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Studies Directed toward the Development of Amide-Linked RNA Mimics: Synthesis of the Monomeric Building Blocks

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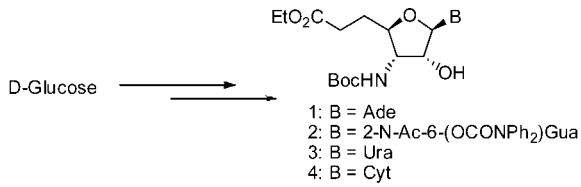
Received May 28, 2008



A general approach toward the synthesis of all four monomeric building blocks of the ribonucleoside amino acids 3′-amino-5′-carboxymethyl-3′,5′-dideoxy nucleosides in their protected forms is described that will facilitate the development of amide-linked RNA mimics.

The recent developments in the area of RNA interference (RNAi)[1] have renewed interest in oligonucleotide-based antisense therapeutics.[2] That gene expression can be regulated by short interfering RNAs (siRNAs) guiding the degradation of the mRNA before it can be translated into protein by the cells' ribosomes is conceptually similar to the antisense oligonucleotide therapy.[3] Whereas traditional small-molecule drugs attack the aberrant proteins, antisense therapy targets the RNAs that control their production.[4] However, use of siRNAs as therapeutics is bogged down by their poor enzymatic stabilities, cellular uptakes, biodistribution, and pharmacokinetics. Chemical modifications can not only address these shortcomings but can also be fine-tuned to reduce toxicity and other side-effects of siRNAs. Various types of chemically modified RNA analogues have been prepared by many groups, and their properties have been studied in details.[5] Replacement of the phosphodiester linkages with amide bonds has also been extensively studied for potential therapeutic applications involving antisense strategy.[6] The advantages of this approach are that it not only facilitates the assembly of such substrates using standard solid- or solution-phase peptide synthesis methods but also would help to enhance the stabilities of these analogues toward nucleases. However, the success of this strategy will depend on the easy availability of the monomeric building blocks,[7] which warrants the development of a robust synthetic strategy for the synthesis of all of the members of the nucleoside amino acids. We have earlier reported the synthesis of a thymidine-based deoxyribonucleoside amino acid that was then cyclooligomerized.[8] Herein, we report the synthesis of four ribonucleoside amino acids, 3′-amino-5′-carboxymethyl-3′,5′-dideoxy nucleosides **1**−**4**, in the protected forms (Figure 1).

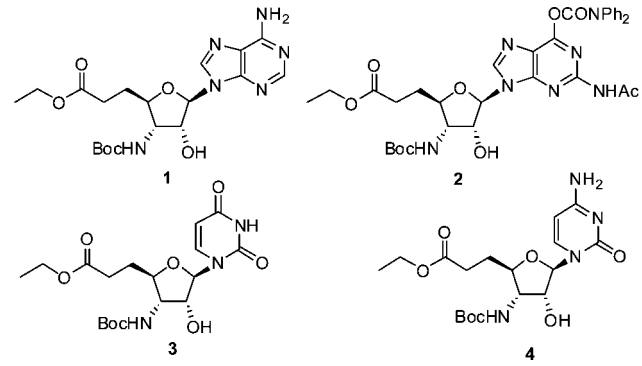


FIGURE 1. Structures of ribonucleoside amino acids **1**−**4**.

For the synthesis of **1**−**4**, we started from the known compound **7** (Scheme 1), which was prepared from glucose diacetonide **5**[9] via **6**[10] according to the reported procedure.[11] Compound **7** was converted to the azido intermediate **8** in two steps, involving formation of a triflate intermediate with Tf_2O

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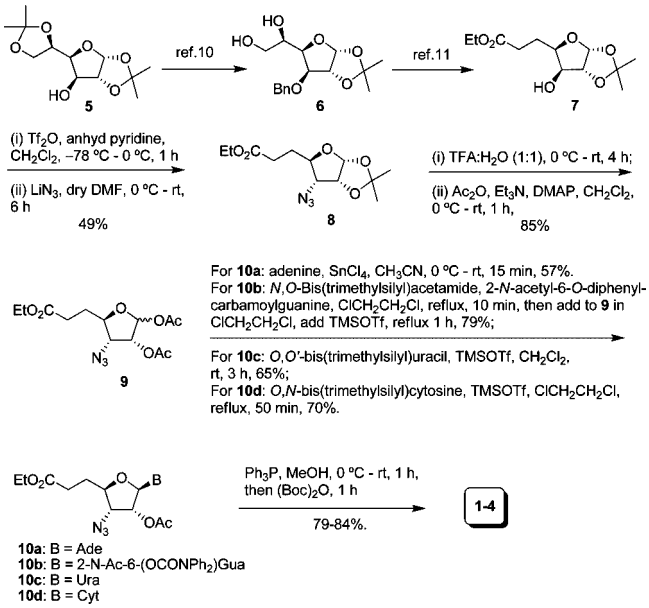
10.1021/jo801156a CCC: $40.75
Published on Web 08/02/2008

SCHEME 1. Synthesis of Ribonucleoside Amino Acids 1−4a



and pyridine in CH_2Cl_2, followed by displacement of the triflate with azide, to give **8** in 49% overall yield.[12]

Acetonide deprotection of **8** with 50% aqueous TFA at 0 °C furnished lactol,[13] which on acetylation with acetic anhydride afforded compound **9** in 85% over two steps. Next, compounds **10a**, **10b**, **10c**, and **10d** were synthesized from **9** under different conditions. The modified nucleoside **10a** was obtained from **9** via $SnCl_4$-mediated glycosylation of unprotected adenine,[7d,14] whereas **10b** was synthesized from **9** using a protocol developed by Zou and Robins.[7d,15] For the synthesis of **10c**[7b] and **10d**,[7c] compound **9** was coupled with bis(trimethylsilyl)uracil and bis(trimethylsilyl)cytosine in the presence of TMSOTf to give **10c** in 65% and **10d** in 70% yields, respectively. Finally, reduction of the azide functionality and methanolysis using Ph_3P in methanol followed by in situ protection of the resulting amine with $(Boc)_2O$ afforded compounds **1**−**4** in good yields.

In summary, we have devised a common strategy for the synthesis of all four nucleoside amino acids, starting from **5**, in moderate overall yields (**1**, 10.4%; **2**, 13.6%; **3**, 11.5%; **4**, 12.2%). Synthesis of the RNA-mimics with these monomeric building blocks for biological interest is under progress and will be reported in due course.

Experimental Section

Synthesis of 8. Dry pyridine (2.0 mL, 24.84 mmol) was added to a solution of **7** (3.8 g, 14.61 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C, followed by triflic anhydride (3.68 mL, 21.92 mmol), added dropwise via syringe. Then the reaction mixture was brought to 0 °C, and stirring was continued for 1 h at 0 °C. It was quenched carefully with aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with $CuSO_4$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The mixture was applied directly to flash chromatography (ethyl acetate−hexane 1:9) to give the triflate, which was directly used for the next step without any characterization.

The triflate was dissolved in dry DMF (30 mL), and lithium azide (1.43 g, 29.23 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 6 h. It was quenched by addition of water (5 mL) at 0 °C, and the mixture was extracted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 8% to 10% EtOAc in petroleum ether eluant) furnished **8** (2.04 g, 49%) as colorless oil. $R_f = 0.4$ (SiO_2, 15% EtOAc in petroleum ether); $[\alpha]^{25}_D = +90.14$ (*c* 1.41, $CHCl_3$); IR (neat) ν_{max} 3446, 2926, 2854, 2107, 1733, 1377, 1257, 1167, 1022, 875, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (d, $J = 3.7$ Hz, 1H), 4.62 (t, $J = 4.5$ Hz, 1H), 4.07 (q, $J = 7.5$ Hz, 2H), 3.99 (m, 1H), 2.90 (m, 1H), 2.52−2.32 (m, 2H), 2.06 (m, 1H), 1.77 (dt, $J = 14.3$, 8.3 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H), 1.21 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 112.9, 103.9, 80.2, 76.3, 64.3, 60.5, 30.2, 27.4, 26.4, 26.2, 14.2; MS (ESIMS) *m*/*z* (%) 308 (100) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{12}H_{19}N_3O_5Na$ $[M + Na]^+$ 308.1222, found 308.1226.

Synthesis of 9. An ice-cold solution of **8** (2.0 g, 7 mmol) in TFA:H_2O (16.8 mL, 1:1) was stirred for 15 min at 0 °C and at room temperature for 4 h. The reaction was then cooled to 0 °C and slowly quenched with solid $NaHCO_3$ until the effervescence ceased. The reaction mixture was then diluted with water and extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give lactol as a thick liquid. The crude product was directly subjected to acetylation.

To a stirred solution of the lactol in CH_2Cl_2 (20 mL) at 0 °C under nitrogen atmosphere was added Et_3N (2.92 mL, 21 mmol). After 10 min, Ac_2O (1.58 mL, 16.8 mmol) followed by DMAP (342 mg, 2.8 mmol) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h at the same temperature. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 15% to 20% EtOAc in petroleum ether eluant) afforded an anomeric mixture **9** (1.95 g, 85%) as colorless oil. $R_f = 0.45$ (SiO_2, 40% EtOAc in petroleum ether); $[\alpha]^{25}_D = +17.16$ (*c* 2.72, $CHCl_3$); IR (neat) ν_{max} 3445, 2931, 2111, 1750, 1440, 1372, 1215, 1102, 1016, 957, 893, 762, 600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.27 (d, $J = 4.4$ Hz, 1H), 4.14 (q, $J = 7.3$ Hz, 2H), 4.04 (dt, $J = 8.0$, 4.4 Hz, 1H), 3.79 (dd, $J = 8.0$, 4.4 Hz, 1H), 2.45 (dd, $J = 13.2$, 7.3 Hz, 2H), 2.18 (s, 3H), 2.08 (s, 3H), 2.13−1.81 (m, 2H), 1.28 (t, $J = 7.3$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ172.6, 172.4, 169.5, 168.8, 97.9, 93.6, 81.8, 80.8, 76.1, 71.8, 63.2, 61.4, 60.6, 30.1, 29.8, 29.5, 28.9, 21.0, 20.5, 20.2, 14.1; MS (ESIMS) *m*/*z* (%) 352 (100) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{13}H_{19}N_3O_7Na$ $[M + Na]^+$ 352.1120, found 352.1116.

Synthesis of 10a. Adenine (98.5 mg, 0.73 mmol) was added to a solution of **9** (200 mg, 0.6 mmol) in dry CH_3CN (2 mL) under nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and $SnCl_4$ (0.14 mL, 1.2 mmol) in dry CH_3CN (1 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 min till the cloudy solution turned clear. The reaction mixture was again cooled to 0 °C, and CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, and the residue was purified by silica gel chromatography (SiO_2, 1% to 2% MeOH in $CHCl_3$ eluant) to afford **10a** (140 mg, 57%) as colorless oil. $R_f = 0.45$ (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D = -2.89$ (*c* 0.405, $CHCl_3$); IR (neat) ν_{max} 3430, 2925, 2112, 1741, 1638, 1216, 761, 669 cm^{-1};

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^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.84 (s, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.94 (q, J = 3.0 Hz, 1H), 5.71 (br s, 2H), 4.65−4.59 (m, 2H), 4.13 (q, J = 6.7 Hz, 2H), 4.09 (m, 1H), 2.48 (dt, J = 16.6, 8.3 Hz, 2H), 2.27−2.05 (m, 2H), 2.19 (s, 3H), 1.22 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 169.8, 155.6, 153.1, 149.3, 139.7, 120.4, 87.9, 80.8, 75.7, 62.9, 60.6, 29.9, 28.0, 20.5, 14.1; MS (ESIMS) *m*/*z* (%) 405 (50) $[M + H]^+$; HRMS (ESIMS) calcd for $C_{16}H_{21}O_5N_8$ $[M + H]^+$ 405.1634, found 405.1651.

Synthesis of 10b. *N*,*O*-Bis(trimethylsilyl)acetamide (0.59 mL, 2.4 mmol) was added to a solution of 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (465 mg, 1.2 mmol) in $ClCH_2CH_2Cl$ (4 mL). The mixture was refluxed for 10 min, cooled to room temperature, and added to a solution of **9** (200 mg, 0.6 mmol) in $ClCH_2CH_2Cl$ (2 mL) at 0 °C. Trimethylsilyl trifluoro-methanesulfonate (0.21 mL, 1.2 mmol) was added dropwise at 0 °C. The brown solution was refluxed for 1 h. The reaction mixture was cooled to 0 °C, and CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, and the residue was purified by silica gel chromatography (SiO_2, 1% to 2% MeOH in $CHCl_3$ eluant) to afford **10b** (315 mg, 79%) as colorless oil. R_f = 0.5 (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = −22.75 (c 1.9, $CHCl_3$); IR (neat) ν_{max} 3428, 2657, 2111, 1736, 1630, 1593, 1383, 1214, 1062, 758, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 8.58 (s, 1H), 7.86 (s, 1H), 7.45−7.18 (m, 10H), 5.86 (dd, J = 5.2, 2.2 Hz, 1H), 5.82 (d, J = 1.5 Hz, 1H), 5.26 (m, 1H), 4.08 (m, 1H), 4.09 (q, J = 3.0 Hz, 2H), 2.55−2.35 (m, 2H), 2.31 (s, 3H), 2.22−2.03 (m, 2H), 2.18 (s, 3H), 1.19 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.9, 169.9, 168.3, 156.2, 153.8, 151.8, 150.1, 143.3, 141.6, 129.2, 127.7, 121.6, 126.5, 88.4, 81.0, 76.2, 62.1, 60.5, 29.7, 27.6, 25.0, 20.5, 14.1; MS (ESIMS) *m*/*z* (%) 680 (65) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{31}H_{31}N_9O_8Na$ $[M + Na]^+$ 680.2193, found 680.2189.

General Procedure (A) (Coupling of Uracil and Cytosine with 9). A suspension of the nucleobase and $(NH_4)_2SO_4$ (trace) in HMDS (2 mL/mmol) was stirred at reflux (with exclusion of moisture) until a clear solution was formed. Volatiles were evaporated, and toluene was added and coevaporated several times. The residue was dried in vacuum, and a solution of the carbohydrate derivative in 1,2-dichloroethane (under N_2) was added. TMSOTf (1.2 equiv) was added at 0 °C, and the solution was brought to room temperature and stirred for 3 h at same temperature for **10c**, being refluxed for 50 min in case of **10d**. The reaction mixture was cooled to 0 °C, and CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography.

Synthesis of 10c. Procedure A was followed with **9** (200 mg, 0.6 mmol), uracil (201 mg, 1.8 mmol), and trimethylsilyl trifluoromethanesulfonate (0.21 mL, 1.2 mmol) in CH_2Cl_2 (5 mL). Chromatographic purification (SiO_2, 2% to 3% MeOH in $CHCl_3$ eluant) afforded **10c** (150 mg, 65%) as colorless oil. R_f = 0.42 (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +50.15 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 3429, 2939, 2871, 2112, 1694, 1450, 1377, 1265, 1120, 1023, 901, 868, 810, 573 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.2 (d, J = 8.2, 1H), 5.77 (dd, J = 8.2, 2.0 Hz, 1H), 5.57 (d, J = 3.4 Hz, 1H), 5.49 (dd, J = 6.1, 3.4 Hz, 1H), 4.15 (q, J = 6.8 Hz, 2H), 3.96 (dt, J = 8.2, 4.1 Hz, 1H), 4.05 (m, 1H), 2.50 (dt, J = 6.8, 3.4 Hz, 2H), 2.2 (s, 3H), 2.18−1.94 (m, 2H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ172.6, 169.9, 162.7, 149.7, 141.2, 103.0, 91.4, 80.5, 75.4, 62.9, 60.7, 30.0, 28.0, 20.5, 14.2; MS (ESIMS) *m*/*z* (%) 404 (40) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{15}H_{19}N_5O_7Na$ $[M + Na]^+$ 404.1182, found 404.1182.

Synthesis of 10d. Procedure A was followed with **9** (200 mg, 0.6 mmol), cytosine (153 mg, 1.38 mmol), and trimethylsilyl trifluoromethanesulfonate (0.21 mL, 1.2 mmol) in $ClCH_2CH_2Cl$ (5 mL). Chromatographic purification (SiO_2, 5% to 6% MeOH in $CHCl_3$ eluant) afforded **10d** (161 mg, 70%) as colorless oil. R_f = 0.40 (SiO_2, 10% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +51.73 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 3426, 2924, 2112, 1729, 1641, 1375, 1216, 760, 669 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 7.5 Hz, 1H), 5.81 (d, J = 7.5 Hz, 1H), 5.59 (dd, J = 6.0, 2.2 Hz, 1H), 5.54 (d, J = 2.2 Hz, 1H), 4.15 (q, J = 6.7 Hz, 2H), 4.07 (dd, J = 9.0, 6.0 Hz, 1H), 3.93 (dt, J = 9.0, 4.5 Hz, 1H), 2.52 (dt, J = 18.1, 9.8 Hz, 2H), 2.18 (s, 3H), 1.98−2.12 (m, 2H), 1.26 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 169.9, 166.0, 155.2, 142.3, 95.3, 92.7, 80.2, 76.0, 63.1, 60.7, 30.2, 28.0, 20.6, 14.2; MS (ESIMS) *m*/*z* (%) 403 (60) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{15}H_{20}N_6O_6Na$ $[M + Na]^+$ 403.1342, found 403.1358.

General Procedure (B). Triphenylphosphine (2 equiv) was added to the carbohydrate derivative (1 equiv) in dry MeOH under nitrogen atmosphere at 0 °C. The reaction mixture was brought to room temperature and stirred at the same temperature for 1 h. To the same reaction mixture $(Boc)_2O$ (1.2 eq) was added at room temperature and the reaction mixture was stirred for 1 h. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.

Synthesis of 1. Procedure B was followed with **10a** (100 mg, 0.24 mmol), Ph_3P (130 mg, 0.49 mmol), and $(Boc)_2O$ (0.068 mL, 0.29 mmol) in MeOH (3 mL). Chromatographic purification (SiO_2, 3% to 4% MeOH in $CHCl_3$ eluant) afforded **1** (90.6 mg, 84%) as white solid (mp = 135 °C). R_f = 0.3 (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +20.42 (*c* 0.93, $CHCl_3$); IR (neat) ν_{max} 3348, 3177, 2977, 2931, 1673, 1610, 1520, 1482, 1370, 1249, 1169, 1099, 1040 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.14 (s, 1H), 7.31 (br s, 2H), 6.6 (d, J = 8.3 Hz, 1H), 5.92 (d, J = 5.2 Hz, 1H), 5.84 (d, J = 2.2 Hz, 1H), 4.54 (m, 1H), 4.18 (dd, J = 15.1, 8.3 Hz, 1H), 3.99 (q, J = 6.7 Hz, 2H), 3.85 (dt, J = 7.5, 3.7 Hz, 1H), 2.36 (dt, J = 18.1, 9.0 Hz, 2H), 2.00−1.79 (m, 2H), 1.40 (s, 9H), 1.23 (br s, 1H), 1.12 (t, J = 6.7 Hz, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 172.4, 169.6, 155.2, 151.5, 151.1, 140.0, 139.9, 89.3, 80.3, 79.1, 78.1, 72.7, 59.7, 55.2, 29.8, 28.1, 13.9; MS (ESIMS) *m*/*z* (%) 437 (60) $[M + H]^+$; HRMS (ESIMS) calcd for $C_{19}H_{29}N_6O_6$ $[M + H]^+$ 437.2143, found 437.2159.

Synthesis of 2. Procedure B was followed with **10b** (100 mg, 0.15 mmol), Ph_3P (79.8 mg, 0.30 mmol), and $(Boc)_2O$ (0.042 mL, 0.18 mmol) in MeOH (3 mL). Chromatographic purification (SiO_2, 2% to 3% MeOH in $CHCl_3$ eluant) afforded **2** (82.8 mg, 79%) as colorless oil. R_f = 0.4 (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +9.68 (*c* 0.63, $CHCl_3$); IR (neat) ν_{max} 3398, 3305, 3109, 3071, 2926, 2856, 1708, 1620, 1589, 1449, 1285, 1165, 1061, 910, 862, 730, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 8.50 (br s, 1H), 8.11 (s, 1H), 7.22−7.48 (m, 10H), 6.64 (m, 1H), 5.75 (d, J = 5.8 Hz, 1H), 5.70 (m, 1H), 4.67 (m, 1H), 4.12 (q, J = 7.3, 2H), 3.98 (m, 1H), 3.29 (m, 1H), 2.45−2.56 (m, 2H), 2.19 (s, 3H), 1.82−2.02 (m, 2H), 1.46 (s, 9H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 168.6, 156.2, 153.5, 151.1, 150.3, 141.9, 141.6, 129.2, 127.2, 127.1, 126.4, 126.1, 125.9, 121.5, 92.1, 85.9, 79.8, 74.2, 60.5, 55.9, 30.6, 29.7, 29.1, 28.3, 24.9, 14.2; MS (ESIMS) *m*/*z* (%) 712 (100) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{34}H_{39}N_7O_9Na$ $[M + Na]^+$ 712.2701, found 712.2699.

Synthesis of 3. Procedure B was followed with **10c** (100 mg, 0.26 mmol), Ph_3P (137 mg, 0.52 mmol), and $(Boc)_2O$ (0.072 mL, 0.31 mmol) in MeOH (3 mL). Chromatographic purification (SiO_2, 3% to 4% MeOH in $CHCl_3$ eluant) afforded **3** (87.8 mg, 81%) as colorless oil. R_f = 0.45 (SiO_2, 5% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +74.83 (*c* 0.77, $CHCl_3$); IR (neat) ν_{max} 3430, 3363, 3316, 3211, 2978, 2931, 1676, 1508, 1459, 1372, 1255, 1163, 1097, 912, 857, 816, 771, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 5.80 (d, J = 8.5 Hz, 1H), 5.71 (s, 1H), 5.39 (d, J = 8.5 Hz, 1H), 4.26 (m, 1H), 4.14 (q, J = 7.5 Hz, 2H), 4.04 (m, 1H), 3.82 (m, 1H), 2.57−2.48 (dt, J = 16.1, 8.5,

2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.44 (s, 9H), 1.26 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 164.0, 155.6, 150.6, 139.3, 102.2, 92.5, 82.2, 80.1, 75.0, 60.6, 54.9, 31.0, 29.6, 28.2, 14.2; MS (ESIMS) *m*/*z* (%) 436 (100) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{18}H_{27}N_3O_8Na$ $[M + Na]^+$ 436.1690, found 436.1676.

Synthesis of 4. Procedure B was followed with **10d** (100 mg, 0.26 mmol), Ph_3P (137 mg, 0.52 mmol), and $(Boc)_2O$ (0.072 mL, 0.31 mmol) in MeOH (3 mL). Chromatographic purification (SiO_2, 5% to 6% MeOH in $CHCl_3$ eluant) afforded **4** (86.6 mg, 80%) as white solid (mp = 98 °C). $R_f = 0.4$ (SiO_2, 10% MeOH in $CHCl_3$); $[\alpha]^{25}_D = +99.65$ (*c* 0.87, $CHCl_3$); IR (neat) ν_{max} 3754, 3454, 2925, 2854, 1638, 1458, 1093 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.55 (d, $J = 7.7$ Hz, 1H), 7.31−7.14 (m, 2H), 6.48 (d, $J = 7.7$ Hz, 1H), 5.79 (d, $J = 5.4$ Hz, 1H), 5.74 (d, $J = 7.7$ Hz, 1H), 5.6 (d, $J = 1.5$ Hz, 1H), 4.03 (q, $J = 6.9$ Hz, 2H), 3.98 (m, 1H), 3.72 (m, 1H), 2.47−2.31 (m, 2H), 1.97−1.77 (m, 2H), 1.38 (s, 9H), 1.23 (s, 1H), 1.16 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 172.4, 165.4, 155.2, 154.7, 147.5, 141.5, 94.0, 91.9, 79.5, 78.1, 73.0, 59.8, 30.1, 28.9, 28.1, 14.0; MS (ESIMS) *m*/*z* (%) 435 (60) $[M + Na]^+$; HRMS (ESIMS) calcd for $C_{18}H_{28}N_4O_7Na$ $[M + Na]^+$ 435.1850, found 435.1831.

Acknowledgment. The authors wish to thank DST, New Delhi for financial support (SR/S1/OC-01/2007); UGC and CSIR, New Delhi for research fellowships (PKG and D.K.).

Supporting Information Available: General experimental procedures and the copies of ^{1}H and ^{13}C NMR spectra for compounds **1**−**4**, **8**, **9**, and **10a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801156A