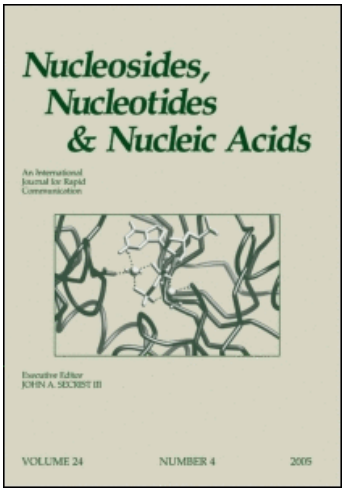

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C1' Acylated Derivatives of 2'-Deoxyuridine. Photolabile Precursors of 2'-Deoxyuridin-1'-yl

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C1' ACYLATED DERIVATIVES OF 2'-DEOXYURIDINE. PHOTOLABILE PRECURSORS OF 2'-DEOXYURIDIN-1'-YL.

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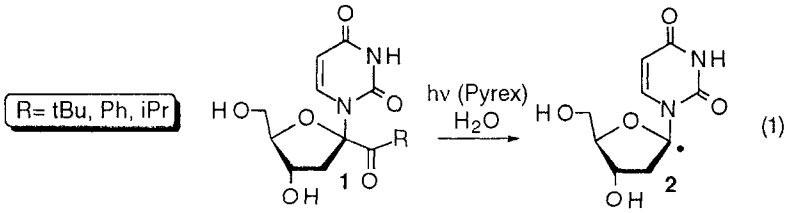
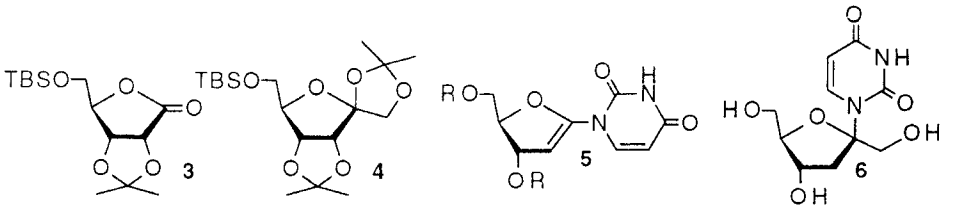
Abstract. C1' acylated derivatives of 2'-deoxyuridine (**1a-c**) were synthesized from 1-[3-deoxy-β-D-psicofuranosyl]uracil (**6**). The acyl group is introduced via the C1' aldehyde (**11**). Following nucleophilic addition, the ketones (**1a-c**) are obtained via periodinane oxidation and desilylation with NH_4F.

Modified nucleosides have the potential of exhibiting interesting and useful biological activity. Several groups have reported on the synthesis of novel nucleosides that are substituted at the C1' position. A variety of general approaches have been employed in order to produce alkyl, cyano, phosphono, and even *O*-acyl C1' substituted nucleosides.[1-6] To our knowledge, no examples of C1' acylated nucleosides have been reported. While C1' acylated nucleosides could be useful as therapeutic agents, we were interested in **1** as potential photolabile precursors for mechanistic studies concerned with the role of **2** in nucleic acid strand damage (eqn. 1).[7]

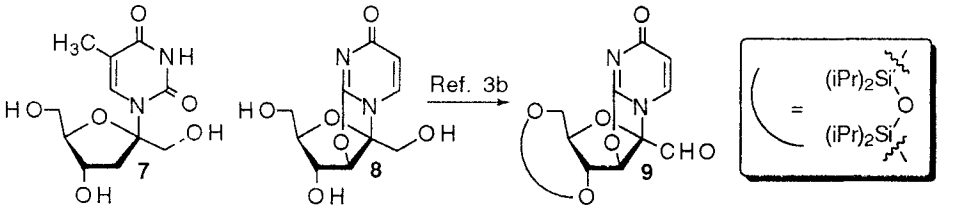


(1)

Based upon previous reports, we anticipated being able to prepare **1** from a variety of modified nucleoside synthons, including **3**, **4** and **5**.[2,4,5] However, we chose to use

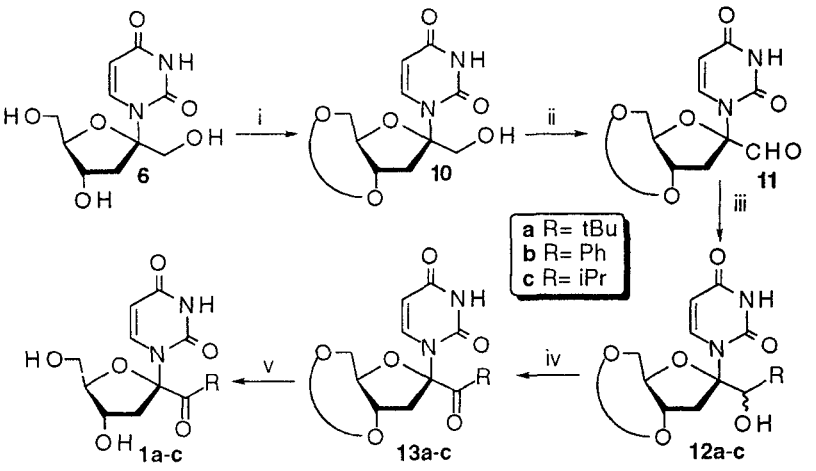


1-[3-deoxy-β-D-psicofuranosyl]uracil (**6**), which was available in large quantities, as the starting point for **1**.[1] The greatest stumbling block in the synthesis of **1** from **6** was expected to be the selective protection of the 4' and 6' (fructose numbering) hydroxyl groups. Moderate selectivity has been reported for the dimethoxytritylation of **7**, as well as protection of **8** using 1,3-dichloro-1,1,3,3-tetrakisisopropyldisiloxane.[3b,8] In principle, **1** could have been synthesized from **9**. However, we were concerned that conditions needed to effect opening of the cyclonucleoside might be incompatible with the functionality (e.g. disiloxane, aldehyde) present later in the synthesis.



Consequently, we chose to synthesize **1** from **6** via intermediate **11** (Scheme 1). Although disiloxane formation proceeds in low yield (26%), 47% of **6** is recoverable by desilylating the unwanted silyloxy products. Swern oxidation of **10** proceeds quantitatively, and in practice, **11** can be used without purification. Reduction of **11** with *tert*-BuLi yielded **12a** as an inseparable mixture of diastereomers in moderate yield. Similarly, reduction with PhLi resulted in a separable mixture of benzyl alcohols (**12b**) in 85% yield. Less satisfactory results were obtained for the formation of the isopropyl ketone (**1c**). Reduction of **11** with isopropyl magnesium bromide produced **12c** as a separable mixture of diastereomers in a combined yield of 42%. A significant amount of **10** (58%) was also obtained, due to β-hydride transfer from the Grignard reagent.

Carrying out the reduction with isopropyl lithium eliminated the formation of **10**, but did not increase the yield of **12c**. Each of the alcohols (**12a-c**) were readily oxidized with either CrO_3-pyridine-Ac_2O, or Dess-Martin periodinane. However, the latter was found to be more convenient. Deprotection of the silylated ketones was effected using NH_4F in refluxing MeOH.



[a]Key: i) 1,3-Dichlorotetraisopropyldisiloxane, pyridine ii) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2 iii) RLi, THF iv) Dess-Martin periodinane, CH_2Cl_2 v) NH_4F, MeOH

Scheme 1[a]

Irradiation of **1a-c** in the presence of (0.2 M) cyclohexa-1,4-diene, in CD_3CN, under anaerobic conditions, results in high yields of a mixture of α,β-deoxyuridine.[7] The α,β-deoxyuridine formed is completely protonated, which is consistent with the trapping of 2'-deoxyuridin-1'-yl (**2**). Ketones **1a-c** are stable to the reagents used to chemically synthesize and deprotect oligonucleotides. Hence, **1a-c** should be useful for carrying out mechanistic studies concerning the involvement of **2** in nucleic acid damage.

Experimental.

General Procedures: ^1H and ^{13}C NMR spectra were recorded on Bruker AM 270 and 300 spectrometers. Chemical shifts are reported in parts per million (ppm) relative to the respective solvent. IR spectra were recorded on a Perkin-Elmer series 1600 FTIR. Elemental analyses were performed by M-H-W laboratories. Et_3N, DMSO, pyridine, CH_2Cl_2 and CH_3CN were freshly distilled from CaH_2 prior to use. THF was freshly distilled from Na^0/benzophenone ketyl. All reactions were conducted under N_2 atmosphere. Flash chromatography was carried out using silica gel (230-400 mesh).[9]

Preparation of 10. Psicofuranosyluracil (**6**, 2.87 g, 11.1 mmol) was dried by azeotroping from pyridine (2 x 5 mL). Dried **6** was dissolved in pyridine (120 mL), and 1,3-dichloro-1,1,3,3-tetrakisisopropyldisiloxane (3.85 g, 12.3 mmol) in pyridine (15 mL) was added at -20°C over the course of 2.5 h. After allowing the reaction to stir and warm

to room temperature overnight, it was quenched with saturated $NaHCO_3$. The solvents were removed in vacuo, and the residue was taken up in EtOH (100 mL). The solids were filtered, and the salts washed with EtOH (3 x 25 mL). Silica gel (30 g) was added, and after removing the solvent in vacuo, it was applied to a column of silica (150 g). The column was eluted with EtOAc: Hex (1:1), which were increased to EtOAc: Hex (3:2) upon commencement of product elution. The column was washed with EtOH in order to elute polar products. Disiloxane **10** (1.43 g, 26%) was obtained as an oil. Psicofuranosyluracil (**6**) could be recovered from the mixture of undesired silylated nucleosides by desilylation with NH_4F in MeOH. ^1H NMR ($CDCl_3$) δ 8.56 (bd s, 1H), 7.93 (d, 1H, J= 8.5 Hz), 5.64 (d, 1H, J= 8.5 Hz), 4.31 (m, 1H), 4.02 (m, 4H), 3.82 (dd, 1H, J= 2.5, 8 Hz), 2.92 (dd, 1H, J= 6.8, 13.5 Hz), 2.47 (t, 1H, J= 6 Hz), 2.40 (dd, 1H, J= 10.5, 13.5 Hz), 0.98 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 150.3, 141.9, 100.6, 97.2, 85.1, 67.9, 65.2, 60.1, 39.4, 17.4, 17.2, 17.1, 16.9, 16.8, 13.4, 13.0, 12.8, 12.4; IR (film) 3445, 2944, 2868, 1709, 1691, 1679, 1462, 1300, 1118, 1038 cm^{-1}; Anal. calcd. for $C_{22}H_{40}N_2O_7Si_2$: C, 52.77; H, 8.05; N, 5.59. Found: C, 52.52; H, 7.89; N, 5.60.

Preparation of 11. DMSO (0.22 g, 2.8 mmol) in CH_2Cl_2 (9 mL) was added dropwise to oxalyl chloride (0.175 g, 1.38 mmol) in CH_2Cl_2 (7 mL) at -60°C. After stirring for 10 min, **10** (0.62 g, 1.22 mmol) was added in CH_2Cl_2 (9 mL). After stirring for 35 min at -60°C, Et_3N (0.66 g, 6.43 mmol) was added. The mixture was stirred briefly at -60°C, before warming to room temperature. The reaction mixture was quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, and washed with 1% HCl (75 mL), followed by 5% $NaHCO_3$ (75 mL), and brine (100 mL). After drying over $MgSO_4$, the solvents were removed in vacuo to yield 0.56 g (91%) of **11**. An analytical sample could be obtained via flash chromatography (EtOAc: CH_2Cl_2; 1:1). However, in practice **11** was carried on without further purification. mp 148-148.5°C; ^1H NMR ($CDCl_3$) δ 9.22 (s, 1H), 8.78 (bd s, 1H), 7.90 (d, 1H, J= 8 Hz), 5.75 (d, 1H, J= 8 Hz), 4.39 (m, 1H), 4.13 (d, 1H, J= 14 Hz), 3.95 (dd, 1H, J= 2.6, 14 Hz), 3.74 (dd, 1H, J= 1.5, 9 Hz), 3.09 (dd, 1H, J= 10.3, 13.4 Hz), 2.33 (dd, 1H, J= 8, 13.4 Hz), 0.91 - 1.08 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 187.7, 163.7, 150.4, 139.1, 102.2, 92.6, 85.2, 66.7, 58.8, 37.0, 25.4, 24.6, 17.4, 17.3, 17.2, 17.1, 17.0, 16.9, 16.7, 13.4, 12.8, 12.4. IR (film) 2946, 2894, 2868, 1745, 1700, 1464, 1386, 1301, 1276, 1118, 1077, 1056, 1038 cm^{-1}; Anal. calcd. for $C_{22}H_{38}N_2O_7Si_2$: C, 52.98; H, 7.68; N, 5.62. Found: C, 53.13; H, 7.82; N, 5.61.

Preparation of 12a. To **11** (402 mg, 0.81 mmol) in THF (5 mL) at -78°C was added a solution of *tert*-BuLi (1.08 mL, 1.5 M) in hexanes. The solution was stirred for 3 h, at

which time it was quenched by the addition of 0.3 N NaOAc (1 mL), and allowed to warm to room temperature. The solution was diluted with EtOAc (45 mL), washed with H_2O (30 mL), and brine (40 mL). After drying over $MgSO_4$, the secondary alcohol (243 mg, 54%) was obtained as a mixture of diastereomers by flash chromatography (EtOAc: Hexanes; 1:4). The alcohol (**12a**) was very unstable, and was typically oxidized immediately. ^1H NMR ($CDCl_3$) δ 9.15 (bd s, 1H), 8.08 (d, 1H, J= 8 Hz, minor), 8.00 (d, 1H, J= 8 Hz, major), 5.69 (dd, 1H, J= 2,8 Hz), 4.21 - 3.85 (m, 4H), 3.12 - 2.95 (m, 1H), 2.91 (d, 1H, J= 9 Hz, major), 2.78 - 2.55 (m, 1H), 2.40 (d, 1H, J= 9.5 Hz), 2.03 (d, 1H, J= 9.5 Hz), 1.26 - 0.82 (m, 37H).

Preparation of 12b. Aldehyde **11** (450 mg, 0.90 mmol) was reduced with PhLi (2 eq.) as described above for the preparation of **12a**. Flash chromatography (EtOAc:CH_2Cl_2; 1:4) yielded two separate diastereomers of **12b**. Diastereomer A (160 mg, 31%): ^1H NMR ($CDCl_3$) δ 8.17 (bd s, 1H), 7.75 (d, 1H, J= 8 Hz), 7.39 - 7.36 (m, 2H), 7.32 - 7.26 (m, 3H), 5.50 (dd, 1H, J= 2.5, 8 Hz), 5.19 (d, 1H, J= 9 Hz), 4.24 (m, 1H), 4.15 (m, 2H), 3.92 (dd, 1H, J= 2.5, 13.5 Hz), 3.56 (td, 1H, J= 2.5, 8 Hz), 3.09 (dd, 1H, J= 6.5, 13.5 Hz), 2.51 (dd, 1H, J= 11.2, 13.5 Hz), 1.04 - 0.88 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 164.4, 151.3, 142.1, 138.5, 133.9, 128.2, 127.7, 100.5, 99.3, 85.4, 76.3, 67.0, 59.4, 39.8, 17.4, 17.2, 17.1, 17.0, 16.9, 16.8, 16.7, 13.4, 13.3, 12.9, 12.8, 12.3; IR(film) 3350, 3036, 2968, 1684, 1456, 1286, 1148, 1119, 1039 cm^{-1}; Anal calcd for $C_{28}H_{44}N_2O_7Si_2$: C, 58.30; H, 7.69; N, 4.86. Found: C, 58.46; H, 7.81; N, 4.67. Diastereomer B (280 mg, 54%): ^1H NMR ($CDCl_3$) δ 7.95 (bd s, 1H), 7.41 (d, 1H, J= 8 Hz), 7.23 - 7.20 (m, 5H), 5.43 (d, 1H, J= 8 Hz), 5.27 (dd, 1H, J= 2.5, 8 Hz), 4.28 (m, 1H), 4.10 (m, 1H), 3.96 (m, 2H), 3.10 (dd, 1H, J= 7, 13 Hz), 2.95 (dd, 1H, J= 10.5, 13 Hz), 2.69 (d, 1H, J= 8 Hz), 1.046 - 0.88 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 163.8, 150.5, 140.8, 138.3, 128.9, 128.6, 127.6, 100.7, 98.3, 87.2, 74.5, 67.9, 60.1, 39.9, 17.8, 17.6, 17.5, 17.4, 17.3, 17.2, 13.8, 13.4, 13.2, 12.8; IR(film) 3398, 3195, 3059, 2946, 2894, 2868, 1682, 1464, 1408, 1383, 1287, 1273, 1148, 1119, 1039 cm^{-1}; Anal. calcd. for $C_{28}H_{44}N_2O_7Si_2$: C, 58.30; H, 7.69; N, 4.86. Found: C, 58.16; H, 7.69; N, 4.66.

Preparation of 12c. Aldehyde **11** (180 mg, 0.36 mmol) was reduced with isopropyl magnesium chloride (2 eq.) as described above for the preparation of **12a**. Flash chromatography (EtOAc:CH_2Cl_2; 1:3) yielded two separate diastereomers of **12c**. In addition, 105 mg (58%) of **10** was isolated from the reaction. Diastereomer A (41 mg, 22%): ^1H NMR ($CDCl_3$) δ 8.47 (bd s, 1H), 8.00 (d, 1H, J= 8 Hz), 5.65 (d, 1H, J= 8 Hz), 4.31 (dd, 1H, J= 2, 10 Hz), 4.23 (m, 1H), 4.19 (m, 1H), 3.95 (dd, 1H, J= 3, 13 Hz), 3.85 (dd, 1H, J= 2, 13 Hz), 2.91 - 2.73 (m, 2H), 1.58 (m, 1H), 1.06 - 0.95 (m, 34H); IR (film) 3400, 3191, 2945, 2868, 1693, 1464, 1385, 1119, 1038 cm^{-1}.

Diastereomer B (38 mg, 20%): ^{1}H NMR ($CDCl_3$) δ 9.51 (bd s, 1H), 8.05 (d, 1H, J= 8 Hz), 5.69 (d, 1H, J= 8 Hz), 4.18 (m, 1H), 4.08 (m, 1H), 3.97 (dd, 1H, J= 2, 15 Hz), 3.75 (dd, 1H, J= 2, 9 Hz), 3.49 (dd, 1H, J= 6, 9 Hz), 2.98 (dd, 1H, J= 6, 14 Hz), 2.65 (dd, 1H, J= 12, 14 Hz), 1.63 (m, 1H), 1.05 - 0.94 (m, 34H); IR (film) 3430, 3190, 2870, 1694, 1465, 1385, 1300, 1250, 1118, 1039, 921.

Preparation of 13a. Dess-Martin periodinane (526 mg, 1.10 mmol) was added to **12a** (243 mg, 0.44 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring for 5 h at room temperature, additional Dess-Martin reagent (526 mg, 1.10 mmol) was added, and the reaction was stirred overnight. The mixture was diluted with EtOAc (75 mL), and washed with cold, saturated $NaHCO_3$ (50 mL), to which $Na_2S_2O_3$ (2.5 g) was added. The organic layer was washed with brine (25 mL), and dried over $MgSO_4$. The residue was purified by flash chromatography (EtOAc: Hex; 1:4) to yield 213 mg of **13a** (88%). ^{1}H NMR ($CDCl_3$) δ 8.68 (bd s, 1H), 8.03 (d, 1H, J= 8 Hz), 5.73 (dd, 1H, J= 1.8, 8.2 Hz), 4.34 (m, 1H), 4.16 (d, 1H, J= 14 Hz), 3.96 (dd, 1H, J= 2.6, 13.5 Hz), 3.69 (dd, 1H, J= 1.7, 9 Hz), 3.42 (dd, 1H, J= 11.5, 13.5 Hz), 2.23 (dd, 1H, J= 6.7, 13.5 Hz), 1.15 - 0.97 (m, 37 Hz); IR (soln) 3184, 3054, 2945, 2867, 1682, 1622, 1463, 1384, 1366, 1299, 1272, 1203, 1149, 1116, 1039 cm^{-1}.

Preparation of 13b. A mixture of diastereomers of alcohol **12b** (205 mg, 0.36 mmol) was oxidized as described above. Flash chromatography (EtOAc:CH_2Cl_2; 1:9) yielded 147 mg of **13b** (72%). ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1H, J= 8 Hz), 7.69 (dd, 2H, J= 1.5, 7 Hz), 7.64 (bd s, 1H), 7.45 (d, 1H, J= 7 Hz), 7.33 (dt, 1H, J= 1.5, 7 Hz), 5.75 (dd, 1H, J= 2.4, 8.3 Hz), 4.45 (m, 1H), 4.25 (d, 1H, J= 14 Hz), 4.01 (dd, 1H, J= 2.5, 14 Hz), 3.86 (dd, 1H, J= 2, 9 Hz), 3.62 (dd, 1H, J= 11.5, 13.5 Hz), 2.35 (dd, 1H, J= 7, 13.5 Hz), 1.11 - 0.96 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 189.7, 163.7, 149.8, 139.2, 134.1, 132.8, 129.1, 128.5, 102.4, 95.7, 86.2, 66.7, 59.2, 39.1, 17.8, 17.7, 17.6, 17.5, 17.3, 17.2, 17.1, 13.8, 13.4, 13.2, 12.7; IR (film) 2946, 2868, 1710, 1462, 1446, 1277, 1249, 1114, 1037 cm^{-1}; Anal. calcd. for: $C_{28}H_{42}N_2O_7Si_2$: C, 58.51; H, 7.36; N, 4.87. Found: C, 58.40; H, 7.61; N, 4.84.

Preparation of 13c. A mixture of diastereomers of alcohol **12c** (92 mg, 0.18 mmol) was oxidized as described above. Flash chromatography (EtOAc:CH_2Cl_2; 1:4) yielded 54 mg of **13c** (59%). ^{1}H NMR ($CDCl_3$) δ 8.99 (bd s, 1H), 7.99 (d, 1H, J= 8 Hz), 5.72 (d, 1H, J= 8 Hz), 4.34 (m, 1H), 4.12 (dd, 1H, J= 1, 14 Hz), 3.95 (dd, 1H, J= 2, 14 Hz), 3.74 (dd, 1H, J= 1, 9 Hz), 3.24 (dd, 1H, J= 12, 14 Hz), 2.75 (sept, 1H, J= 7 Hz), 2.39 (dd, 1H, J= 7, 14 Hz), 1.09 - 0.94 (m, 34H); IR (film) 3255, 2946, 2869, 1688, 1465, 1383, 1297, 1273, 1210, 1148, 1117, 1038, 993 cm^{-1}.

Preparation of 1a. NH_4F (73 mg, 1.96 mmol), and **13a** (51.4 mg, 0.09 mmol) were refluxed in MeOH (4 mL) for 2 h. The reaction mixture was cooled to room temperature, and quenched with saturated $NaHCO_3$ (1 mL). The solvents were removed in vacuo, and the salts were washed with EtOAc (25 mL), filtered, and concentrated. The residue was chromatographed (MeOH: EtOAc: Hexanes; 1:4:5) to yield 28 mg of **1a** (96%). mp: 195 - 196°C; ^{1}H NMR (CD_3CN) δ 8.09 (d, 1H, J= 8 Hz), 5.65 (d, 1H, J= 8 Hz), 4.25 (m, 1H), 3.84 - 3.65 (m, 3H), 3.14 (dd, 1H, J= 7, 14 Hz), 2.25 (dd, 1H, J= 7.5, 14 Hz), 1.15 (s, 9H); IR (film) 3390 (bd), 2962, 1684, 1457, 1419, 1365, 1299, 1227, 1091, 1042 cm^{-1}; Anal. Calcd. for $C_{14}H_{20}N_2O_6$: C; 53.84; H, 6.45; N, 8.97. Found: C, 53.71; H, 6.47; N, 8.89.

Preparation of 1b. Deprotection of **13b** (90 mg, 0.16 mmol) with NH_4F in MeOH, as described above for the preparation of **1a**, yielded 52 mg of **1b** (99%). mp: 188-190.5°C; ^{1}H NMR (MeOH-d_4) δ 8.54 (d, 1H, J= 8 Hz), 7.72 (dd, 2H, J= 1.5, 7 Hz), 7.48 (dd, 1H, J= 1.5, 8 Hz), 7.36 (dd, 2H, J= 7, 8 Hz), 5.73 (d, 1H, J= 8 Hz), 4.42 (dd, 1H, J= 6, 7 Hz), 3.97 (m, 2H), 3.82 (dd, 1H, J= 3, 12 Hz), 3.42 (dd, 1H, J= 9, 14 Hz), 2.47 (dd, 1H, J= 7, 14 Hz); ^{13}C NMR (MeOH-d_4) δ 192.2, 166.1, 151.8, 141.2, 135.6, 133.5, 129.9, 129.2, 102.2, 98.1, 89.7, 69.0, 60.5, 42.1; IR (film) 3361, 2957, 2862, 1708, 1691, 1679, 1447, 1306, 1093, 1038 cm^{-1}; Anal. calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 56.13; H, 5.29; N, 7.79.

Preparation of 1c. Deprotection of **13c** (32 mg, 0.06 mmol) with NH_4F in MeOH, as described above for the preparation of **1a**, yielded 12 mg of **1c** (67%). mp: 162-164°C; ^{1}H NMR (MeOH-d_4) δ 8.21 (d, 1H, J= 8 Hz), 5.70 (d, 1H, J= 8 Hz), 4.32 (dd, 1H, J= 7, 14 Hz), 3.93 (m, 1H), 3.83 (dd, 1H, J= 3, 12 Hz), 3.69 (dd, 1H, J= 4, 12 Hz), 3.08 - 2.95 (m, 2H), 2.55 (dd, 1H, J= 7, 14 Hz), 1.12 (d, 3H, J= 6.5 Hz), 1.03 (d, 3H, J= 6.5 Hz); IR (film) 3350, 2880, 1680, 1453, 1262, 1170, 1048 cm^{-1}.

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