α = 90.30 (5)°, V = 574.6 (8) Å^3, D(calcd) = 1.65 g cm^{-3}, Z = 4. Crystal size: 0.2 × 0.2 × 0.4 mm^3. The structure was solved by direct method (MULTAN78) and refined by block-diagonal Fourier using the UNICS program at Osaka University. The non-hydrogen atoms in **2a** were assigned anisotropic thermal parameters. All hydrogen atoms were located on a different electron density map and were included in structure factors. The final conventional index R is 0.0509. Tables of atomic coordinates, bond distances and angles, and anisotropic temperature coefficients are available as supplementary material.

Acknowledgment. The present work was partially supported by a Saneyoshi Scholarship Foundation.

Registry No. **1a**, 7-30-7; **1b**, 6220-47-9; **1c**, 134419-26-4; **1d**, 134419-27-5; **1e**, 134419-28-6; **1f**, 134419-29-7; **1g**, 6220-48-0; **1h**, 29840-48-0; **1i**, 62968-15-4; **1j**, 62968-21-2; **1k**, 554-01-8; **1l**, 6220-50-4; **2a**, 134419-30-0; **2b**, 134419-31-1; **2c**, 134419-32-2; **2d**, 134419-33-3; **2e**, 134419-34-4; **2f**, 134419-35-5; **2g**, 134419-36-6; **2h**, 134419-37-7; **2i**, 134419-38-8; **2j**, 134419-39-9; **2k**, 134419-41-3; **2l**, 134419-41-3; **4**, 73-40-5; **5**, 645-93-2; **6**, 120-89-8; 4-etoxy-2-(1*H*)-pyrimidinone, 6220-43-5.

Supplementary Material Available: Tables of atomic coordinates, isotropic thermal parameters, bond distances and angles, and X-ray crystallographic data for **2a** (2 pages). Ordering information is given on any current masthead page.

(16) Gehrke, C. W.; Ruyle, C. D. *J. Chromatogr.* **1968**, *38*, 473.
(17) Padgett, W. M.; Hamer, W. F. *J. Am. Chem. Soc.* **1958**, *80*, 803.
(18) Johnson, T. B.; Flint, R. B. *J. Am. Chem. Soc.* **1931**, *53*, 1082.

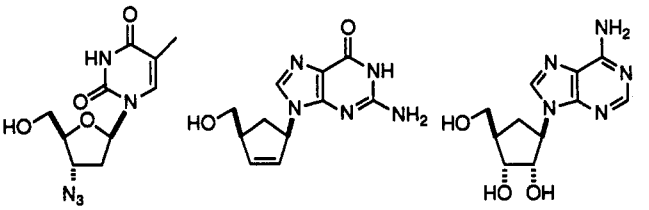
A Short, Enantioselective Synthesis of the Carbocyclic Nucleoside Carbovir

Michael R. Peel,* Daniel D. Sternbach, and M. Ross Johnson

Glaxo Research Institute, Five Moore Drive, Research Triangle Park, North Carolina 27709

Received February 27, 1991

The continued interest in the synthesis of nucleosides and nucleoside analogues is reflected in the successful use of this class of compound as therapy in viral and cancerous diseases.[1] This interest has recently become more focused with the identification of the retrovirus HIV-1 as the causative agent of AIDS (Aquired Immune Deficiency Syndrome) and the finding that certain nucleoside analogues (most notably 3′-azido-2′,3′-dideoxythymidine (AZT), dideoxyinosine (ddI), dideoxyadenosine (ddA), and dideoxycytidine (ddC)) act as potent inhibitors of HIV-1 replication.[2] This antiviral activity is believed to be due to the inhibition of the key viral enzyme reverse transcriptase. In addition, these compounds, by lacking a 3′-hydroxyl function, act as terminators of the growing viral DNA chain. We recently became interested in a carbocyclic nucleoside analogue (carbovir) that was reported by Vince et al.[3] to be a potent inhibitor of reverse transcriptase and so has potential as a therapy against AIDS.



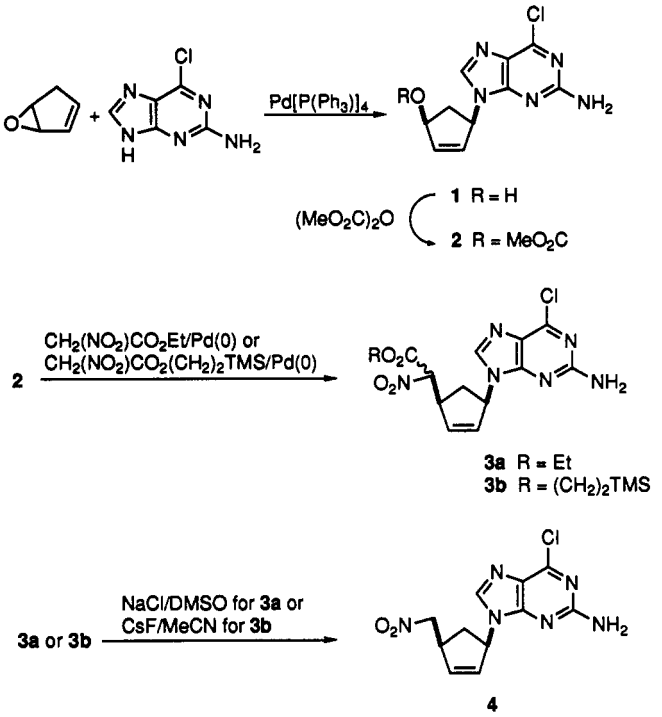
As part of our initial investigations, we required a convenient and flexible synthesis of the compound and analogues. Unfortunately, the published synthesis of carbovir is somewhat lengthy and involves a wasteful resolution procedure as the final step.[4] In order to secure a shorter, more efficient, and preferably enantioselective synthesis of carbovir our attention was focused on some organopalladium chemistry that has precedent in forming cis-1,4-substituted cyclopentenes.[5] Trost recently reported the synthesis of a related carbocyclic nucleoside (aristeromycin) via a route that involved the sequential palladium-catalyzed introduction of a purine base (adenine) followed by another nucleophilic addition of a sulfonyl-stabilized nitronate onto a cyclopentane ring.[6]

In line with this precedent, treatment of cyclopentadiene monoepoxide with 2-amino-6-chloropurine (a commonly used surrogate for the remarkably insoluble purine base guanine) under catalysis by palladium(0) gave the cis-

(1) Hobbs, J. B. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon; Oxford, 1990; Vol. 2, pp 306–322. Isono, K. *J. Antibiotics* **1988**, *XLI*, 1711. Hovi, T. In *Antiviral Agents: The Development and Assessment of Antiviral Chemotherapy*; Field, H. J., Ed.; CRC Press: 1988; Chapter 1, pp 1–12. Jones, M. F. *Chemistry in Britain*, **1988**, 1122. Dolin, R. *Science (Washington, D.C.)* **1985**, *227*, 1296.
(2) Popovic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. *Science* **1984**, *224*, 497. Gallo, R. C. et al *Science* **1984**, *224*, 500. Mitsuya, H.; Weinhold, K. J.; Furman, P. A. et al. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911. Kim, C.-H.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. S. *J. Med. Chem.* **1987**, *30*, 862. Mitsuya, H.; Broder, S. *Nature* **1987**, *325*, 773. Yarchoan, R.; Mitsuya, H.; Myers, C. E.; Broder, S. *N. Engl. J. Med.* **1989**, *321*, 726.
(3) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Owen, W. S.; Kiser, R.; Canonico, P. G.; Schulz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046. Vince, R.; Hua, M. *J. Med. Chem.* **1989**, *33*, 17. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912. Coe, D. M.; Myers, P. L.; Parry, D. M.; Roberts, S. M.; Storer, R. *J. Chem. Commun.* **1990**, 151.
(4) Recently a somewhat shorter synthesis of (−)-carbovir was reported that involved resolution of an early intermediate: Taylor, S. J. C.; Sutherland, A. G.; Lee, C.; Wisdom, R.; Thomas, S.; Roberts, S. M.; Evans, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1120.
(5) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Deardorff, D. R.; Myles, D. C.; Macferrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615. Tsuji, J. *Tetrahedron*, **1986**, *42*, 4401. For a recent Pd(0) catalyzed synthesis of an aristeromycin precursor, see: Deardorff, D. R.; Shulman, M. J.; Sheppeck J. E., II. *Tetrahedron Lett.* **1989**, *30(48)*, 6625.
(6) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621.

0022-3263/91/1956-4990$02.50/0

Scheme I

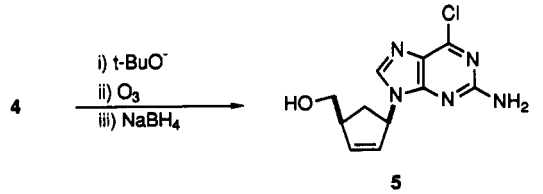


1,4-disubstituted cyclopentene derivative 1 in 86% yield.[7] It is noteworthy that the syn-selective substitution occurs to give only the 1,4 substitution pattern about the cyclopentene ring as determined by ^1H NMR decoupling experiments[8] and that the purine base is alkylated exclusively at N-9. The question of N-9 or N-7 substitution on the purine base was not answered unequivocably until the material was converted to a known carbovir precursor; however, substantial evidence exists to suggest that N-9 is the preferred site of alkylation.[9]

The conversion of alcohol 1 to the corresponding carbonate 2 was most readily accomplished using dimethyl pyrocarbonate (Scheme I). With carbonate 2 in hand, the task of introducing a hydroxymethyl group with retention of configuration was confronted. This problem was addressed by Trost via the palladium-catalyzed introduction of a phenylsulfonylnitromethane unit followed by ozonolysis and reduction.[6] In view of the double bond in the cyclopentene ring of 2 this approach was not immediately attractive; however, numerous examples are recorded of a nitromethyl group acting as a synthon for an aldehyde group and thence an alcohol by reduction, so the nitromethyl-substituted compound was chosen as an attractive intermediate. The conversion of 2 to 4 (via 3a or 3b) was readily accomplished in a regio- and stereoselective manner by the palladium(0)-catalyzed addition of an ester of nitroacetic acid followed by decarboxylation.

The harsh conditions (160 °C) required for the decarboxylation of the ethyl nitroacetate derivative (3a) resulted in difficult to remove byproducts and so led us to develop 2-(trimethylsilyl)ethyl nitroacetate as a mild nitromethyl group synthon. This compound is easily accesible via a transesterification reaction of ethyl nitroacetate and (trimethylsilyl)ethanol.[10] Palladium(0)-catalyzed introduction of the (trimethylsilyl)ethyl nitroacetate was followed by smooth fluoride-induced decarboxylation at moderate temperature (50 °C) to give 4.

Scheme II



The stereo- and regiochemistry of the introduction of the nitromethyl group was anticipated as a result of literature precedent and was confirmed by conversion to a compound of known stereochemistry. It is pertinent to note that the direct introduction of a nitromethyl group using nitromethane was not successful; similarly, malonate and ethyl phenylthioacetate enolates would not undergo this coupling.

The nitromethyl adduct 4 was subjected to a number of conditions reported to effect the conversion of a nitro group to a carbonyl function: OH^-/H^+, aqueous $TiCl_3$, $TiCl_3/NH_4OH$[11] (Scheme II). None of these procedures effected the desired transformation, and in most cases only decomposition of starting material was observed. Despite extensive evidence that suggested that ozone would be expected to attack the double bond in 4, it was suggested that controlled ozonolysis of the more reactive nitronate anion derived from 4 may lead to selective cleavage of this function rather than the olefin.[12] To this end, the nitromethyl derivative 4 was treated with potassium *tert*-butoxide followed by careful addition of a saturated solution of ozone in CH_2Cl_2 and finally with sodium borohydride to give the desired alcohol 5.[13]

The preparation of alcohol 5 represents a formal synthesis of carbovir since simple hydrolysis gives racemic material, while aminolysis followed by enzymatic hydrolysis affords optically pure material.[3] This represents a successful synthesis of racemic carbovir; however, the approach suffers from the losses inherent in a resolution step late in a synthesis. This problem was overcome by use of an optically pure starting material.

Allylic acetate 6 is readily available by the enzymatic desymmetrization of 2-cyclopentene-1,4-diacetate[14] (Scheme III). Treatment of cyclopentene 6 with the preformed potassium salt of 2-amino-6-chloropurine under

(7) Satisfactory NMR, MS, and/or analytical data were obtained for new compounds.

(8) The relative sterochemistry of 1,4-substituted cyclopentenes (cis/trans) can be confidently predicted by correlation with the chemical shift difference between the two protons at C-5 (cis ~ 1 ppm, trans < 0.3 ppm). See: Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

(9) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. *J. Med. Chem.* **1987**, *30*, 1636. Phadtare, S.; Zemlicka, J. *J. Med. Chem.* **1987**, *30*, 437. Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1985**, *26*, 4265. Shaw, G. In *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984, Vol. 5, p 528. Robbins, M. J.; Hatfield, P. W. *Can. J. Chem.* **1982**, *60*, 547.

(10) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.

(11) $KMnO_4$: Kornblum, N.; Erickson, A. S.; Kelly, W. J.; Henggeler, B. *J. Org. Chem.* **1982**, *47*, 4534. $^1O_2$: Williams, J. R.; Unger, L. R.; Moore, R. H. *J. Org. Chem.* **1978**, *43*, 1271. H^+/MeOH: Jacobson, R. M. *Tetrahedron Lett.* **1974**, 3215. $TiCl_3$; McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367. For a comprehensive review of the Nef reaction, see: Pinnick, H. W. In *Organic Reactions*; Wiley: New York, 1990; Vol. 38, pp 655–792.

(12) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.

(13) This compound (5) is an intermediate in the synthesis of Carbovir reported by Vince et al.[3]

(14) *Biotransformations in Preparative Organic Chemistry*; Davies, H. G., Green, R. H., Kelly, D. R., Roberts, S. M., Eds.; Academic Press: London, 1989. Mori, K.; Sugai, T. *Synthesis*, **1988**, 19. Deardorff, D. R.; Matthews, A. J.; McMeekin, S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298. Fluka no. 00850.

palladium(0) catalysis led smoothly to 1 in optically pure form (58%).[15] The optical integrity of 1 was established by analysis of ^1H NMR spectra of Mosher esters derived from both racemic and optically pure 1. With the synthesis of optically pure 1 secured, this represents an enantioselective synthesis of carbovir in an efficient and convergent manner.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were determined on a Varian VXR 300 spectrometer in $CDCl_3$ and were referenced to residual $CHCl_3$ (7.24 ppm, ^1H) or $CDCl_3$ (77.0 ppm, ^{13}C). Mass spectra were recorded on either a Hewlett-Packard 5988A GC/mass spectrometer or a JEOL SX102 mass spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at the sodium D lines using a 1 mL/10 cm cell. Microanalyses were performed by Atlantic Microlab, Inc., GA. TLC was carried out using Whatman 2.5 × 7.5 cm (250-μm layer) plates. Column chromatography was performed using 32–63 mesh flash silica gel. Ozonolysis was carried out using an OREC 03v10-0 ozonator.

***cis*-(±)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (1).** To a stirred solution of 2-amino-6-chloro-9*H*-purine (4.0 g, 23.7 mmol) in dry dimethyl sulfoxide (40 mL) at room temperature under N_2 was added tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.23 mmol), and the mixture was stirred for 2 min. The solution was cooled to 0 °C, and a solution of cyclopentadiene monoepoxide (2.1 g, 25.6 mmol) in dry tetrahydrofuran (20 mL) was added over 15 min. The resulting yellow solution was allowed to warm to room temperature over 3 h and stirred overnight (~16 h). The clear, yellow solution was evaporated to a viscous oil that was taken up in dichloromethane (50 mL) and filtered through a small pad of Celite. The solvent was evaporated, and the residue was purified by silica gel chromatography using (i) ethyl acetate followed by (ii) 10:1 ethyl acetate–methanol as eluent to give the title compound as a white solid, 5.14 g (86%): mp 160–162 °C; ^1H NMR δ 7.83 (s, 1 H), 6.34 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.85 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.34 (d, J = 10 Hz, 1 H), 5.26 (dq, J_1 = 9 Hz, J_2 = 2 Hz, 1 H), 5.12 (br s, 2 H), 4.85 (br t, J = 9 Hz, 1 H), 2.97 (ddd, J_1 = 15 Hz, J_2 = 9 Hz, J_3 = 7 Hz, 1 H), 2.13 (br d, J = 15 Hz, 1 H); high-resolution FAB-MS calcd for $C_{10}H_{10}OCl$ 252.0649 (MH^+), found 252.0641.

***cis*-(±)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-yl Methyl Carbonate (2).** Dicarbonic acid, dimethyl ester (2 g, 15 mmol) was added dropwise to a stirred solution of *cis*-(±)-4-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (2.0 g, 8 mmol) and 4-(dimethylamino)pyridine (3 mg) in dry dichloromethane (20 mL) at room temperature, and stirring was continued for 20 min. Additional dicarbonic acid, dimethyl ester (2 g) was added and the mixture was stirred for a further 20 min, whereupon the mixture became clear. The solvent was evaporated, and the residue was taken up in dichloromethane (20 mL) and treated with dicarbonic acid, dimethyl ester (2 g). This evaporation/retreatment with dicarbonic acid, dimethyl ester sequence was repeated until no starting material remained by TLC. The solution was finally evaporated to afford a white solid, (2.36 g, 96%): mp 120–123 °C; ^1H NMR δ 7.83 (s, 1 H), 6.37 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 6.18 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.66 (m, 1 H), 5.54 (m, 1 H), 5.22 (br s, 2 H), 3.80 (s, 3 H), 3.10 (dt, J_1 = 15 Hz, J_2 = 8 Hz, 1 H), 2.00 (dt, J_1 = 15 Hz, J_2 = 3 Hz, 1 H); high-resolution FAB-MS calcd for $C_{12}H_{12}N_5O_3Cl$ 309.0629 (M^+), found 309.0613. Anal. Calcd for $C_{12}H_{12}ClN_5O_3$: C, 46.53; H, 3.91; N, 22.61. Found: C, 46.41; H, 3.92; N, 22.53.

[1α,4α(*R)]-(±)-2-Amino-6-chloro-9-[4-[nitro(ethoxycarbonyl)methyl]-2-cyclopenten-1-yl]-9*H*-purine and [1α,4α(*S**)]-(±)-2-Amino-6-chloro-9-[4-[nitro(ethoxycarbonyl)methyl]-2-cyclopenten-1-yl]-9*H*-purine (3a).** To a stirred solution of *cis*-(±)-4-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ylmethylcarbonate (1.50 g, 4.85 mmol) and nitroacetic acid, ethyl ester (0.68 g, 5.11 mmol) in dry tetrahydrofuran (20 mL) at room temperature under N_2 was added tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.13 mmol) and the resulting yellow solution was stirred for 90 min. The solvent was evaporated, and the residue was purified by silica gel chromatography using as eluent 1:1 hexanes–ethyl acetate followed by 100% ethyl acetate to give the title compound (1.65 g, 93%) as an off-white solid. The product is an inseparable mixture of diastereoisomers: ^1H NMR δ 7.73 and 7.72 (2s, 1 H), 6.11 and 6.07 (2dt, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.95 (m, 1 H), 5.60 and 5.58 (2d, J = 5.5 Hz, 1 H), 5.53 (m, 1 H), 5.26 (br s, 2 H), 4.29 (m, 2 H), 3.77 (m, 1 H), 2.97 (m, 1 H), 2.05 and 1.94 (2dt, J_1 = 14.5 Hz, J_2 = 6 Hz, 1 H), 1.29 (m, 3 H); high-resolution FAB-MS calcd for $C_{14}H_{15}N_6O_4Cl$ 367.0922 (MH^+), found 367.0913. Anal. Calcd for $C_{14}H_{15}N_6O_4Cl$: C, 45.84; H, 4.12; N, 22.92. Found: C, 45.57; H, 4.15; N, 22.63.

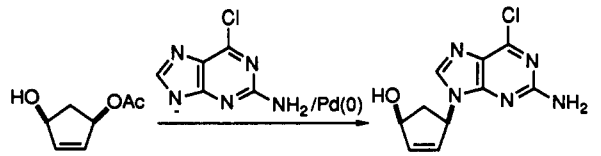
***cis*-(±)-2-Amino-6-chloro-9-[4-(nitromethyl)-2-cyclopenten-1-yl]-9*H*-purine (4).** A mixture of [1α,4α(*R**)]-(±)-2-amino-6-chloro-9-[4-[nitro(ethoxycarbonyl)methyl]-2-cyclopenten-1-yl]-9*H*-purine and [1α,4α(*S**)]-(±)-2-amino-6-chloro-9-[4-[nitro(ethoxycarbonyl)methyl]-2-cyclopenten-1-yl]-9*H*-purine (1.13 g, 3.08 mmol), sodium chloride (1.0 g, 17 mmol), and water (0.2 mL, 20 mmol) in dimethyl sulfoxide (15 mL) was heated at ~150 °C for 4 h. The solvent was evaporated at reduced pressure, and the black residue was taken up in ethyl acetate and filtered through a small plug of Celite. The filtrate was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated to leave a light brown solid. This solid was purified by silica gel chromatography using 1:1 hexanes–ethyl acetate as eluent to give the title compound as a white solid (0.66 g, 66%): ^1H NMR δ 7.72 (s, 1 H), 6.14 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.98 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.56 (m, 1 H), 5.07 (br s, 2 H), 4.61 (dd, J_1 = 12.5 Hz, J_2 = 6.5 Hz, 1 H), 4.56 (dd, J_1 = 12.5 Hz, J_2 = 7.5 Hz, 1 H), 3.59 (m, 1 H), 2.96 (dt, J_1 = 14.5 Hz, J_2 = 8.5 Hz, 1 H), 1.87 (dt, J_1 = 14.5 Hz, J_2 = 6.5 Hz, 1 H); high-resolution FAB-MS calcd for $C_{11}H_{11}N_6O_2Cl$ 295.0710 (MH^+), found 295.0714.

***cis*-(±)-2-Amino-6-chloro-9-[4-(nitromethyl)-2-cyclopenten-1-yl]-9*H*-purine (4; Alternate Procedure).** To a stirred solution of *cis*-(±)-4-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ylcarbonic acid, methyl ester (1.95 g, 6.3 mmol) and nitroacetic acid, 2-(trimethylsilyl)ethyl ester (1.30 g, 6.3 mmol) in dry tetrahydrofuran (30 mL) at room temperature under N_2 was added tetrakis(triphenylphosphine)palladium(0) (0.3 g, 0.26 mmol), and the mixture was stirred for 30 min. The solvent was evaporated to leave an orange oil (2.76 g). This oil was dissolved in dry acetonitrile (20 mL), and cesium fluoride (2.0 g, 13 mmol) was added. The mixture was heated at 50 °C under N_2 for 24 h. The resulting suspension was cooled to room temperature, diluted with dichloromethane (30 mL), and filtered through a small pad of Celite. The solvent was evaporated, and the residue was purified by silica gel chromatography using (i) 1:1 hexane–ethyl acetate and (ii) ethyl acetate as eluent to give the title compound (1.15 g, 62%). Physical and spectral data are as described previously.

***cis*-(±)-2-Amino-6-chloro-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-9*H*-purine (5).** To a stirred solution of *cis*-(±)-2-amino-6-chloro-9-[4-(nitromethyl)-2-cyclopenten-1-yl]-9*H*-purine (0.085 g, 0.29 mmol) in dry tetrahydrofuran (2 mL) at −20 °C under N_2 was added potassium *tert*-butoxide (0.034 g, 0.3 mmol), and the mixture was stirred for 15 min. Dry methanol (1 mL) was added, and the mixture was cooled to −78 °C. In a separate flask, ozone was bubbled through dry dichloromethane (8 mL) at −78 °C for 10 min to generate a saturated solution. This saturated solution of ozone was then added to the solution of nitronate anion, and the mixture was stirred at −78 °C for 10 min. Sodium borohydride (0.025 g, 0.65 mmol) was added to the solution, and the cooling bath was removed. The solution was allowed to warm to room temperature over 30 min. The solvent was evaporated under reduced pressure, and the residue was taken up in water (2 mL) and carefully neutralized using aqueous sodium hydroxide solution (2 N). The aqueous solution was extracted with dichloromethane, and the organic extracts were washed with sat-

(15) During the course of this work a report appeared that demonstrated that optically pure allylic acetates such as 5 could be alkylated by nucleophiles under palladium(0) catalysis. See: Deardorff, D. R.; Linde R. G., II; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759.

Scheme III



6 Optically pure 1

urated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent, followed by purification by silica gel chromatography using (i) 1:1 hexanes–ethyl acetate and (ii) ethyl acetate as eluent gave recovered *cis*-(+/−)-2-amino-6-chloro-9-[4-(nitromethyl)-2-cyclopenten-1-yl]-9*H*-purine (0.023 g, 27%) followed by the title compound (0.024 g, 33%): ^{1}H NMR δ 7.89 (s, 1 H), 6.14 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz), 5.79 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz), 5.51 (m, 1 H), 5.18 (br s, 2 H), 3.84 (dd, J_1 = 10.5 Hz, J_2 = 4 Hz, 1 H), 3.73 (dd, J_1 = 10.5 Hz, J_2 = 4 Hz, 1 H). 3.09 (m, 1 H), 2.79 (dt, J_1 = 14.5 Hz, J_2 = 9 Hz, 1 H), 1.97 (dt, J_1 = 14.5 Hz, J_2 = 5.5 Hz, 1 H). The data were identical with an authentic sample.

(1*S*,4*R*)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (1). To a stirred solution of 2-amino-6-chloropurine (0.2 g, 1.18 mmol) in dry DMSO (2 mL) at room temperature under N_2 was added potassium *tert*-butoxide (135 mg, 1.2 mmol), and the mixture was stirred for 20 min. Tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.04 mmol) was added, and the mixture was cooled to 0 °C. To this mixture was added a solution of (1*R*,3*S*)-4-cyclopentene-1,3-diol, 1-acetate (0.17 g, 1.19 mmol) in dry tetrahydrofuran (2 mL) over 10 min, and the resulting mixture was stirred at room temperature for 18 h. The solvents were removed by evaporation at reduced pressure, and the residue was slurried in dichloromethane (approximately 25 mL) and filtered. The filtrate was evaporated, and the residue was purified by chromatography on silica gel using (i) EtOAc followed by (ii) 10:1 EtOAc–MeOH as eluent to give (1*S*,4*R*)-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (174 mg, 58%): $[\alpha]_D$ +24° (*c* = 2.5, MeOH); mp 157–159 °C; ^{1}H NMR δ 7.81 (s, 1 H), 6.31 (d, J = 5.5 Hz, 1 H), 5.82 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.23 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1 H), 5.08 (br s, 2 H), 4.81 (br d, J = 9 Hz, 1 H), 2.95 (ddd, J_1 = 15 Hz, J_2 = 9 Hz, J_3 = 7 Hz, 1 H), 2.10 (br d, J = 15 Hz, 1 H); high-resolution FAB-MS calcd for $C_{10}H_{10}N_5OCl$ 252.0649 (MH^+), found 252.0646. Anal. Calcd, for $C_{10}H_{10}N_5OCl$: C, 47.72; H, 4.00; N, 27.83. Found: C, 47.81; H, 4.05; N, 27.73.

Nitroacetic Acid, 2-(Trimethylsilyl)ethyl Ester. To a stirred solution of ethyl nitroacetate (5.0 g, 37.6 mmol) and 2-(trimethylsilyl)ethanol (6.0 mL, 4.95 g, 42 mmol) in dry benzene (100 mL) was added titanium tetraisopropoxide (1.0 mL, 0.95 g, 3.4 mmol), and the mixture was heated at reflux with collection of the distillate. After 1 h, approximately 25 mL of distillate had been collected and the mixture was allowed to cool to 40 °C. Water (2 mL) was added, and the mixture was stirred at room temperature for 15 min. The solvents were evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2 (100 mL). The solution was dried over $MgSO_4$ and filtered through a small pad of Celite, and the solvent was evaporated. The residue was purified by bulb-to-bulb distillation to give the title compound as a colorless liquid, (6.10 g, 79%): bp 90–95 °C (0.3 mm Hg; ^{1}H NMR δ 5.12 (s, 2 H), 4.33 (m, 2 H), 1.04 (m, 2 H), 0.02 (s, 9 H); EI-MS m/z 178 ($MH^+ - C_2H_4$). Anal. Calcd for $C_7H_{15}NO_4Si$: C, 40.95; H, 7.36; N, 6.82. Found: C, 41.04; H, 7.37; N, 6.85.

Registry No. (±)-1, 134628-01-6; (+)-1, 134679-77-9; 2, 134628-02-7; 3a (isomer 1), 134628-03-8; 3a (isomer 2), 134679-75-7; 3b (isomer 1), 134628-05-0; 3b (isomer 2), 134679-76-8; 4, 134628-04-9; 5, 118237-87-9; 6, 60410-16-4; $CH_2(NO_2)CO_2Et$, 626-35-7; $CH_2(NO_2)CO_2(CH_2)_2TMS$, 134628-06-1; 2-amino-6-chloropurine, 10310-21-1; (±)-cyclopentadiene monoepoxide, 54460-11-6; (−)-carbovir, 120443-30-3; (±)-carbovir, 118353-05-2.

Supplementary Material Available: Proton NMR spectra of racemic 1 and 4 (2 pages). Ordering information is given on any current masthead page.

Aromatic Fluorination by Silver-Ion Promoted Decomposition of Aryl Diazo Sulfides: Efficient Utilization of Substoichiometric Levels of Fluoride Ion

Serkos A. Haroutounian,† James P. DiZio,‡ and John A. Katzenellenbogen*,‡

Department of Chemistry, Agricultural University of Athens, Votanicos, Athens 301, Greece, and Department of Chemistry, University of Illinois, 1209 West California Street, Urbana, Illinois 61801

Received February 1, 1991 (Revised Manuscript Received May 3, 1991)

Introduction

The thermal decomposition of aryl diazonium tetrafluoroborates or hexafluorophosphates (the Baltz–Schiemann reaction and variants, Scheme I) is widely used as a method for preparing aromatic fluoro compounds.[1] Within certain structural and functional constraints, yields vary from moderate to good.[1b] The Baltz–Schiemann reaction, however, is not well suited for fluorination with the short-lived, positron-emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min).[2] The reaction is inefficient since, at most, only one-quarter (with BF_4^-) or one-sixth (with PF_6^-) of the total added activity can be incorporated; even more serious is the fact that products with very high specific activity cannot be produced, as exchange of the radiofluorine with the stable fluorine of the counterions (BF_4^- and PF_6^-) results in extensive dilution of activity.[2,3] This situation has stimulated a search for alternative approaches to aromatic fluorination that would be better suited for the efficient preparation of high specific activity fluorine-18 labeled products.[2,4-6] While nucleophilic aromatic substitution has proved to be effective in achieving high specific activity radiofluorination of arene systems with electron-withdrawing groups,[5,6] this approach is not well suited for the direct synthesis of electron-rich arenes. Here, the use of diazonium ions or various precursors appears to be the only alternative, and in this regard, aryl dialkyltriazenes, first used in aromatic fluorination by Wallach in the late 1880's,[7] have been reinvestigated, but have, in general, been found to be unsatisfactory for fluorine radiolabeling.[4]

In this report we present an alternative approach utilizing aryl diazo sulfides—we describe the preparation of several model aryl diazo sulfides[8] and their fluorination with excess, stoichiometric, and substoichiometric levels of fluoride ion. The most satisfactory results come from the use of silver ion to generate the diazonium ion from the diazo sulfide. This reaction appears to be well suited for aromatic fluorination at the tracer level (Scheme II).

Results and Discussion

The aryl diazo sulfides **3a–e** were prepared in nearly quantitative yield by thiophenol quenching of the aryl diazonium salt **2a–e** (prepared by treatment of the corresponding aniline **1a–e** with nitrous acid; Scheme III).[8] The aryl diazo sulfides are orange to red liquids that are moderately stable (electron poor) to unstable (electron rich) at room temperature, but can be stored indefinitely at −20 °C. For purposes of comparison, some of the corresponding triazene systems were also prepared (**10a–c**). The diazo sulfide systems were selected to represent an

† Agricultural University of Athens.
‡ University of Illinois.

0022-3263/91/1956-4993$02.50/0