in vacuo (bp 110–118 °C, 15 Torr), and 2.1 g of product was collected. The product was dissolved in 5 mL of glacial CH_3COOH and slowly added to a stirred suspension of CrO_3 (2.1 g, 21 mmol) in 15 mL of CH_3COOH. After being stirred for 2 h at room temperature, the reaction mixture was poured into water (50 mL) and extracted with petroleum ether (3 × 30 mL); the organic phase was washed with saturated $NaHSO_3$ (3 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and water (50 mL) and dried over anhydrous $CaCl_2$. Evaporation of the solvent and vacuum distillation afforded the compound (+)-(*S*)-**7** (0.88 g, 5.4 mmol, 42.5%): bp 105–109 °C (15 Torr) (lit.[10] bp 125–127 °C, 24 Torr); $\alpha^{25}_D = +5.3°$ ($l = 1$) (lit.[10] α^{25}_Dmax = +39.6° ($l = 1$)).

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Supplementary Material Available: Characterization data (boiling point, ^1H NMR, and MS) for compounds **1b–h**, **2**, and (+)-(*S*)-**7** (4 pages). Ordering information is given on any current masthead page.

The Synthesis of 3(5)-[(2-Hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide, an Acyclic Analogue of 4-Deoxypyrazofurin

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Pyrazofurin (pyrazomycin) (**1**) (Figure 1), one of the *C*-nucleoside antibiotics,[1] has generated considerable interest due to its marked antiviral[2] and antitumor[3] activities. Syntheses of 4-deoxypyrazofurin (**2**)[4,5] were stimulated by its structural relationship to (i) the parent compound, (ii) the broad spectrum antiviral agent ribavirin (**3**),[2] and (iii) to the antitumor agent tiazofurin (**4**).[6]

A major development in antiviral chemotherapy in recent years has been the recognition that potent antiviral activity is displayed by certain nucleoside analogues in which the ribose moiety is replaced by a truncated riboacyclic residue.[7] Significant examples include 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) (**5**),[8] which is used clinically to treat herpes infections, 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine (DHPG, ganciclovir),[9] which posseses antiherpetic activity, and (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA],[10] which exhibits broad spectrum antiviral activity.

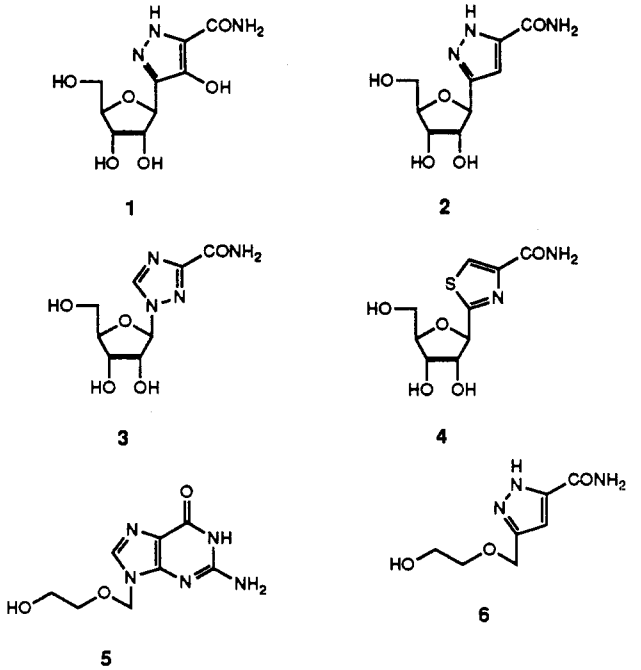

Figure 1.

With these facts in mind, 3(5)-[(2-hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide (**6**) emerges as an interesting target since it combines structural features found in both 4-deoxypyrazofurin (**2**) and acyclovir (**5**). The synthesis of **6** (Scheme I) is described herein from the protected pyrazole ester **7**, which is prepared via the regiospecific[11] 1,3-dipolar cycloaddition of the previously unknown diazoalkane **8** and methyl propiolate. The preparation of **8** became the initial synthetic goal.

The results of previous synthetic efforts in our laboratory,[12] and the laboratories of others,[13] indicated that the diazo functionality of **8** could be readily prepared from the corresponding nitrile. A search of the literature[14,15] revealed that a desirable nitrile precursor (that is, **9** of Scheme I) could be prepared via the Lewis acid catalyzed reaction of cyanotrimethylsilane and 1,3-dioxolane (Scheme I). This was accomplished to give **9** using zinc iodide as the catalyst. Since the trimethylsilyl protecting group was not expected to withstand the subsequent conditions required for preparation of the diazoalkane, it was removed by treatment with citric acid in methanol, and the resultant alcohol **10** was protected as the benzyl ether **11** by treatment with sodium hydride followed by benzyl bromide. The nitrile moiety of **11** was reduced efficiently with lithium aluminum hydride to yield the corresponding amine, which was directly converted to amide **12** with acetic anhydride/triethylamine in diethyl ether. Dinitrogen tetroxide was then utilized to convert amide **12** into its *N*-nitroso derivative **13**. The desired

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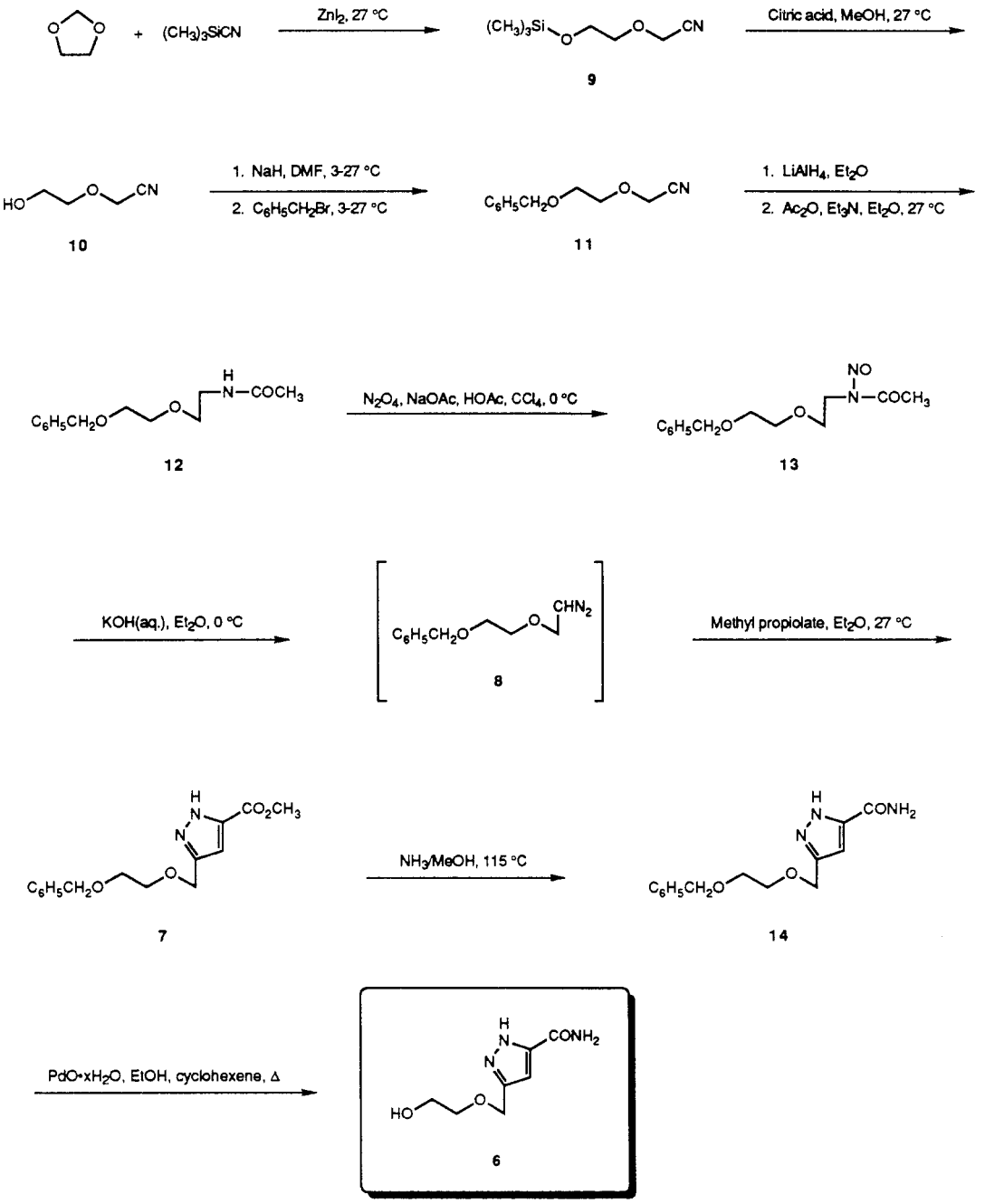
0022-3263/90/1955-5535$02.50/0

Scheme I



diazoalkane dipolarophile **8** was obtained by exposure of **13** to aqueous potassium hydroxide.

With **8** available, its cycloaddition with methyl propiolate proceeded cleanly to give pyrazole **7** as the only detectable regioisomer. The conversion of ester **7** to amide **14** was accomplished by treatment with ammonia in methanol in a sealed glass tube. Deprotection of **14** using palladium oxide/cyclohexene[16] in refluxing ethanol afforded the title compound **6**.

The regiochemistry of the cycloaddition reaction was confirmed by examination of the ^1H and ^{13}C NMR spectra of pyrazole **7**. It has been shown that the chemical shifts of H-3, H-4, and H-5 of the pyrazole ring fall in characteristic regions.[17] Specifically, H-3 and/or H-5 of alkyl and/or acyl substituted pyrazoles tend to exhibit chemical shifts downfield of 7.25 ppm, whereas H-4 tends to appear upfield of 7.0 ppm. The pyrazole ring proton of the cycloadduct exhibited a chemical shift of 6.76 ppm, falling well within the range described for H-4 in pyrazole ring systems. Additionally, the shift observed for **7** is consistent with the chemical shift of 6.63 ppm reported[4] for H-4 of **2**. This trend was further supported by comparison with the ^1H NMR data reported for methyl 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole-3(5)-carboxylate[18] (**15**,

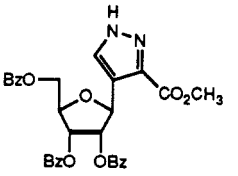


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Figure 2.

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a regioisomeric ester of **2**, Figure 2) in which H-5 exhibited a shift of 7.87 ppm. The ^{13}C NMR spectra provided additional evidence since a heteronuclear coupling experiment performed on **7** showed that the carbon atom at 107.18 ppm was bonded to a hydrogen. The chemical shift for this carbon is similar to that observed for C-4 (104.51 ppm) in pyrazole.[19]

The biological properties of **6** will be reported as they become available.

Experimental Section

Materials and Methods. Melting points were recorded on a Mel-Temp capillary melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. IR spectra were recorded on a Beckman Model FT 1100 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 and 22.5 MHz, respectively) in $CDCl_3$ or DMSO-d_6 referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck silica gel 60-F_{254} precoated silica gel plates, with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Aldrich silica gel (230–400 mesh, 60 Å), eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

5-(Trimethylsiloxy)-3-oxapentanenitrile (9).[15] A mixture of freshly distilled 1,3-dioxolane (15.41 g, 208 mmol), freshly prepared cyanotrimethylsilane[20] (20.64 g, 200 mmol), and anhydrous zinc iodide (500 mg) was stirred under N_2 at 27 °C in an oven-dried flask. The reaction mixture slowly became yellow, and aliquots were taken to follow the course of the reaction by ^1H NMR spectroscopy. When the reaction was complete (48 h), a distillation head was attached to the reaction vessel and the product was distilled directly, yielding **9** (22.1 g, 61%) as a clear, colorless liquid: bp 79–81 °C at 1 Torr (lit.[15] bp 40–45 °C at 0.4 Torr); IR (neat, cm^{-1}) 2960, 2870, 1466, 1433, 1250, 1140, 1100, 950, 850; ^1H NMR (90 MHz, $CDCl_3$) δ 4.39 (s, 2 H, CH_2), 3.73 (m, 4 H, CH_2CH_2), 0.10 (s, 9 H, $SiMe_3$); ^{13}C NMR (22.5 MHz, $CDCl_3$) 115.90, 74.39, 60.83, 56.43, 4.78 ppm. Anal. Calcd for $C_7H_{15}NO_2Si$: C, 48.52; H, 8.73; N, 8.08. Found: C, 48.31; H, 8.39; N, 7.81.

5-Hydroxy-3-oxapentanenitrile (10).[15] To a stirred solution of citric acid monohydrate (2.83 g, 14.74 mmol) in 150 mL of MeOH was added 14.3 g (82.6 mmol) of **9**. After 30 min, the solution was neutralized with saturated K_2CO_3 solution, and the volume of the solution was reduced by ca. 50% in vacuo. The resultant solution was then diluted with 115 mL of saturated brine and extracted with 10% 2-propanol/$CHCl_3$ (4 × 170 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated in vacuo to give a light yellow liquid. The liquid was distilled using a Kugelrohr apparatus to give **10** (6.75 g, 81%) as a clear, colorless liquid: bp 94–96 °C at 1 Torr (lit.[15] bp 55 °C at 0.1 Torr); IR (neat, cm^{-1}) 3400, 2933, 2880, 2250, 1450, 1360, 1115, 1080, 895; ^1H NMR (90 MHz, $CDCl_3$) δ 4.35 (s, 2 H, CH_2), 3.73 (m, 4 H, CH_2CH_2), 3.17 (br s, 1 H, D_2O exch, OH); ^{13}C NMR (22.5 MHz, $CDCl_3$) 115.90, 72.67, 60.97, 56.36 ppm. Anal. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.20; H, 6.99; N, 13.55.

5-(Benzyloxy)-3-oxapentanenitrile (11).[15] A solution composed of **10** (3.46 g, 34.3 mmol) dissolved in 20 mL of DMF was added dropwise under Ar to a stirred slurry of 97% NaH (1 g, 40.4 mmol) in 25 mL of DMF cooled to 3 °C in an oven-dried flask. Upon completion of the addition, the reaction was allowed to warm to 27 °C, and the stirring was continued for 30 min. After this period of time, the reaction mixture was recooled to 3 °C, and 7 g (41 mmol) of benzyl bromide was added dropwise. The reaction mixture was allowed to warm to 27 °C, and the stirring was continued for 6 h. The mixture was then cooled to 3 °C, and 1 mL of H_2O was added dropwise to quench the reaction. The reaction mixture was allowed to warm to 27 °C, and stirring was continued for 0.5 h. The mixture was partitioned between 100 mL of H_2O and 100 mL of benzene, the benzene layer was collected, and the aqueous layer was further extracted with benzene (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to give a brown syrup. The crude syrup was purified using a Kugelrohr distillation apparatus to yield pure **11** (3.9 g, 60%) as a clear, colorless syrup: bp 140 °C at 1 Torr (lit.[15] bp 100 °C at 0.25 Torr); IR (neat, cm^{-1}) 3080, 3030, 2920, 2880, 2250, 1468, 1360, 1105, 890, 740, 700; ^1H NMR (90 MHz, $CDCl_3$) δ 7.31 (s, 5 H, ArH), 4.53 (s, 2 H, benzyl CH_2), 4.25 (s, 2 H, OCH_2CN), 3.66 (m, 4 H, CH_2CH_2); ^{13}C NMR (22.5 MHz, $CDCl_3$) 137.82, 128.45, 127.74, 116.10, 73.30, 70.70, 69.02, 56.56 ppm. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.90; H, 6.55; N, 6.99.

1-Acetamido-2-[2-(benzyloxy)ethoxy]ethane (12). A suspension of 1.2 g (28.99 mmol) of $LiAlH_4$ in 50 mL of anhydrous Et_2O was prepared in an oven-dried three-neck flask equipped with a gas inlet, a mechanical stirrer, a pressure equalizing addition funnel, a gas bubbler, and a condenser. A solution of **11** (5.46 g, 28.59 mmol) in 20 mL of anhydrous Et_2O was added dropwise, under Ar, at such a rate so as to keep the ether solution at reflux. Stirring was continued for 1 h after the addition was completed. After this time, the reaction was quenched by the careful successive addition of 1.2 mL of H_2O, 1.2 mL of 15% NaOH solution, and 3.6 mL of H_2O. Stirring was continued until a grannular white precipitate formed. Filtration of the mixture yielded a clear, colorless ether filtrate, which was dried (Na_2SO_4), filtered, and concentrated in vacuo to yield 5-(benzyloxy)-3-oxapentylamine, which was used without further purification to prepare **12**: IR (neat, cm^{-1}) 3350, 3290, 3050, 2920, 2890, 1610, 1460, 1360, 1100, 750, 700.

5-(Benzyloxy)-3-oxapentylamine was dissolved in 50 mL of Et_2O and treated with 5.79 g (57.2 mmol) of Et_3N and 3.65 g (35.7 mmol) of Ac_2O. The reaction mixture was stirred for 12 h at 27 °C, after which time the Et_2O was removed using a rotary evaporator. The resulting light brown syrup was dissolved in 250 mL of benzene, and the organic phase was washed with saturated $NaHCO_3$ solution (2 × 100 mL) and saturated brine (100 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo to give a light brown syrup. Kugelrohr distillation of the brown syrup yielded **12** (5.97 g, 88% from **11**) as a clear, colorless syrup: bp 180 °C at 1 Torr; IR (neat, cm^{-1}) 3296, 3080, 2950, 2880, 1720, 1653, 1553, 1460, 1283, 1190, 1135, 1100, 750, 700; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5 H, ArH), 6.41 (br s, 1 H, NH), 4.56 (s, 2 H, benzyl CH_2), 3.64 (s, 4 H, OCH_2CH_2O), 3.51 (m, 4 H, OCH_2CH_2N), 1.90 (s, 3 H, $COCH_3$); ^{13}C NMR (22.5 MHz, $CDCl_3$) 170.22, 137.98, 128.45, 127.80, 73.30, 70.21, 69.83, 69.40, 39.28, 23.08 ppm. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.65; H, 7.94; N, 5.84.

Methyl 3(5)-{[2-(Benzyloxy)ethoxy]methyl}pyrazole-5-(3)-carboxylate (7). A mixture composed of **12** (3 g, 12.65 mmol) dissolved in 80 mL of a 1:1 mixture of CCl_4–glacial HOAc containing 6 g of anhydrous NaOAc was cooled to 3 °C in an ice/water bath, treated with 5 mL of liquid N_2O_4, and then stirred for 1.5 h at 3 °C. Following this period, the solution was poured over 500 mL of ice/H_2O with subsequent vigorous stirring of the resultant mixture for 0.5 h. The organic layer was then separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 125 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo to yield 1-(*N*-nitrosoacetamido)-2-[2-(benzyloxy)ethoxy]ethane (**13**) (3.36 g, 100%) as a light green syrup. This syrup showed no IR absorption at 3296 cm^{-1} (NH) or 1653 cm^{-1} (CO) to suggest unreacted **12**. *N*-Nitrosoamide **13** made in this way was used immediately for subsequent reactions: IR (neat, cm^{-1}) 3080, 3040, 2882, 1735, 1505, 1485, 1250, 1115, 962, 948, 795, 745, 700.

N-Nitrosoamide **13** (3.25 g, 12.23 mmol) was dissolved in 50 mL of Et_2O and mixed vigorously with an ice-cold solution of 8.5 g of KOH dissolved in 15 mL of H_2O. The mixture was stirred at 3 °C for 45 min, after which the IR spectrum of the ether layer showed the formation of a strong band at 2067 cm^{-1} (CHN_2) and no band at 1505 cm^{-1} (NO). The reaction mixture was then diluted with Et_2O (100 mL) and H_2O (200 mL), and the layers were separated. The Et_2O layer was washed with H_2O (50 mL) and

(18) Albrecht, H. P.; Repke, D. B.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 2176.
(19) From spectra recorded in our laboratory.
(20) Reetz, M. T.; Chatziiosifidis, I. *Synthesis* **1982**, 330.

dried rapidly first by swirling the ether phase over KOH pellets and decantation followed by anhydrous $MgSO_4$. Following filtration, the golden-colored filtrate containing 1-diazo-2-[2-(benzyloxy)ethoxy]ethane (**8**) was used immediately in subsequent reactions: IR (neat, cm^{-1}) 3090, 3032, 2067, 1463, 1368, 1250, 1100, 750, 700.

The aforementioned filtrate containing **8** was added to a solution of 1.25 g (15 mmol) of methyl propiolate in 10 mL of anhydrous Et_2O. The mixture was stirred at 27 °C for 4 h, after which TLC analysis (hexane/EtOAc, 1:1) indicated that the reaction had proceeded to completion (during this time, the solution color changed from golden to light yellow). The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (EtOAc/hexane, 1:1) yielding **7** (2.16 g, 59% from **12**) as a colorless syrup: R_f = 0.5 (silica, EtOAc/hexane, 75:25); IR (neat, cm^{-1}) 3233, 3010, 2885, 1725, 1450, 1233, 1100, 750; ^1H NMR (90 MHz, $CDCl_3$) δ 12.98 (br s, 1 H, pyrazole NH), 7.28 (s, 5 H, ArH), 6.76 (s, 1 H, pyrazole H-4), 4.61 (s, 2 H, pyrazole-CH_2), 4.53 (s, 2 H, $ArCH_2O$), 3.86 (s, 3 H, CH_3), 3.63 (s, 4 H, OCH_2CH_2O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 161.78, 144.23, 140.44, 137.57, 128.14, 127.54, 107.18, 72.99, 69.42, 69.04, 64.32, 51.75 ppm. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.85; H, 6.10; N, 9.54.

3(5)-{[2-(Benzyloxy)ethoxy]methyl}pyrazole-5(3)-carboxamide (14). A solution of **7** (0.9 g, 3.1 mmol) in 15 mL of freshly distilled MeOH was saturated with NH_3 at 3 °C, and the resulting mixture was heated in a sealed glass tube at 115 °C for 40 h. Upon cooling, TLC analysis (EtOAc/hexane, 75:25) indicated that the reaction had proceeded to completion. The solution was then concentrated in vacuo, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/H_2O, 65:10:4, lower phase) to yield **14** (0.8 g, 94%) as a white solid. Recrystallization of this material from EtOH/benzene afforded white crystals: mp 86–88 °C; R_f = 0.43 (silica, $CHCl_3$/MeOH/H_2O, 65:10:4, lower phase); IR (KBr, cm^{-1}) 3360, 3200, 3090, 2880, 2800, 1680, 1660, 1610, 1580, 1510, 1410, 1360, 1305, 1105, 766, 690; ^1H NMR (90 MHz, $CDCl_3$/DMSO-d_6) δ 12.83 (br s, 1 H, pyrazole NH), 7.30 (s, 5 H, ArH), 6.73 (s, 1 H, pyrazole H-4), 4.49 (br s, 2 H, $CONH_2$), 4.60 (s, 2 H, pyrazole-CH_2), 4.52 (s, 2 H, $ArCH_2O$), 3.64 (s, 4 H, OCH_2CH_2O); ^{13}C NMR (22.5 MHz, $CDCl_3$/DMSO-d_6) 164.31, 145.62, 141.23, 138.03, 128.34, 127.74, 127.58, 105.37, 73.14, 69.51, 69.40, 64.14 ppm. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.31; H, 6.23; N, 15.05.

3(5)-[(2-Hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide (6). A solution of 500 mg (91.8 mmol) of **14** in 20 mL of a 3:1 mixture of EtOH/cyclohexene was treated with 100 mg of $PdO{\cdot}xH_2O$. The mixture was refluxed for 1 h, after which TLC analysis ($CHCl_3$/MeOH/H_2O, 65:10:4, lower phase) showed complete loss of starting material. The reaction mixture was cooled and filtered through a pad of Celite that had been prewashed with hot EtOH; the Celite pad was then washed with hot EtOH, and the combined filtrates were concentrated in vacuo. The resulting pale yellow syrup was purified by column chromatography using silica gel (MeCN/H_2O, 94:6) to yield **6** (310 mg, 95%) as a white solid. Recrystallization from EtOH/MeCN afforded **6** as white needles: mp 123–124 °C; R_f = 0.5 (silica, MeCN/H_2O, 94:6); IR (KBr, cm^{-1}) 3360, 3200, 3090, 2985, 2910, 2875, 1670, 1610, 1510, 1410, 1105, 765, 685; ^1H NMR (90 MHz, DMSO-d_6) δ 13.20 (br s, 1 H, D_2O exch, pyrazole NH), 7.52 (br d, 2 H, D_2O exch, NH_2), 6.57 (s, 1 H, pyrazole H-4), 4.51 (s, 2 H, pyrazole-CH_2), 3.47 (s, 1 H, D_2O exch, OH), 3.37 (m, 4 H, CH_2CH_2); ^{13}C NMR (22.5 MHz, DMSO-d_6) 163.55, 146.76, 141.12, 104.77, 71.46, 62.52, 60.03 ppm. Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.47; H, 6.12; N, 22.68.

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Registry No. **2**, 129149-35-5; **6**, 129149-36-6; **7**, 129149-37-7; **8**, 129149-38-8; **9**, 118599-67-0; **10**, 118599-68-1; **11**, 118599-66-9; **12**, 129149-39-9; **13**, 129149-40-2; **14**, 129149-41-3; $(CH_3)_3SiCN$, 7677-24-9; 1,3-dioxolane, 646-06-0; methyl propiolate, 922-67-8.

Additions and Corrections

Vol. 55, 1990

Jean-Noël Denis, Arlene Correa, and Andrew E. Greene*. An Improved Synthesis of the Taxol Side Chain and of RP 56976.

Page 1957, column 2. The title of this paper should be "An Improved Synthesis of the Side Chains of Taxol and RP 56976".