Application of (Chloromethyl)aluminum 2-(2-Propenyl)anilide in the Conversion of γ- and δ-Lactones into Protected Hydroxy Acids

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A series of γ- and δ-lactones including several aldonolactones were reacted with (chloromethyl)aluminum 2-(2-propenyl)anilide to produce the corresponding hydroxy amides. Protection using [(trimethylsilyl)ethoxy]methyl chloride, (2-methoxyethoxy)methyl chloride, methoxymethyl chloride, *tert*-butyldimethylsilyl chloride, or *tert*-butyldiphenylsilyl chloride followed by ozonolysis gave the protected *N*-(γ- or δ-hydroxyacyl)indole derivatives. Mild saponification gave indole and the acetal- or silyl-protected hydroxy acid.

Introduction

Recently, we needed a method to convert a γ-lactone into a protected α-hydroxy carboxylic acid chloride or related reactive acylating reagent. Unfortunately this apparently trivial process is often difficult to carry out.[1,2] For example, the attempted derivatization of γ- or δ-hydroxy acids frequently results in relactonization rather than hydroxyl protection. In contrast γ- or δ-hydroxy amides are much more reluctant to lactonize due to the reduced electrophilicity of the amide carbonyl. Thus, we sought to develop an experimentally simple and general procedure to prepare protected hydroxy carboxylic acids via amide intermediates. It is clear in such an approach that, subsequent to hydroxyl derivatization, the amide carbonyl should be activated to facilitate hydrolysis. Barton and co-workers[3] have demonstrated that carboxylic acids may be protected as acylhydrazines or -hydrazones. Deprotection was affected via oxidation and hydrolysis of the resultant more electrophilic acyl diazonium salt or an equivalent species. Additionally, Barton showed that acylpyrazolines, -imidazolines, -indolines, etc., were more readily hydrolyzed following oxidation of the nitrogen substituent to produce the corresponding heteroaromatic ring system. Although the acylhydrazine and hydrazone protection strategy was applied in cephalosporin synthesis, the "latent" heteroaromatic protective groups were not applied to demanding synthetic problems. Herein we report experimental details[4] on the use of 2-(2-propenyl)-anilides as latent equivalents for acylindoles and thereby as carboxylic acid protecting groups.[5]

Results and Discussion

The saccharinic acid lactone **1**[6] was converted via isopropylide formation, sodium borohydride reduction, and periodate cleavage into the erythrose derivative **2a**. Oxidation of lactol **2a** (95%) using *N*-iodosuccinimide and tetrabutylammonium iodide[7] gave the corresponding lactone **2b** (87%). δ-Lactone **4b** (42%) was prepared from L-rhamnal[8] via O-methylation,[9] hydroxymercuration,[10] and DMSO–acetic anhydride oxidation.[11] The other lactones **6**,[12] **7**,[13] **8**,[14] **9**,[15] **10**,[16] and **11**[17] were all prepared by using established procedures. γ-Butyrolactone reacted smoothly with 2-(2-propenyl)aniline and dimethylaluminum chloride

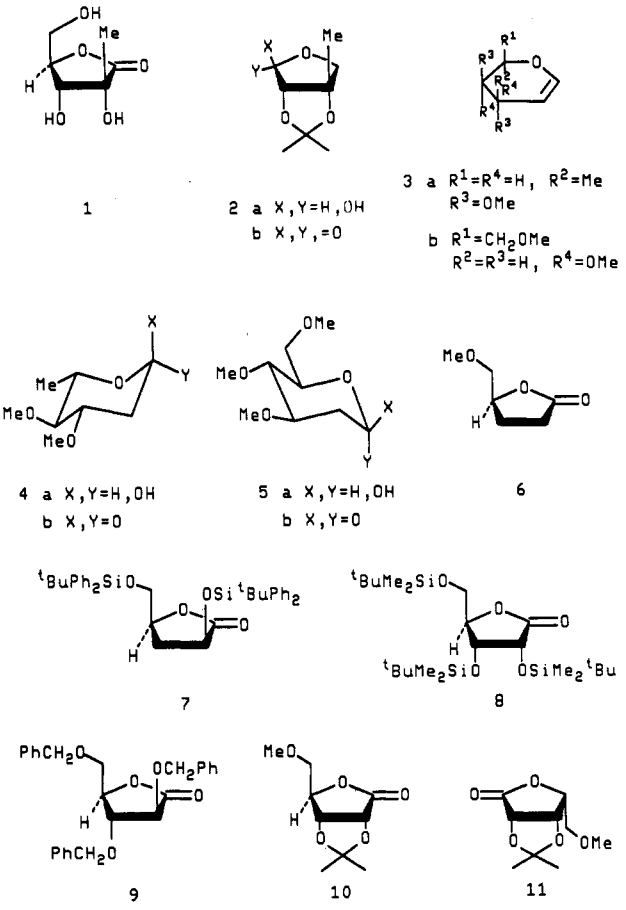

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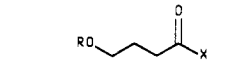
Table I. Conversion of γ- and δ-Lactones into Protected γ- and δ-Hydroxy Carboxylic Acids

entry	amide (%)	protected amide (%)	indole (%)	carboxylic acid
1	**12a** (80)	**12b** (100)	**12d** (69)	**12f** (68)[c]
2	*a*	**12c** (84)[b]	**12e** (93)	**12g** (54)
3	**13a** (99)	**13b** (86)	*a*	**13e** (67)[c]
4	*a*	**13c** (78)[b]	**13d** (61)	**13f** (75)
5	*a*	**14a** (62)[b]	**14b** (57)	**14c** (88)
6	**15a** (82)	**15b** (76)	*a*	**15c** (62)[c]
7	**16a** (79)	**16b** (95)	*a*	**16c** (63)[c]
8	**17a** (83)	**17b** (99)	**17c** (95)	**17d** (58)
9	*a*	**18a** (51)[b]	**18b** (68)	**18c** (81)
10	*a*	**19a** (88)[b]	**19b** (79)	**19c** (87)
11	**20a** (79)	**20b** (98)	*a*	**20c** (60)[c]
12	*a*	**21a** (90)[b]	**21b** (69)	**21c** (76)
13	*a*	**22a** (42)[b]	**22b** (42)	**22c** (82)

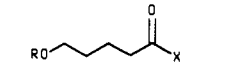
[a] Intermediate not isolated. [b] Yield based on starting γ- or δ-lactone. [c] Yield based on protected amide.

in dichloromethane[18] solution to produce the corresponding anilide **12a** (80%). This material was protected as the 2-[(trimethylsilyl)ethoxy]methyl (SEM)[19] ether **12b** (100%). Subsequent ozonolysis of **12b** with a dimethyl sulfide workup[20] readily gave the *N*-acylindole[21] **12d**.

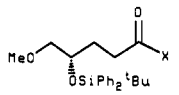
We anticipated, on the basis of the known chemistry of acylindoles,[22] that saponification of **12d** should be facile. Thus reaction of **12d** with potassium *tert*-butoxide in wet diethyl ether according to the excellent Gassman procedure[23] gave the target carboxylic acid **12f** in respectable overall yield from the amide **12b** (68%).



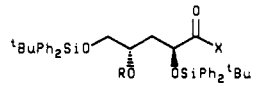
12 a R=H, X=NHAr
b R=$Me_3SiCH_2CH_2OCH_2$, X=NHAr
c R=$^tBuPh_2Si$, X=NHAr
d R=$Me_3SiCH_2CH_2OCH_2$, X=1-indolyl
e R=$^tBuPh_2Si$, X=1-indolyl
f R=$Me_3SiCH_2CH_2OCH_2$, X=OH
g R=$^tBuPh_2Si$, X=OH



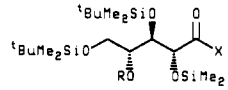
13 a R=H, X=NHAr
b R=$^tBuMe_2Si$, X=NHAr
c R=$^tBuPh_2Si$, X=NHAr
d R=$^tBuPh_2Si$, X=1-indolyl
e R=$^tBuMe_2Si$, X=OH
f R=$^tBuPh_2Si$, X=OH



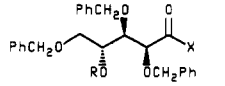
14 a X=NHAr
b X=indolyl
c X=OH



15 a R=H, X=NHAr
b R=$^tBuMe_2Si$, X=NHAr
c R=$^tBuMe_2Si$, X=OH

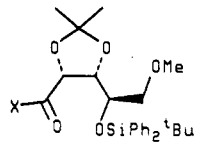


16 a R=H, X=NHAr
b R=$MeOCH_2CH_2OCH_2$, X=NHAr
c R=$MeOCH_2CH_2OCH_2$, X=OH

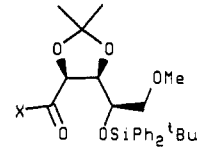


17 a R=H, X=NHAr
b R=$SiPh_2{}^tBu$, X=NHAr
c R=$SiPh_2{}^tBu$, X=1-indolyl
d R=$SiPh_2{}^tBu$, X=OH

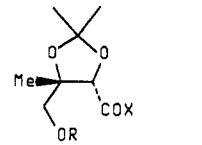
Using comparable reactions, γ-butyrolactone, δ-valerolactone, and the lactones **2b**, **4b**, **5b**, and **6**–**11** were converted into the corresponding protected 2-(2-propenyl)-anilides, acylindoles, and protected γ- or δ-hydroxy acids (Table I). In entries 9 and 10 the acyl indoles **18b** and **19b** were hydrolyzed using lithium hydroxide in aqueous THF at reflux. The use of the Gassman hydrolysis resulted in partial C-2 epimerization in these systems. In entries 12 and 13 methanolic potassium hydroxide was used in the hydrolysis step. β-Elimination was a major problem on reacting **21b** with potassium *tert*-butoxide in wet diethyl ether.



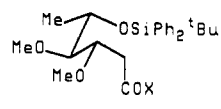
18 a X=NHAr
b X=1-indolyl
c X=OH



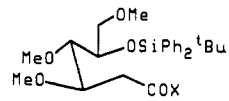
19 a X=NHAr
b X=1-indolyl
c X=OH



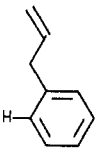
20 a R=H, X=NHAr
b R=CH_2OMe, X=NHAr
c R=CH_2OMe, X=OH



21 a X=NHAr
b X=1-indolyl
c X=OH



22 a X=NHAr
b X=1-indolyl
c X=OH

In structures 12-20 NHAr = 

It is clear from the results in Table I that the method is mild, efficient, and general. Both diverse acetal and silyl protecting groups are retained in the reaction and undesirable relactonization completely suppressed. The method is especially useful for the synthesis of functionalized aldonic acids needed for redox glycosidation.[24]

Experimental Section

General Procedures. All reactions were carried out under dry N_2 at room temperature unless otherwise stated. Low reaction temperatures are recorded as bath temperatures. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were all recorded at room temperature. Microanalyses were determined at Galbraith Laboratories, Knoxville, TN, or by G. D. Searle and Co., Skokie, IL.

Column chromatography was carried out on E. Merck silica gel 60, 230–400 mesh ASTM, analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates. Hexanes refer to the redistilled ACS reagent with boiling range 35–60 °C. The following solvents were purified by distillation: CH_2Cl_2 (from CaH_2, N_2), Et_2O (from Ph_2CO–Na, N_2), THF (from Ph_2CO–Na, N_2), DMF (from CaH_2, N_2) and $^iPr_2NEt$ (from CaH_2, N_2). Organic extracts were dried over Na_2SO_4 or $MgSO_4$, filtered, and rotary evaporated at ≤50 °C; involatile oils

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were further evaporated at <2 mmHg. Samples for combustion analysis were purified by rechromatography with rotary evaporation (<40 °C) of the appropriate fractions and further evaporation (<0.1 mmHg) for ≥12 h, or for solid compounds by recrystallization.

***N*-[2-(2-Propenyl)phenyl]-2,3,5-tri-*O*-benzyl-D-arabinamide (17a).** Me_2AlCl in CH_2Cl_2 (1 M; 1.91 mL) was added to *o*-allylaniline[25] (255 mg) in CH_2Cl_2 (10 mL) at room temperature under nitrogen. After 15 min the solution was cooled to −20 °C, and lactone **9**[15] (800 mg) in CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued for a further 2 h. The solution was quenched by adding to phosphate buffer (pH 7). The aqueous phase was extracted with CH_2Cl_2 (2×), the extracts were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica (eluant Et_2O–hexanes, 1:1) to give the amide **17a** (876 mg, 83%) as a colorless syrup: $[\alpha]_D$ +1.3° (*c* 0.96, $CHCl_3$); TLC R_f 0.3 (silica; Et_2O–hexanes, 3:2); IR (CH_2Cl_2) 3380, 1680, 1580, 1520, 1100, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 8.07 (d, 1 H, *J* = 8.0 Hz), 7.49–7.02 (m, 19 H), 5.77–5.67 (m, 1 H), 4.88 (dd, 1 H, *J* = 1.6 Hz, *J* = 10.4 Hz), 4.81 (dd, 1 H, *J* = 1.6 Hz, *J* = 17.2 Hz), 4.72 (d, 1 H, *J* = 11.6 Hz), 4.68 (d, 1 H, *J* = 11.6 Hz), 4.53–4.45 (m, 4 H), 4.39 (d, 1 H, *J* = 11.2 Hz), 4.10 (dd, 1 H, *J* = 2.0 Hz, *J* = 9.2 Hz), 4.04–3.98 (m, 1 H), 3.68 (dd, 1 H, *J* = 3.2 Hz, *J* = 9.4 Hz), 3.61 (dd, 1 H, *J* = 4.4 Hz, *J* = 9.4 Hz), 3.12–3.01 (m, 2 H), 2.55 (d, 1 H, *J* = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 137.6, 137.5, 136.8, 135.3, 135.0, 130.0, 129.4, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.3, 124.9, 122.1, 116.8, 80.1, 80.0, 74.7, 74.6, 73.4, 70.4, 69.2, 35.7; mass spectrum (EI) *m/e* 551 ($M^{\cdot+}$), 460, 327, 294, 280, 219, 133, 107. Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 76.06; H, 6.79; N, 2.53.

4-*O*-(*tert*-Butyldiphenylsilyl)-*N*-[2-(2-propenyl)phenyl]-2,3,5-tri-*O*-benzyl-D-arabinamide (17b). *tert*-Butyldiphenylsilyl chloride[26] (200 mg), imidazole (186 mg), 4-(dimethylamino)pyridine (0.1 g), alcohol **17a** (400 mg), and DMF (0.6 mL) were stirred together for 18 h at room temperature. The solution was diluted with H_2O (25 mL) and extracted with Et_2O (2 × 25 mL), and the organic extracts were dried ($MgSO_4$) and evaporated. Chromatography on silica (eluant Et_2O–hexanes, 1:9) gave **17b** (570 mg, 99%) as a white crystalline solid: mp 113 °C (from hexanes); TLC R_f 0.2 (silica; Et_2O–hexanes, 1:9); $[\alpha]_D$ +3.6° (*c* 0.9, $CHCl_3$); IR (CH_2Cl_2) 3386, 1690, 1590, 1530, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1 H), 8.14 (d, 1 H, *J* = 8.4 Hz), 7.73–7.66 (m, 4 H), 7.40–7.03 (m, 22 H), 6.96 (d, 2 H, *J* = 8.0 Hz), 5.57–5.47 (m, 1 H), 4.69 (dd, 1 H, *J* = 1.6 Hz, *J* = 10.2 Hz), 4.64 (dd, 1 H, *J* = 1.6 Hz, *J* = 17.2 Hz), 4.57 (d, 1 H, *J* = 10.8 Hz), 4.52 (d, 1 H, *J* = 11.2 Hz), 4.48–4.38 (m, 3 H), 4.33–4.25 (m, 2 H), 4.14 (d, 1 H, *J* = 11.6 Hz), 4.07 (d, 1 H, *J* = 11.6 Hz), 3.64–3.60 (m, 2 H), 2.92–2.81 (m, 2 H), 1.08 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 138.1, 137.9, 136.9, 136.0, 135.9, 135.4, 134.8, 134.1, 133.4, 129.9, 129.6, 129.5, 128.9, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 124.6, 121.7, 116.8, 81.2, 81.0, 75.2, 73.6, 72.5, 72.3, 70.9, 35.5, 27.1, 19.4; mass spectrum (EI) *m/e* 790 ($M + H^+$) 733, 654, 404, 314, 280, 181. Anal. Calcd for $C_{51}H_{55}NO_5Si$: C, 77.51; H, 7.02; N, 1.77. Found: C, 77.53; H, 6.92; N, 1.75%.

1-[4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,5-tri-*O*-benzyl-D-arabinonyl]indole (17c). Ozone was bubbled through a solution of the amide **17b** (500 mg) in CH_2Cl_2 (40 mL) at −78 °C to a blue end point. The mixture was purged with N_2, and Me_2S (5 mL) and oxalic acid (20 mg) were added. The reaction mixture was warmed up to room temperature and heated to reflux overnight. Evaporation and chromatography on silica (eluant Et_2O–hexanes, 1:9) gave **17c** (465 mg, 95%) as a colorless oil: $[\alpha]_D$ +3.2° (*c* 2.56, $CHCl_3$); TLC R_f 0.3 (silica; Et_2O–hexanes, 1:9); IR (CH_2Cl_2) 1690, 1450, 1340, 1105, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, 1 H, *J* = 8.4 Hz), 7.94 (d, 1 H, *J* = 3.6 Hz), 7.70 (d, 2 H, *J* = 7.2 Hz), 7.62 (d, 2 H, *J* = 7.6 Hz), 7.53 (d, 1 H, *J* = 8.0 Hz), 7.40–7.00 (m, 21 H), 6.90 (d, 2 H, *J* = 8.0 Hz), 6.43 (d, 1 H, *J* = 4.0 Hz), 5.00 (d, 1 H, *J* = 2.8 Hz), 4.56 (d, 1 H, *J* = 10.8 Hz), 4.51 (d, 1 H, *J* = 10.4 Hz), 4.38–4.26 (m, 4 H), 4.12 (d, 1 H, *J* = 11.6 Hz), 4.05 (d, 1 H, *J* = 11.6 Hz), 3.54 (d, 2 H, *J* = 2.8 Hz), 1.08 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 138.0, 137.3, 136.8, 136.0, 135.9, 133.8, 133.1, 130.2, 129.7, 129.5, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 126.4, 124.8, 124.0, 120.5, 116.9, 109.1, 81.6, 81.2, 74.8, 72.7, 72.6, 72.3, 70.6, 27.1, 19.4; mass spectrum (EI) *m/e* 716, 388, 298, 253, 199, 117, 91; high-resolution mass spectrum (FAB) calcd for $C_{50}H_{51}NO_5Si$ ($M + Li^+$) 780.3698, found ($M + Li^+$) 780.3686.

4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,5-tri-*O*-benzyl-D-arabinonic Acid (17d). KO^{t}Bu (260 mg) was added to **17c** (300 mg) in Et_2O (40 mL) and H_2O (40 μL), and the mixture was stirred overnight at room temperature. The solution was added to aqueous $NaHCO_3$, but the carboxylic acid did not extract into the aqueous layer. The Et_2O solution was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica (eluant Et_2O–hexanes, 1:1) to give **17d** (100 mg, 58%) as white needles: mp 116 °C (from hexanes–acetone); $[\alpha]_D$ +10.3° (*c* 3.15, $CHCl_3$); TLC R_f 0.1 (silica; Et_2O–hexanes, 1:1); IR (CH_2Cl_2) 3200–2500, 1720, 1440, 1330, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2 H, *J* = 8.0 Hz), 7.64 (d, 2 H, *J* = 8.0 Hz), 7.41–7.10 (m, 21 H), 4.57 (d, 2 H, *J* = 10.8 Hz), 4.51 (d, 1 H, *J* = 11.2 Hz), 4.39 (d, 1 H, *J* = 2.4 Hz), 4.28 (d, 1 H, *J* = 10.8 Hz), 4.22–4.14 (m, 3 H), 4.09 (d, 1 H, *J* = 11.6 Hz), 3.58–3.48 (m, 2 H), 1.07 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 137.8, 137.6, 136.7, 136.0, 135.9, 133.8, 133.2, 129.8, 129.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 80.7, 78.3, 74.7, 73.4, 72.7, 72.0, 70.5, 27.1, 19.3; mass spectrum (EI) *m/e* 616, 525, 417, 223, 181. Anal. Calcd for $C_{42}H_{46}O_6Si$: C, 74.75; H, 6.87. Found: C, 74.61; H, 6.84.

(4*R*,5*R*)-2,2-Dimethyl-5-[2-methoxy-1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-*N*-[2-(2-propenyl)phenyl]-1,3-dioxolane-4-carboxamide (18a). To a stirred solution of *o*-allylaniline (1.92 g) in dry CH_2Cl_2 (10 mL) at room temperature under N_2 was added Me_2AlCl in hexanes (1.0 M; 14.5 mL). After 15 min 2,3-*O*-isopropylidene-5-*O*-methyl-D-ribono-1,4-lactone (**10**)[16] (2.20 g) in dry CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred for 2.5 h and quenched by adding to phosphate buffer (pH 7), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic phases were dried ($MgSO_4$). Evaporation gave crude 2-(2-propenyl)-1-(2,3-*O*-isopropylidene-5-*O*-methyl-D-ribono)anilide. This was dissolved in dry DMF (15 mL), and imidazole (2.5 g), 4-(dimethylamino)pyridine (500 mg), and *tert*-butylchlorodiphenylsilane (3.75 g) were added. The mixture was stirred under N_2 for 40 h, quenched with H_2O (300 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with 2 N HCl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The viscous liquid was chromatographed on silica (eluant hexanes–Et_2O, 7:3), and the product **18a** (3.20 g, 51%) was obtained as a colorless syrup: $[\alpha]_D$ −6.5° (*c* 1.17, $CHCl_3$); TLC R_f 0.5 (silica; hexanes–Et_2O, 7:3); IR (neat) 1705, 1600, 1535, 1465, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 8.05 (d, 1 H, *J* = 8.4 Hz), 7.78–7.70, 7.31–7.42 (2 m, 10 H), 7.22–7.16 (m, 1 H), 7.11 (dd, 1 H, *J* = 1.6 and 7.4 Hz), 7.07–7.01 (m, 1 H), 5.99–5.88 (m, 1 H), 5.11 (dd, 1 H, *J* = 1.6 and 10.0 Hz), 4.98 (dd, 1 H, *J* = 1.6 and 17.2 Hz), 4.55 (dd, 1 H, *J* = 2.0 and 8.4 Hz), 4.52–4.48 (m, 1 H), 4.43 (d, 1 H, *J* = 8.4 Hz), 3.59 (dd, 1 H, *J* = 4.6 and 10.5 Hz), 3.42 (dd, 1 H, *J* = 6.4 and 10.5 Hz), 3.31 (d, 2 H, *J* = 5.6 Hz), 2.96 (s, 3 H), 1.61 (s, 3 H), 1.34 (s, 3 H), 1.02 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 136.1, 135.9, 135.2, 134.1, 133.9, 130.0, 129.5, 129.4, 128.7, 127.4, 127.35, 127.33, 124.7, 122.2, 116.8, 109.0, 80.2, 75.6, 73.3, 70.3, 58.3, 36.0, 27.0, 26.6, 23.6, 19.4; mass spectrum (EI) *m/e* 558 (M^+ − Me), 518, 517, 516, 426, 384, 267, 228, 213, 199, 189, 174, 160, 153, 139, 118, 100. Anal. Calcd for $C_{34}H_{43}NO_5Si$: C, 71.17; H, 7.55. Found: C, 70.89; H, 7.66.

***N*-[2,3-*O*-Isopropylidene-5-*O*-methyl-4-*O*-(*tert*-butyldiphenylsilyl)-D-ribonyl]indole (18b).** Ozone was bubbled through a stirred solution of the anilide **18a** (3.20 g) in dry CH_2Cl_2 (500 mL) at −78 °C until the reaction mixture turned blue/purple. The mixture was purged with N_2, and Me_2S (24 mL) was added. The solution was allowed to reach room temperature, oxalic acid (250 mg) was added, and the solution was heated at reflux for 24 h. Additional Me_2S (8 mL) and oxalic acid (200 mg) were added, and heating was continued for 24 h more. Me_2S and CH_2Cl_2 were removed at reduced pressure, and the residue was purified by chromatography on silica (eluant hexanes–Et_2O, 8:2)

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to give **18b** (2.15 g, 68%) as a colorless solid: $[\alpha]_D$ -30.7° (*c* 0.90, $CHCl_3$); TLC R_f 0.4 (silica; hexanes-Et_2O, 4:1); IR (neat) 1717, 1545, 1455, 1310, 1210, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1 H, J = 8.4 Hz) 7.65-7.50 and 7.40-7.17 (2 m, 14 H), 6.55 (d, 1 H, J = 4.0 Hz), 5.20 (d, 1 H, J = 6.0 Hz), 4.69 (dd, 1 H, J = 6.0 and 6.6 Hz), 4.63-4.50 (m, 1 H), 3.41 (dd, 1 H, J = 4.8 and 10.6 Hz), 3.34 (dd, 1 H, J = 2.6 and 10.6 Hz), 2.88 (s, 3 H), 1.51 (s, 3 H), 1.44 (s, 3 H), 0.82 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 135.9, 135.8, 135.7, 134.0, 133.3, 130.3, 129.5, 129.4, 127.4, 127.2, 125.1, 124.4, 123.9, 120.7, 117.0, 111.1, 109.6, 78.9, 74.8, 73.4, 70.8, 58.0, 26.7, 26.7, 25.6, 19.1; mass spectrum (EI) *m/e* 542, (M^+ - Me), 500, 410, 368, 332, 304, 255, 213, 199, 184, 158, 153, 144, 135, 117. Anal. Calcd for $C_{33}H_{39}NO_5Si$: C, 71.06; H, 7.05; N, 2.56. Found: C, 70.88; H, 7.18; N, 2.54.

2,3-*O*-Isopropylidene-5-*O*-methyl-4-*O*-(*tert*-butyldiphenylsilyl)-D-ribonic Acid (18c). A solution of LiOH (170 mg) in H_2O (3 mL) was added to a stirred solution of the indole derivative **18b** (570 mg) in THF (40 mL), and the mixture was refluxed for 3.5 h. The reaction mixture was poured into H_2O (100 mL), acidified to pH 4 by the careful addition of orthophosphoric acid, and extracted with EtOAc (4 × 50 mL). The combined extracts were dried (Na_2SO_4), and the EtOAc was removed under reduced pressure. Chromatography on silica gave (eluant Et_2O-hexanes, 1:4) indole and (eluant Et_2O-hexanes, 4:1) **18c** (380 mg, 81%) as a white solid: mp 168-170 °C (from Me_2CO/hexanes); $[\alpha]_D$ -22.5° (*c* 1.43, $CHCl_3$); TLC R_f 0.2 (silica; hexanes-Et_2O, 1:4); IR (KBr) 3500-2700, 1756, 1210, 1105, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.70 and 7.46-7.35 (m, 10 H), 4.56 (d, 1 H, J = 7.2 Hz), 4.38 (dd, 1 H, J = 2.6 and 7.2 Hz), 4.30-4.20 (m, 1 H), 3.48 (dd, 1 H, J = 5.0 and 10.2 Hz), 3.26 (dd, 1 H, J = 3.8 and 10.2 Hz), 3.46 (s, 3 H), 1.70 (s, 3 H), 1.37 (s, 3 H), 1.06 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 136.3, 136.0, 135.8, 134.0, 132.7, 129.8, 129.7, 127.6, 127.5, 109.8, 79.7, 74.7, 73.6, 70.2, 58.7, 26.7, 26.5, 26.1, 19.3; mass spectrum (EI) *m/e* 443 (M^+ - Me), 401, 369, 343, 311, 281, 269, 265, 255, 241, 237, 221, 213, 205, 199, 195, 189, 163, 153, 139, 129. Anal. Calcd for $C_{25}H_{34}O_6Si$: C, 65.47; H, 7.47. Found: C, 65.34; H, 7.41.

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Registry No. **1**, 492-30-8; **2a**, 120927-76-6; **2b**, 114877-78-0; **3a**, 53657-41-3; **3b**, 16740-98-0; **3b** (triacetyl analogue), 2873-29-2; **3b** (triol), 13265-84-4; α-**4a**, 120964-47-8; β-**4a**, 120964-48-9; **4b**, 120927-77-7; α-**5a**, 120927-78-8; β-**5a**, 120927-79-9; **5b**, 51224-22-7; **6**, 96845-45-3; **7**, 114877-77-9; **8**, 92512-25-9; **9**, 14233-64-8; **10**, 71671-16-4; **11**, 56119-03-0; **12a**, 114877-74-6; **12b**, 114877-90-6; **12c**, 120927-80-2; **12d**, 114877-75-7; **12e**, 120927-88-0; **12f**, 114877-76-8; **12g**, 118715-16-5; **13a**, 114877-79-1; **13b**, 120927-81-3; **13c**, 120927-82-4; **13d**, 120927-89-1; **13e**, 87729-39-3; **13f**, 118715-27-8; **14a**, 120927-83-5; **14b**, 120927-90-4; **14c**, 118715-38-1; **15a**, 114877-80-4; **15b**, 114904-27-7; **15c**, 114877-87-1; **16a**, 114904-26-6; **16b**, 114877-83-7; **16c**, 114877-86-0; **17a**, 114877-82-6; **17b**, 114877-85-9; **17c**, 120927-73-3; **17d**, 114877-89-3; **18a**, 120942-48-5; **18a** (deprotected alcohol), 120927-74-4; **18b**, 120927-75-5; **18c**, 118715-10-9; **19a**, 120927-84-6; **19b**, 120927-91-5; **19c**, 120927-94-8; **20a**, 114877-81-5; **20b**, 114877-84-8; **20c**, 114877-88-2; **21a**, 120927-86-8; **21a** (alcohol), 120927-85-7; **21b**, 120927-92-6; **21c**, 118715-53-0; **22a**, 120927-87-9; **22b**, 120927-93-7; **22c**, 120927-95-9; Me_2AlCl, 1184-58-3; *o*-allylaniline, 32704-22-6; rhamnal, 53657-42-4; γ-butyrolactone, 96-48-0; δ-valerolactone, 542-28-9.

Supplementary Material Available: Full experimental details for the preparation and authentication of all new compounds described in this paper (30 pages). Ordering information is given on any current masthead page.

Impact of a Basal Nitro Group on the Density Characteristics of Select [4]Peristylane Derivatives

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Several [4]peristylanes have been prepared that share in common a nitro group at C-9 of the basal cyclobutane ring. The synthetic entry of this class of molecules begins by Diels-Alder addition of nitro(trimethylsilyl)acetylene to tricyclo[5.2.1.$0^{2,6}$]deca-2,5,8-triene. This cycloaddition proceeds stereospecifically from below-plane to deliver a functionalized *syn*-sesquinorbornatriene. In characteristic fashion, this adduct can be cleanly epoxidized at its central double bond from the exo direction and subsequently irradiated to give the cage compound **10**. Periodate cleavage prior to or following desilylation delivers the required 9-nitro[4]peristylane-2,6-diones, the carbonyl functionalities in which have been transformed in stepwise fashion into *gem*-dinitro groups. Density measurements performed on four key compounds have disclosed that the 9-nitro group does not exert in general an effect that increases crystal density relative to the parent system.

Although the [4]peristylane framework was first prepared only a short while ago,[1] its rigid structural network consisting of four mutually fused cyclopentane rings surrounding a cyclobutane base is recognized to allow close molecular packing within crystalline derivatives. Particularly dramatic are the notable increases in density that accompany the conversion of diketone **1** (ρ = 1.42 g/cm^3)[2] to the *endo,endo*-dinitro compound **2** (ρ = 1.54 g/cm^3)[3] and ultimately to the tetranitro system **3** (ρ = 1.70 g/cm^3).[3] In an attempt to develop properties more closely approaching the ρ = 2 plateau so highly desirable for high density

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