treatment started 24 h after the inoculation of the tumor cells. Animals received nine injections from day 1 to 9. Cytostatic activity was determined by comparing median survival times with that of untreated control animals.

***tert*-Butyl β-Fluorooxaloacetate (3).** To a solution of 2.4 g of potassium in 57 mL of dry *tert*-butyl alcohol were added 12.8 g (64 mmol) of di-*tert*-butyl oxalate and 8 g (60 mmol) of *tert*-butyl fluoroacetate,[16] and the mixture was refluxed for 3 h. The yellowish-brown solution was cooled to room temperature, and 200 mL of 5% aqueous sodium hydroxide was added. The water layer was extracted with ether, and after acidification (pH 6, HCl) the product was obtained by ether extraction. Drying and evaporation of solvent produced 13 g (50 mmol, 83%) of **3** as a slightly colored oil: IR ($CHCl_3$) 3500 (OH, hydrated C=O), 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.5 (*tert*-butyl), 5.02 (1, d, J_{H-F} = 47 Hz, C-H of the hydrated form), 5.72 (0.75 d, J_{H-F} = 48 Hz, C-H of free **3**).

(*E*)- and (*Z*)-Di-*tert*-butyl 2-Amino-3-fluoro-2-butene-1,4-dioate [(*E*)- and (*Z*)-2]. Method A. A solution of 15 g (53 mmol) of di-*tert*-butyl β,β-difluoroaspartate[3] (**1**) and 9.8 g (79 mmol) of diazabicyclo[4.3.0]nonene in 200 mL of tetrahydrofuran was refluxed for 5 h. After the solution was cooled, 300 mL of petroleum ether (bp 60-80 °C) was added and the decanted solution filtered through Hy-flow. Solvents were evaporated, and the residue was purified by column chromatography (silica; ethyl acetate—petroleum ether, 1:5). A mixture of *E* and *Z* isomers (*Z*/*E* = 20:1) was obtained as a colorless oil in 96% yield (13.5 g, 52 mmol).

Method B. A solution of di-*tert*-butyl fluorooxaloacetate (**3**; 4.8 g, 18 mmol) and 15 g (0.2 mol) of ammonium acetate in 75 mL of dry methanol was kept at room temperature until the starting material had been converted according to TLC (4 days). The solution was poured into 5% Na_2CO_3 solution and the mixture extracted with ether. Drying ($MgSO_4$) and evaporating the solvents produced 4.05 g of **2** (15 mmol, 85%) as a colorless oil ($Z/E \approx 1:1$). (*E*)-**2**: IR ($CHCl_3$) 3500, 3380 (NH_2), 1710, 1680 (C=O), 1625 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.53 (18, s, *t*-Bu), 5.3-5.6 (2, NH_2). (*Z*)-**2**: IR ($CHCl_3$) 3520, 3420 (NH_2), 1740-1710 (C=O), 1655 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.55 (18, s, *t*-Bu), 4.0 (2, NH_2).

***erythro*- and *threo*-Di-*tert*-butyl β-Fluoroaspartate (4a and 4b).** The mixture of enamines **2** (12 g, 46 mmol) was stirred at room temperature with 3.2 g (50 mmol) of sodium cyanoborohydride in a mixture of 120 mL of dry methanol and 30 mL of dry acetic acid (distilled over P_2O_5) for 16 h. The solution was slowly added to 5% sodium carbonate and the water layer was extracted with ether. Combined ether extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was dissolved in petroleum ether (bp 60-80 °C). Cooling the solution yielded 5.0 g of **4a**. From the mother liquor an additional 1.6 g of **4a** and 0.02 g of **4b** were obtained by column chromatography (silica; petroleum ether-ethyl acetate, 2:1): total yield of **4a**, 6.69 g (25 mmol, 55%); mp 53-55 °C (petroleum ether); IR ($CHCl_3$) 3520 (NH_2), 1760-1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.43 (18, s, *t*-Bu), 1.80 (2, s, NH_2), 3.85 (1, d × d, J_{H-F} = 22, J_{H-H} = 2.5 Hz, C_α-H), 4.97 (1, d × d, J_{H-F} = 44, J_{H-H} = 2.5 Hz, C_β-H); ^{19}F NMR ($CDCl_3$) δ -91 (d × d, J_{H-F} = 47 Hz). Anal. ($C_{12}H_{22}FNO_4$) C, H, F, N. Total yield of **4b**, 0.02 g (1%); mp 73-75 °C (petroleum ether); IR ($CHCl_3$) identical with **4a**; ^1H NMR ($CDCl_3$) δ 1.48 (9, s, *t*-Bu), 1.51 (9, s, *t*-Bu), 1.65 (2, s, NH_2), 3.85 (1, d × d, J_{H-H} = 2, J_{H-F} = 31 Hz, C_α-H), 5.19 (1, d × d, J_{H-H} = 2, J_{H-F} = 29 Hz, C_β-H). Anal. ($C_{12}H_{22}FNO_4$) C, H, F, N.

***erythro*-β-Fluoroaspartic Acid (5a).** A solution of 3.7 g (14 mmol) of **4a** in 20 mL of trifluoroacetic acid was refluxed for 1 h. The solvent was evaporated and the residue was taken up in water. Upon addition of acetone, the free amino acid crystallized (1.6 g, 10.5 mmol, 75%): mp 174 °C dec; IR (KBr) 3600-2500 (COOH, NH_3^+), 1760 (NH_3^+), 1720 (C=O), 1600 cm^{-1} (COO^-); ^1H NMR (D_2O) δ 4.27 (1, d × d, J_{H-F} = 27, J_{H-H} = 2.5 Hz, C_α-H), 5.11 (1, d × d, J_{H-F} = 50, J_{H-H} = 2.5 Hz, C_β-H); ^{19}F NMR (D_2O) δ -193 (d × d, J_{H-F} = 28, J_{H-F} = 48 Hz). Anal. ($C_4H_6FNO_4$) C, H, F, N.

β-Methyl *erythro*-2-Fluoro-3-aminosuccinate Hydrochloride (6). To 1.5 mL of dry methanol, cooled to -18 °C, was added 0.27 mL of purified thionyl chloride. After the mixture reacted for 0.5 h, 0.5 g (3.3 mmol) of *erythro*-β-fluoroaspartic acid was introduced and the mixture was stirred at -18 °C for 2 h and at 20 °C for 1.5 h. Addition of 8 mL of dry ether produced 0.6 g (3.0 mmol) of the product as a white solid (90%): mp 167-170 °C (methanol/ether); IR (KBr) 3200-2500 (COOH, NH_3^+), 1770, 1750-1730 cm^{-1} (C=O); ^1H NMR (CD_3OD) δ 3.90 (3, s, CH_3), 4.77 (1, d × d, J_{H-H} = 2, J_{H-F} = 28 Hz, C_3-H), 5.58 (1, d × d, J_{H-H} = 2, J_{H-F} = 46 Hz, C_2-H). Anal. ($C_5H_9ClFNO_4$) C, H, F, N.

***erythro*-β-Fluoroasparagine (7).** In 100 mL of dry methanol, saturated with gaseous ammonia at 0 °C, 1.05 g (5 mmol) of monoester **6** was dissolved and the solution kept overnight at 4 °C, whereupon **7** crystallized. The mixture was stirred for an additional 5 h at 20 °C. Cooling to 4 °C and filtering produced 0.65 g (4.15 mmol) of **7** (83%) as a white solid: mp 210-213 °C dec; IR (KBr) 3400, 3200 (NH_2), 3000-2400 (COOH, NH_3^+), 1650, 1590 cm^{-1}; ^1H NMR (D_2O, NaOD) δ 3.83 (1, d × d, J_{H-H} = 2.5, J_{H-F} = 26 Hz, C_α-H), 5.15 (1, d × d, J_{H-H} = 2.5, J_{H-F} = 50 Hz, C_β-H). Anal. ($C_4H_7FN_2O_3$) C, H, F, N.

Acknowledgment. The authors express their gratitude to Drs. H. Schenk, K. Goubitz, and A. R. Overbeek of the Crystallographic Laboratory of the University of Amsterdam for the X-ray analysis of **5a** and to Dr. G. Atassi, Institut Jules-Bordet, University of Brussels, for the in vivo antitumor screening.

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Synthesis and Antileukemic Activity of 1-Methyl-2,5-diphenyl-3,4-bis(hydroxymethyl)-, 1,2,3-Triphenyl-4,5-bis(hydroxymethyl)-, and 1-Methyl-2,3-diphenyl-4,5-bis(hydroxymethyl)pyrrole Bis(*N*-methylcarbamate)[1]

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The syntheses for the bis(*N*-methylcarbamates) **3**, **4a**, **4b**, and **5** are described. All four compounds were active in the in vivo P388 lymphocytic leukemia assay, with **3** being the most active.

In earlier reports, we described the preparation and antileukemic activity of 1-phenyl-2,5-dimethyl-3,4-bis(hydroxymethyl)pyrrole bis(*N*-methylcarbamate)[2] (**1**) and 1,2-dimethyl-3,4-bis(hydroxymethyl)-5-phenylpyrrole bis(*N*-methylcarbamate)[3] (**2**), as well as a series of ana-

(1) Vinylogous Carbinolamine Tumor Inhibitors. 6. For paper 5 in this series see: (b) Anderson, W. K.; McPherson, H. L., Jr.; New, J. S. *J. Heterocycl. Chem.*, in press.

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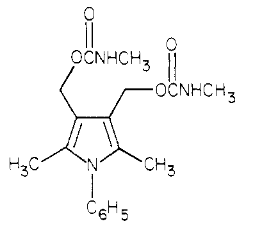

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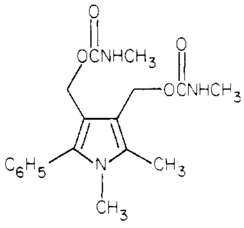

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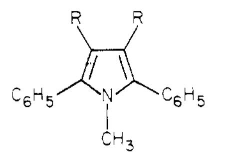
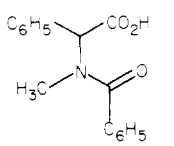
logues of each. The pronounced antineoplastic activity observed with these and related systems[4] has stimulated considerable interest in our laboratories in the structure–activity requirements for this general class of compounds. This report describes the preparation and antileukemic activity of a series of phenyl-substituted compounds which represent additional pyrrole-substitution patterns.

The compounds prepared for this study were 1-methyl-2,5-diphenyl-3,4-bis(hydroxymethyl)pyrrole bis(*N*-methylcarbamate) (**3**), 1,2,3-triphenyl-4,5-bis(hydroxymethyl)pyrrole bis(*N*-methylcarbamate) [**4a**; along with the 1-(4′-methoxyphenyl) analogue, **4b**], and 1-methyl-2,3-diphenyl-4,5-bis(hydroxymethyl)pyrrole bis(*N*-methylcarbamate) (**5**).

Chemistry. The 2,5-diphenyl compound, **3**, was pre-



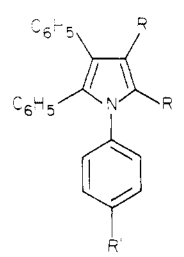


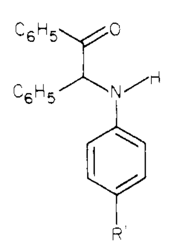
3, R = $CH_2OC(=O)NHCH_3$
6, R = CO_2CH_3
7, R = CH_2OH

8

pared from the known[5] dimethyl 1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (**6**) by reduction with lithium aluminum hydride and acylation of the resulting diol, **7**, with methyl isocyanate. The diester **6** was prepared from 2-phenylsarcosine (**8**, prepared by treatment of α-bromophenylacetic acid with methylamine followed by benzoylation) in a cyclodehydration–cycloaddition reaction sequence with acetic anhydride–dimethyl acetylenedicarboxylate (DMAD).

The 1,2,3-triphenyl compounds, **4a** and **4b**, were pre-





4a, R = $CH_2OC(=O)NHCH_3$; R′ = H
b, R = $CH_2OC(=O)NHCH_3$; R′ = OCH_3
9a, R = CO_2CH_3; R′ = H
b, R = CO_2CH_3; R′ = OCH_3
10a, R = CH_2OH; R′ = H
b, R = CH_2OH; R′ = OCH_3

11a, R′ = H
b, R′ = OCH_3

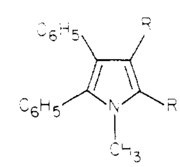
pared from the diesters **9a** and **9b** by $LiAlH_4$ reduction and acylation (methyl isocyanate) of the resulting diols **10**. The α-amino ketone **11a** was synthesized in two steps (thionyl chloride in pyridine followed by treatment with aniline) from benzoin;[6] **11b** was prepared directly from benzoin by treatment with *p*-methoxyaniline in ethanol–glacial acetic acid.[7] Treatment of **11** with DMAD (2 equiv) in methanol heated under reflux gave the pyrrole diesters **9**.[6]

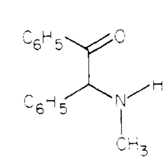
Table I

no.	anal.[a]	% yield	recrystn solvent	mp, °C
3	C, H, N	93	EtOAc-(*i*-Pr)$_2$O	178-179
4a	C, H, N	83	EtOAc-(*i*-Pr)$_2$O	157-158
4b	C, H, N	72	EtOAc-(*i*-Pr)$_2$O	182-183
5	C, H, N[b]	61	EtOAc-(*i*-Pr)$_2$O	148-149
6		51	methanol	144-145[c]
7	C, H, N	99	EtOAc-pet. ether	139-140
9a		63	ethanol	164-165[d]
9b	C, H, N	65	ethanol	182-183
10a	C, H, N	71	EtOAc-pet. ether	171-173
10b	C, H, N	73	EtOAc-pet. ether	172-173
11a		72	ethanol	95.5-96[e]
11b		83	ethanol	93-94[f]
12	C, H, N	75	ethanol	142-143
13	C, H, N[b]	74	EtOAc-pet. ether	149-150
14		63	ethanol	128-239[g]

[a] Unless otherwise indicated, analyses for the elements indicated were within ±0.4% of the theoretical values. [b] The theoretical values for C, H, and N were based on the molecular formula plus $0.2H_2O$ which could not be removed. [c] Lit. mp 147-148 °C (ref 5). [d] Lit. mp 165.4-167 °C (ref 6). [e] Lit. mp 97-98 °C (ref 6). [f] Lit. mp 92-92.5 °C (ref 7). [g] Lit. mp 240 °C (ref 9).

The 2,3-diphenyl compound **5** was prepared in a manner similar to **4**. *N*-Methyldesylamine (**14**, isolated as the hydrochloride salt to avoid dimerization[8] to 2,5-dihydro-2,3,5,6-tetraphenylpyrazine) was prepared by treatment of benzoin with aqueous methylamine.[8] Treatment of **14** with DMAD–sodium acetate gave **12**. The usual reduction–acylation sequence gave **5**.





5, R = $CH_2OC(=O)NHCH_3$
12, R = CO_2CH_3
13, R = CH_2OH

14

Biological Activity and Discussion. The activity data for **3**, **4a**, **4b**, and **5** (compared with data for **1** and **2**) against mouse P388 lymphocytic leukemia (PS) are given in Table II. It is readily apparent that **3** is the preeminent compound in this group. The compound is active, with no acute toxicities apparent, over the 16-fold dose range examined; it is reasonably potent (T/C_{max} = 205 at 20 mg/kg), and host inanition is minimal. The 2,3-diphenyl compound, **5**, in which the two potential reactive functions are on the pyrrole α and β carbons (rather than the β and β′ carbons as in **3**), would appear to be somewhat inferior to **3**. Substitution of the third phenyl

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Table II. Antileukemic Activity (P388 Lymphocytic Leukemia) of the Bis(*N*-methylcarbamates)[a,b]

no.	dose, mg/kg[c]	toxicity, day surv[d]	animal wt loss, T − C	% T/C
3	40	6/6	−4.4	124
	20	6/6	−2.8	205
	10	6/6	−2.1	164
	5	6/6	−1.0	135
	2.5	6/6	−1.1	135
4a[e]	200	6/6	−2.4	171
	100	6/6	−0.6	144
	50	6/6	−1.1	126
	25	6/6	+0.1	117
	12.5	6/6	−0.2	110
4b[e]	200	6/6	−1.3	135
	100	6/6	−1.0	124
	50	6/6	−0.8	119
	25	6/6	+0.5	119
	12.	6/6	+0.3	106
5[f]	100	5/6	−6.1	
	50	6/6	−2.5	171
	25	6/6	−3.2	160
	12.5	6/6	−1.4	164
	6.25	6/6	−1.1	138
	3.13	6/6	−0.8	128
	1.56	6/6	−2.3	102
1[g,h]	25	6/6	−1.7	148
	12.5	5/6	−1.3	145
	6.25	5/6	−2.1	134
2[i]	100	5/6	−6.0	<70
	50	6/6	−4.6	90
	25	6/6	−3.9	145
	12.5	6/6	−3.3	130
	6.25	6/6	−2.5	135

[a] Determined under the auspices of the National Cancer Institute, DHEW. For general screening procedures and data interpretation, see: Geran, R. I.; Greenberg, N. H.; McDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3(2)*, 1. [b] Ascitic fluid containing ca. 6 × 10^6 cells was inoculated (ip route) into male CD_2F_1 mice; in this assay median, survival survival times of % T/C ≥ 120 are considered significant. [c] The compounds were administered by the ip route in a distilled water–Tween 80 suspension. A total of nine daily doses were given starting 24 h after tumor inoculation. [d] Recorded on the 5th day (i.e., 4 days after the first injection of compound). [e] Control group I; control animals body weight change was +1.6 g. [f] Control group II; control group II animals body weight change was +1.3 g. [g] Control group III; control group animals body weight change was +1.3 g. [h] Female mice were used in this test and the drug was administered in a hydroxypropylcellulose (Klucel) suspension; see ref 2. [i] Control group IV; control animals average body weight change was +1.9 g; see ref 3.

ring on the pyrrole nucleus as in **4a** and **4b** produces a marked reduction in activity. Finally, both of the diphenylpyrroles, **3** and **5**, appear to have superior activity compared to **1** or **2**.

Further in vivo studies have been initiated to evaluate the efficacy of **3** against a panel of solid tumors. In addition, the series represented by the two "lead" structures **3** and **5** will be extended in order to examine those structural features which are important to the biological activity of these compounds.

Experimental Section

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. Infrared spectra were determined for KBr wafers (unless otherwise specified) with a Perkin-Elmer 237 or 227B spectrophotometer. NMR spectra were determined for $CDCl_3$ solutions (unless otherwise specified) containing 1% (v/v) tetramethylsilane as an internal standard with a Varian T-60A or FT-80 spectrometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga.

1-Methyl-2,5-diphenyl-3,4-bis(hydroxymethyl)pyrrole Bis(*N*-methylcarbamate) (3). A solution of *N*-benzoyl-2-phenylsarcosine (**8**; 38.45 g, 0.14 mol),[5] acetic anhydride (150 mL), and dimethyl acetylenedicarboxylate (40 mL, 0.32 mol) was stirred in a flask equipped with a reflux condenser and a gas bubbler to monitor CO_2 evolution. The mixture was heated to 90 °C (oil bath temperature) and maintained at this temperature for 1 h *after* gas evolution had stopped. The mixture was concentrated to dryness in vacuo and the residue was crystallized twice to yield dimethyl 1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (**6**).[5]

A solution of **6** (25.00 g, 0.072 mol) in dichloromethane (150 mL) was added dropwise to a stirred mixture of lithium aluminum hydride (6.00 g, 0.16 mol) in anhydrous ether (300 mL) at 0 °C. The stirred mixture was then heated under reflux for 40 min and cooled in an ice bath. The excess hydride was *cautiously* destroyed by the sequential addition of water (6.0 mL), 15% NaOH (6.0 mL), and water (18.0 mL); the mixture was filtered and the inorganic residue was washed with boiling ethyl acetate. The filtrate was concentrated to dryness in vacuo and the solid residue was crystallized to yield **7**: IR 3250, 2850, 1590, 1475, 1350, 1000, 780, 700 cm^{-1}; ^1H NMR δ 3.27 (s, 2-OH), 3.33 (s, 3-H), 4.55 (s, 4-H), and 7.42 (s, 10-H); ^{13}C NMR δ 33.24, 56.38 (2-C), 120.40 (2-C), 127.60 (2-C), 128.41 (4-C), 130.56 (4-C), 131.73 (2-C), 133.39 (2-C).

Methyl isocyanate (8.0 mL, 0.14 mol) was added to a solution of the diol **7** (7.000 g, 0.024 mol) and triethylamine (0.5 mL) in dichloromethane (50 mL), and the mixture was heated under reflux for 11 h. The mixture was then concentrated to dryness in vacuo and the solid residue was crystallized twice to give **3**: IR 3311, 2941, 1683, 1540, 1258, 1129, 959 cm^{-1}; ^1H NMR δ 2.68 (s, 3-H), 2.76 (s, 3-H), 3.34 (s, 3-H), 5.00 (br s, 2-NH), 5.06 (s, 4-H), 7.43 (s, 10-H).

1-(4′-Methoxyphenyl)-2,3-diphenyl-4,5-bis(hydroxymethyl)pyrrole Bis(*N*-methylcarbamate) (4b). A mixture of **11b** (20.0 g, 0.063 mol) and dimethyl acetylenedicarboxylate (17.9 g, 0.126 mol) in methanol (200 mL) was heated under reflux for 3 h. The reaction mixture was cooled, and the crystalline product was collected by filtration and washed with methanol until colorless. One recrystallization gave **9b** as white needles: IR 2950, 1695, 1420, 1180, 1000, 750 cm^{-1}; ^1H NMR δ 3.66 (s, 3-H), 3.70 (s, 3-H), 3.75 (s, 3-H), 6.8–7.1 (m, 14-H).

Reduction of **9b** was carried out as described for **6** to give **10b** as fluffy white crystals: ^1H NMR δ 1.6 (br s, 2-OH), 3.67 (s, 3-H), 4.44 (s, 2-H), 4.65 (s, 2-H), 6.6–7.2 (m, 14-H). Acylation of **10b** as described for **7** gave **4b** as a white crystalline solid: ^1H NMR δ 2.62 (s, 3-H), 2.80 (s, 3-H), 3.77 (s, 3-H), 4.75 (br m, 2-NH), 5.07 (s, 2-H), 5.15 (s, 2-H), and 6.7–7.2 (m, 14-H).

1-Methyl-2,3-diphenyl-4,5-bis(hydroxymethyl)pyrrole Bis(*N*-methylcarbamate) (5). A mixture of *N*-methyldesylamine hydrochloride (**14**), dimethyl acetylenedicarboxylate, and sodium acetate was heated under reflux for 1 h.[10] Two drops of concentrated HCl were added and the mixture was refluxed for an additional 15 min. The reaction mixture was poured over crushed ice and the mixture was extracted with dichloromethane. The combined dichloromethane extracts was dried (Na_2SO_4) and concentrated to dryness in vacuo. Two crystallizations gave dimethyl 1-methyl-2,3-diphenylpyrrole-3,4-dicarboxylate (**12**) as a white microcrystalline solid: ^1H NMR δ 3.69 (s, 6-H), 3.78 (s, 3-H), 6.85–7.3 (m, 10-H).

Reduction of **12** as described for **6** gave **13** as fluffy white crystals: ^1H NMR δ 1.0 (br s, 2-OH), 3.7 (s, 3-H), 4.6 (s, 3-H), 4.7 (s, 3-H), 7.0–7.3 (m, 10-H). Acylation of **13** as described for **4b** gave **5** as a white crystalline solid: ^1H NMR δ 2.80 (s, 3-H), 2.90 (s, 3-H), 3.40 (s, 3-H), 4.70 (br s, 2-NH), 4.90 (s, 2-H), 5.10 (s, 2-H), and 6.9–7.2 (m, 10-H).

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