Stereoselective Synthesis of 2′-Amino-2′,3′-dideoxynucleosides by Nitrone 1,3-Dipolar Cycloaddition: A New Efficient Entry Toward d4T and Its 2-Methyl Analogue†

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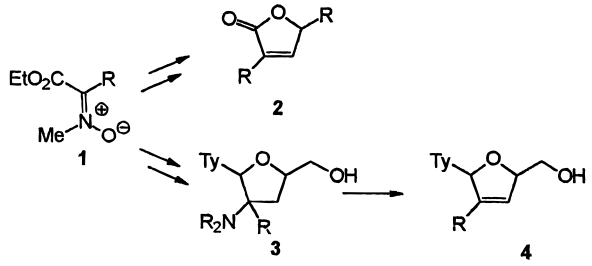
An efficient access to 2′-(dimethylamino)-2′,3′-dideoxynucleosides is reported. The synthetic strategy relies on the 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones to allyl acetate, followed by reductive ring opening to substituted lactones, DIBALH reduction to the corresponding 3-(dimethylamino)tetrahydro-2-furanols, and coupling with silylated thymine. The removal of the dimethylamino group by Cope elimination affords a new formal synthesis of d4T and analogous unsaturated 2′,3′-dideoxynucleosides.

Introduction

The development of new methodologies enabling the synthesis of unnatural nucleosides plays a significant role in the search for new antitumor and antiviral agents. Following the discovery of AZT, DDC, DDI, and d4T as potent antiviral agents[1] acting as competitive inhibitors of the viral reverse transcriptase (RT),[2] the preparation of modified nucleosides with structural alterations in the heterocyclic ring, the sugar moiety, or both has become a very active research area, and new synthetic methods have been designed and developed.[3]

Saturated and unsaturated 2′,3′-dideoxynucleosides, containing different functionalities and lacking the 3′-hydroxyl group, are expected to terminate viral DNA synthesis after their incorporation in the chains.[4] In this context, a number of recent synthetic efforts have been focused on this type of nucleoside analogue.[5] The syntheses are largely classified into two approaches. The first is based on the structural modification of the sugar part of intact nucleosides available from natural sources, and the second consists of the coupling of suitably modified sugars with nucleoside bases, eventually followed by formation of a double bond at the 2′,3′ position.

Scheme 1



In connection with our previous reports on the synthesis of 2(5*H*)furanones,[6] involving the 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones **1**, followed by reductive ring opening of the *N*,*O*-heterocyclic nucleus to unsaturated *γ*-lactones **2**, we have now extended this utility to provide a new and direct entry to nucleoside analogues **3**, containing an amino function at the 2′ positions.[7] Furthermore, the synthetic scheme employed can be directed toward the synthesis of modified unsaturated 2′,3′-dideoxynucleoside **4** (Scheme 1).

Results and Discussion

The synthetic design, reported in Scheme 2, involved the formation of a key intermediate, the tetrahydrofuran acetate **11**, which could then be condensed with various nucleoside bases**.** Our experiments were carried out as follows. The initial 1,3-dipolar cycloaddition of nitrone **5** with allyl acetate at 75 °C for 48 h in a sealed tube afforded an epimeric mixture of 5-substituted isoxazolidines **6** (95% yield) as exclusive adducts. It is note-

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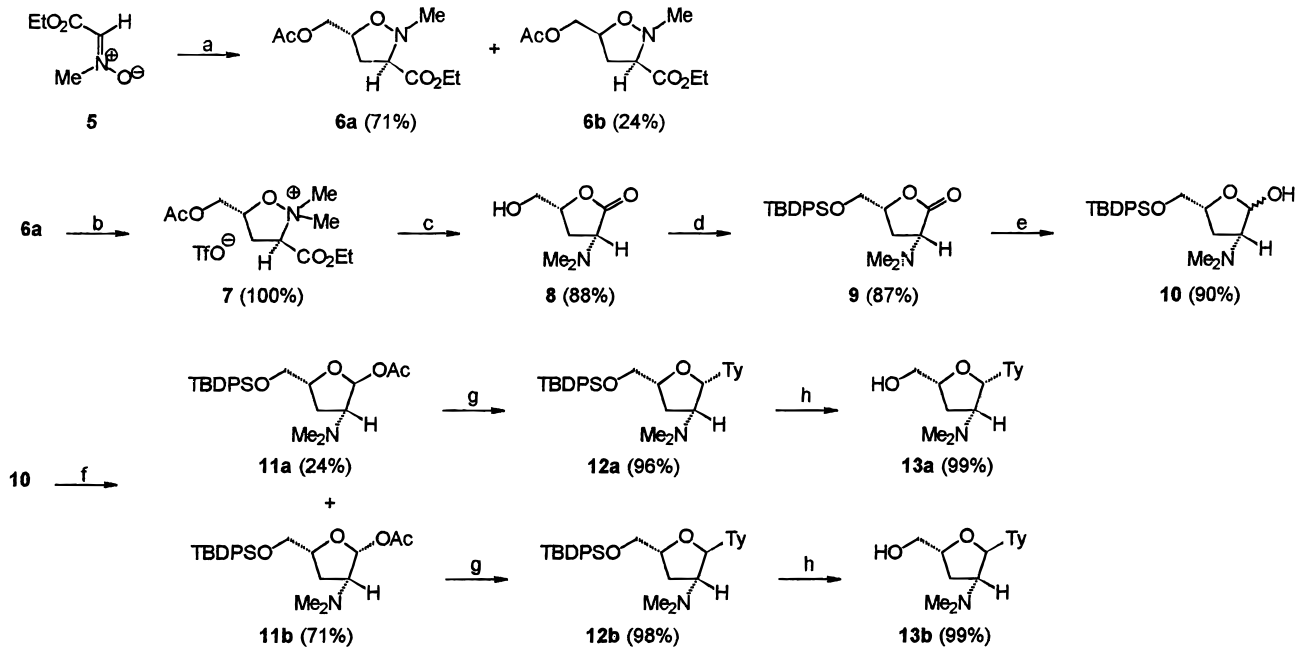
Scheme 2[a]



[a] Reaction conditions: (a) allyl acetate, 75 °C, 48 h; (b) TfOMe, CCl_4, 0 °C, 3 h; (c) H_2, Pd/C, 70 °C, 36 h; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 3 h; (e) DIBALH, toluene, −78 °C, 3 h; (f) AcCl, pyridine, CH_2Cl_2, 0 °C, 4 h; (g) *O*,*O*′-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, overnight; (h) TBAF, THF, 3 h.

worthy that the 1,3-dipolar cycloaddition proceeded with a good stereoselectivity giving the trans isomer **6a** as the major product (3:1 ratio). Treatment of **6a** with methyl triflate, leading to **7**, followed by catalytic hydrogenation (H_2/Pd in methanol), gave the cis 3-(dimethylamino)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone (**8**) in 88% yield. Its formation is the result of the intramolecular lactonization following the reductive ring opening and involving the CO_2Et group at position 3 in the *N*,*O*-ring. After protection of the C_5 hydroxyl group with TBDPSCl, direct reduction of **9** with DIBALH (1.2 equiv) provided the epimeric lactols **10**; acetylation of **10** led to a readily separable mixture of the acetates **11a** and **11b** in 46% global yield starting from nitrone **5**.

Compounds **11a** and **11b** were obtained in a 1:3 relative ratio; the respective configurations were determined by ^{1}H NMR NOE experiments. Thus, whereas **11b** showed NOE correlation between H_1 and H_4, no NOE effects between the same protons have been observed for **11a**.

We next explored the coupling reaction with silylated thymine according to the procedure of Niedballa and Vorbrüggen.[8] Nucleosidation, which occurred in high yields (96−98%), was carried out in dichloromethane at 0 °C in the presence of $SnCl_4$ as catalyst and proceeded with a very high stereoselectivity to afford nearly exclusively a single isomer, i.e., **12a** (β-isomer) from **11a** and **12b** (α-isomer) from **11b**. The ^{1}H NMR of the crude reaction mixture reveals only traces (∼1:40 relative ratio) of the other stereoisomer.

Finally, deprotection of compounds **12** with TBAF gave the modified 2′,3′-dideoxynucleosides **13** in a quantitative yield.

The stereochemistry of thymine analogues **12** and **13** was determined by NOE experiments, using the unequivocal configuration of the $H_{4'}$ proton as reference. Thus, β-nucleosides **12a** and **13a** show NOE correlations between $H_{1'}-H_{4'}$, $H_{2'}-H_{3'b}$, and $H_{3'b}-H_{4'}$, whereas α-nucleosides **12b** and **13b** showed NOE effects between $H_{2'}-H_{3'a}$ and $H_{3'a}-H_{4'}$.

The generality of the synthetic scheme has also been tested by the preparation of the 2′-methyl analogue, starting from *C*-methoxycarbonyl-*C*,*N*-dimethyl nitrone (**14**) (Scheme 3). The reaction with allyl acetate gave rise to a 1:1.2 mixture of adducts **15** (as observed by ^{1}H NMR), which was reacted with methyl triflate, subjected to hydrogenolytic ring cleavage to afford lactones **17**, and then protected at the hydroxyl function by treatment with TBDPSCl to afford **18a** and **18b**, which have been separated by flash chromatography. The subsequent DIBALH reduction proceeded with complete stereoselectivity to give exclusively tetrahydro-2-furanols **19a** (from **18a**) and **19b** (from **18b**).

The stereochemistry of **19a** and **19b** has been determined by NOE experiments. Irradiation of H_4 in **19b** gave rise to a NOE effect for H_1, the methyl group at C_2, and the downfield resonance of the methylene proton at C_3, thereby indicating a cis relationship of these protons. Conversely, in compound **19a**, no NOE on H_1 was observed by irradiation of H_4, whereas positive NOE enhancement is evidenced for the *N*-Me_2 group and the aromatic protons.

Compounds **19a** and **19b** were then acetylated and coupled with silylated thymine to give, after deprotection of the CH_2OH group at $C_{5'}$, the nucleosides **22a** and **22b**.

This method may be applied to other pyrimidine and purine nucleosides to synthesize the corresponding 2-aminoribonucleoside analogues.

The reported methodology has been further investigated to provide a new efficient entry toward unsaturated 2′,3′-dideoxynucleosides. Thus, d4T (**24**) and its methyl analogue **26** were synthesized after elimination of the

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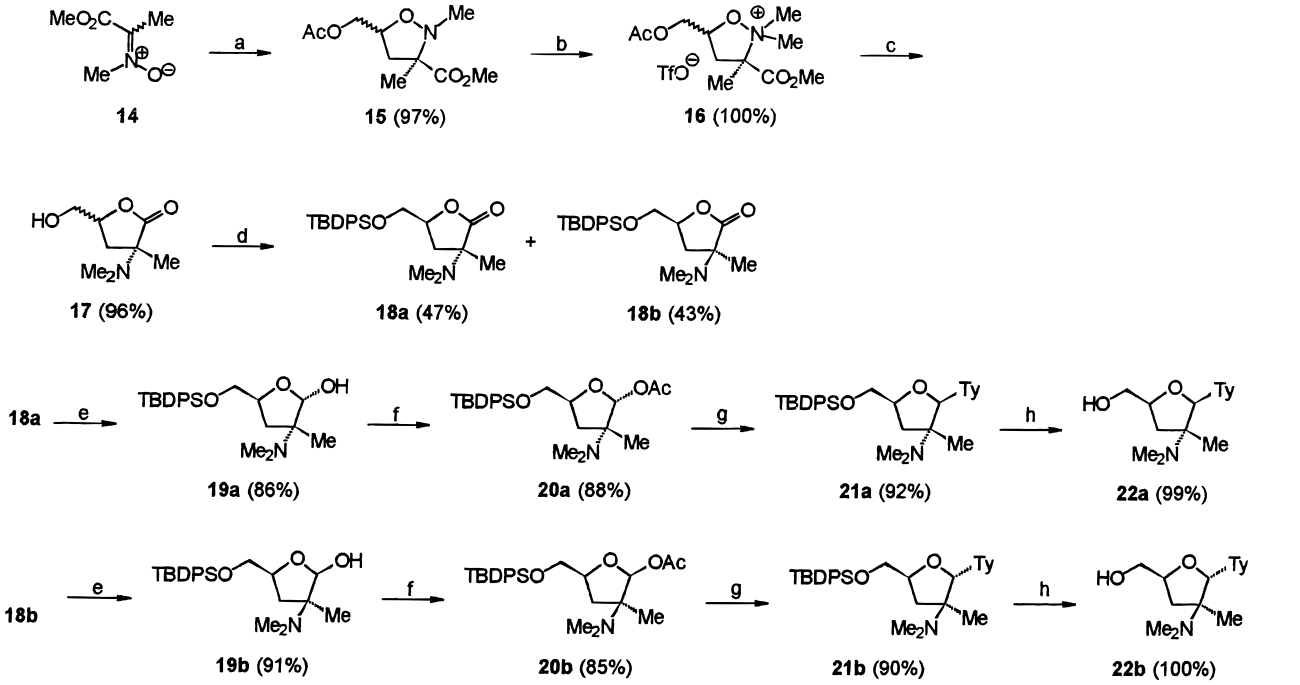
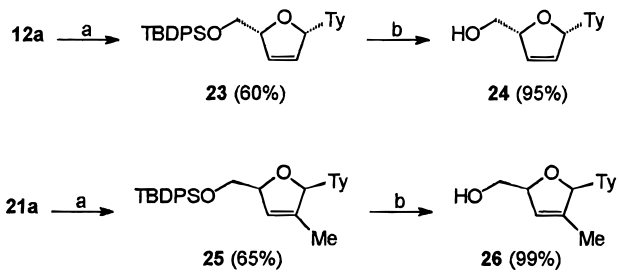
Scheme 3[a]



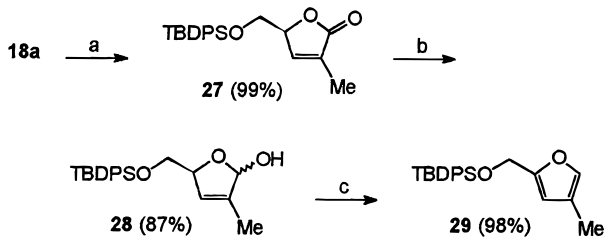
[a] Reaction conditions: (a) allyl acetate, 75 °C, 48 h; (b) TfOMe, CCl_4, 0 °C, 3 h; (c) H_2, Pd/C, 70 °C, 36 h; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 3 h; (e) DIBALH, toluene, −78 °C, 3 h; (f) AcCl, pyridine, CH_2Cl_2, 0 °C, 4 h; (g) *O*,*O*′-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, overnight; (h) TBAF, THF, 3 h.

Scheme 4[a]



[a] Reaction conditions: (a) *m*-CPBA, CH_2Cl_2, 0 → 50 °C, 3.5 h; (b) TBAF, THF, 3 h.

Scheme 5[a]



[a] Reaction conditions: (a) *m*-CPBA, CH_2Cl_2, 0 → 25 °C, 3.5 h; (b) DIBALH, toluene, −78 °C, 3 h; (c) AcCl, piridine, CH_2Cl_2, 0 °C, 4 h.

N-dimethylamino group in **12a** and **21a**, respectively, performed according to a Cope elimination by treatment with *m*-CPBA (60−65% yield) followed by TBAF treatment (Scheme 4).[5b,c,9]

The alternative approach to synthesize **24** and **26**, by introduction of the unsaturated bond before the coupling reaction with the silylated thymine, has been explored with unsuccessful results. In fact, DIBALH reduction of the butenolide **27**, obtained via Cope elimination from **18a**, afforded the compound **28** which on further acetylation furnished the *tert*-butyl[(4-methyl)-2-furyl)methoxy]-diphenylsilane (**29**) (Scheme 5). Previous publications describe 2,3-unsaturated pentafuranosides as sensitive to both acidic and basic conditions, leading to furan derivatives.[10]

This reported procedure for the synthesis of d4T is, however, weakened by the consideration that the tetrahydro-2-furanyl acetate precursor **11a** (Scheme 2) is obtained only as a minor product during the DIBALH stereoselective reduction of the cis lactone **9** (**10a**:**10b** ratio = 1:3). Nonetheless, we have overcome the problem by performing the epimerization of **9** with DBU, followed by DIBALH reduction, which afforded a mixture of the tetrahydro-2-furanols (**31**; 3:1 ratio). After conversion into the corresponding acetyl derivatives, **32a** and **32b** were separated, and then **32a** was transformed into d4T through the 2′-dimethylamino nucleoside **33a**, according to the above-reported procedure. Moreover, **33a** can be also converted in **34a** by reaction with TBAF (Scheme 6).

In conclusion, the novel [3 + 2] cycloaddition methodology outlined herein provides an efficient access to 2′-dimethylaminonucleosides; furthermore, the reaction can be directed toward the synthesis of unsaturated 2′,3′-dideoxynucleosides. The designed scheme constitutes an

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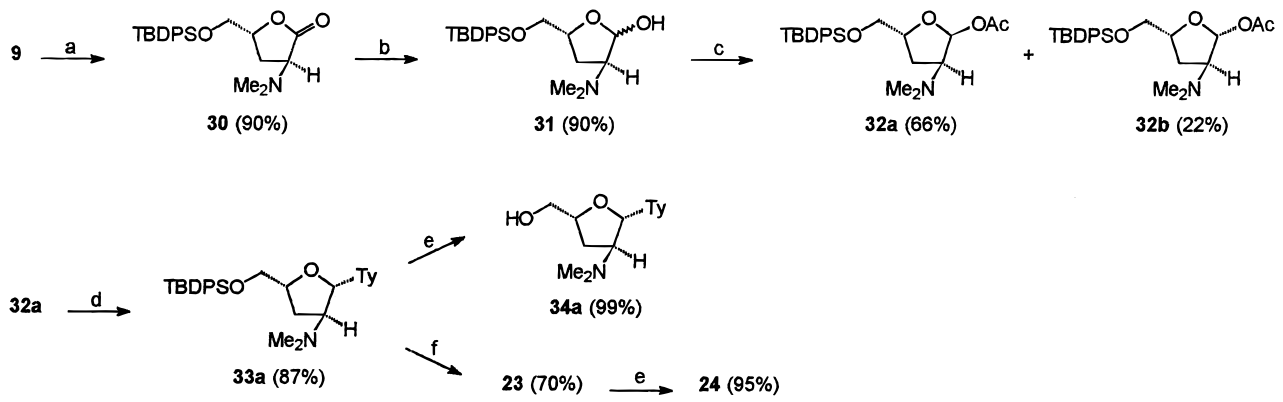
Scheme 6[a]



[a] Reaction conditions: (a) DBU, benzene, 80 °C, 4 h; (b) DIBALH, toluene, −78 °C, 3 h; (c) AcCl, pyridine, CH_2Cl_2, 0 °C, 4 h; (d) *O*,*O*′-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, overnight; (e) TBAF, THF, 3 h; (f) *m*-CPBA, CH_2Cl_2, 0 → 25 °C, 3.5 h.

excellent alternative to previously reported approaches and shows its versatility in the potential construction of other nucleosides with different purine and pyrimidine bases. Additionally, hydrogenation of the 2′,3′-double bond could represent an alternative synthetic pathway to saturated dideoxynucleosides as DDC, DDI, and 3TC.[11] Exploitations of the scope and potential of this synthetic scheme, in the aim of the obtainment of optically active dideoxynucleosides, are also in progress.

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were recorded at 200 or 500 MHz (^{1}H) and at 50 or 125 MHz (^{13}C) and are reported in ppm downfield from TMS. Thin-layer chromatography was done on Merck coated plate 60 F_{254}. Silica gel chromatography was done with Acros (0.035−0.07 mm). All reactions involving air-sensitive agents were conducted under nitrogen atmosphere. All reagents were purchased from Aldrich or Acros Chimica and were used without further purification. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. Nitrones **5** and **14** were prepared according to literature method.[12]

(3*RS*,5*RS*)- and (3*RS*,5*SR*)-5-[(Acetyloxy)methyl]-3-ethoxycarbonyl-2-methyl isoxazolidine (6a and 6b). A solution of *C*-ethoxycarbonyl-*N*-methyl nitrone (**5**) (2.25 g, 17 mmol) in allyl acetate (40 mL) was heated at 75 °C, in a sealed tube, for 48 h. The reaction mixture (**6a**:**6b** epimeric ratio = 3:1) was evaporated, and the residue was purified by column chromatography (cyclohexane/ethyl acetate 7:3). First eluted fraction give **6a** (2.78 g, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, 3H, J = 7.2 Hz), 2.10 (s, 3H), 2.28 (m, 1H, H_4), 2.61 (m, 1H, H_4), 2.81 (s, 3H), 3.35 (m, 1H, H_3), 4.05 (dd, 1H, J = 6.4, 12.6 Hz), 4.23 (q, 2H, J = 7.2 Hz), 4.25 (dd, 1H, J = 3.9, 12.6 Hz), 4.34 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 19.2, 21.1, 34.6, 61.59, 63.9, 69.2, 78.2, 168.1, 170.0. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.98; H, 7.39; N, 6.08. Further eluted product was **6b** (0.943 g, 24%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H, J = 7.2 Hz), 2.09 (s, 3H), 2.26 (m, 1H, H_4), 2.65 (m, 1H, H_4), 2.78 (s, 3H), 3.43 (m, 1H, H_3), 4.13 (dd, 1H, J = 6.3, 12.5 Hz), 4.20 (q, 2H, J = 7.2 Hz), 4.22 (dd, 1H, J = 4.1, 12.5 Hz), 4.36 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.4, 24.1, 41.1, 60.1, 62.4, 67.9, 75.2. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.97; H, 7.45; N, 6.09.

(3*RS*,5*RS*)-5-({[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}-methyl)-3-(dimethylamino)dihydro-2(3*H*)-furanone (9). A solution of **6a** (3.00 g, 13 mmol) and methyl trifluoromethanesulfonate (1.75 mL, 15.6 mmol) in dry CCl_4 was stirred at 0 °C for 3 h. At the end of this time, the reaction mixture was evaporated under reduced pressure, and the residue, identified as (3*RS*,5*RS*)-5-[(acetyloxy)methyl]-3-etoxycarbonyl-2,2-dimethylisoxazolidinium trifluoromethanesulfonate (**7**) (100% yield, sticky oil), was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (t, 3H, J = 7.2 Hz), 2.15 (s, 3H), 3.03 (m, 1H, H_4), 3.24 (m, 1H, H_4), 3.67 (s, 6H), 4.02 (m, 2H), 4.39 (q, 2H, J = 7.2 Hz), 4.85 (m, 1H, H_3), 5.01 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7, 19.2, 30.5, 51.7, 56.5, 62.7, 64.4, 77.4, 83.3, 163.1, 163.5.

A solution of **7** (3.93 g, 10 mmol) in 50 mL of methanol was stirred under a hydrogen atmosphere with 10% Pd on activated carbon for 36 h at 70 °C. After removal of catalyst by Celite filtration, to the filtrate was added 10 mL of a 10% $NaHCO_3$ aqueous solution. The solvent was evaporated under reduced pressure, and the residue was than purified by column chromatography ($CHCl_3$/MeOH 97:3) to give (3*RS*,5*RS*)-3-(dimethylamino)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone (**8**) (1.39 g, 88%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.26 (m, 2H, H_4), 2.43 (s, 6H), 3.02 (bs, 1H), 3.63 (m, 1H, H_3), 3.91 (m, 2H), 4.49 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.0, 41.8, 63.2, 64.1, 77.5, 174.6. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.96; H, 8.25; N, 8.78.

A mixture of **8** (2.52 g, 15.8 mmol), *tert*-butyldiphenylsilyl chloride (TBDPSCl, 4.53 mL, 17.4 mmol), and imidazole (2.37 g, 34.8 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 3 h at 0 °C. The solvent was evaporated, and the residue was purified by silica gel column (cyclohexane/ethyl acetate 1:1) to give **9** (5.48 g, 87%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9H), 2.19 (ddd,

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1H, J = 6.0, 8.5, 12.5 Hz, H_{4a}), 2.33 (ddd, 1H, J = 11.0, 12.5, 12.5 Hz, H_{4b}), 2.43 (s, 6H), 3.72 (dd, 1H, J = 8.5, 12.5, Hz, H_3), 3.75 (dd, 1H, J = 3.6, 11.6 Hz), 3.93 (dd, 1H, J = 3.1, 11.6 Hz), 4.41 (dddd, 1H, J = 3.1, 3.6, 6.0, 11.0 Hz, H_5), 7.39−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 24.3, 26.7, 41.6, 64.2, 64.3, 76.7, 127.8, 129.9, 132.6, 133.0, 135.5, 135.6, 174.6. Anal. Calcd for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.33; H, 7.84; N, 3.50.

(2*SR*,3*RS*,5*RS*) and (2*RS*,3*RS*,5*RS*)-5-({[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanyl acetate (11a and 11b). To a stirred solution of **9** (1.99 g, 5 mmol) in anhydrous toluene (10 mL) at −78 °C under nitrogen was added DIBALH (10 mL, 1.0 M solution in toluene) dropwise while the reaction temperature was mantained below −70 °C. The reaction mixture was stirred for 3h and then was quenched with ethyl acetate (1 mL). The mixture was left to warm to room temperature, water (1 mL) was added, and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95:5) to afford an anomeric mixure (1:3) of (2*RS*,3*RS*,5*RS*) and (2*SR*,3*RS*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanol (**10**) (1.80 g, 90%). Minor isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9H), 1.67 (m, 1H, H_3), 2.04 (m, 1H, H_3), 2.24 (s, 6H), 2.82 (m, 1H, H_2), 3.75 (m, 2H, H_5), 3.95 (bs, 1H), 4.35 (m, 1H, H_4), 5.37 (d, 1H, J = 3.0 Hz, H_1), 7.36−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 26.8, 31.8, 43.4, 65.8, 73.4, 78.0, 100.9, 127.6, 129.6, 133.4, 135.6. Major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 9H), 1.75 (m, 1H, H_3), 2.07 (m, 1H, H_3), 2.28 (s, 6H), 2.58 (m, 1H, H_2), 3.73 (m, 2H, H_5), 3.94 (bs, 1H), 4.22 (m, 1H, H_4), 5.20 (d, 1H, J = 4.0 Hz, H_1), 7.33−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 26.8, 30. 8, 34.4, 67.3, 69.9, 79.2, 95.2, 127.6, 129.6, 133.3, 135.6.

To a solution of acetyl chloride (0.195 mL, 2.75 mmol) and pyridine (0.21 mL, 2.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added dropwise a dichloromethane solution (10 mL) of lactols **10** (1.00 g, 2.5 mmol). The reaction mixture was stirred for 4 h; the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH 97:3). First eluted product was a colorless oil which was identified as **11b** (0.784 g, 71%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9H), 1.86 (ddd, 1H, J = 7.8, 9.7, 13.5 Hz, H_3), 2.07 (s, 3H), 2.15 (ddd, 1H, J = 5.8, 7.8, 13.5 Hz, H_3), 2.26 (s, 6H), 3.15 (ddd, 1H, J = 2.4, 2.4, 7.8 Hz, H_2), 3.76 (dd, 1H, J = 5.2, 10.8 Hz, H_5), 3.84 (dd, 1H, J = 4.6, 10.8 Hz, H_5), 4.29 (dddd, 1H, J = 4.6, 5.2, 5.8, 9.7 Hz, H_4), 6.24 (d, 1H, J = 2.4 Hz, H_1) 7.37−7.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 21.3, 26.8, 30.4, 42.8, 65.1, 71.5, 79.8, 99.7, 127.6, 129.6, 133.3, 135.56, 135.59, 170.1; MS (FAB) m/z 442 (MH^+). Further eluted product was **11a** (0.265 g, 24%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 1.89 (ddd, 1H, J = 9.5, 11.5, 12.1 Hz, H_3), 1.96 (s, 3H), 2.20 (ddd, 1H, J = 6.3, 6.9, 11.5 Hz, H_3), 2.29 (s, 6H), 2.72 (ddd, 1H, J = 4.1, 6.9, 12.1 Hz, H_2), 3.66 (dd, 1H, J = 5.2, 10.6 Hz, H_5), 3.74 (dd, 1H, J = 5.4, 10.6 Hz, H_5), 4.31 (dddd, 1H, J = 5.2, 5.4, 6.3, 9.5 Hz, H_4), 6.25 (d, 1H, J = 4.1 Hz, H_1), 7.32−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 21.6, 26.7, 30.6, 44.9, 67.0, 69.2, 80.5, 95.2, 127.6, 129.6, 133.2, 133.3, 135.48, 135.53, 170.7; MS (FAB) m/z 442 (MH^+).

1-[(2*SR*,3*RS*,5*RS*)-3-(Dimethylamino)-5-(hydroxymethyl)tetrahydro-2-furanyl]-thymine (13a). Under a nitrogen atmosphere, *O,O′-bis*(trimethylsilyl)thymine (0.820 g, 3.0 mmol) and **11a** (0.265 g, 0.6 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). This solution was cooled to 0 °C, and $SnCl_4$ (1.0 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 9:1) to afford 1-[(2*SR*,3*RS*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]-oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanyl]thymine (**12a**) (0.292 g, 96%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9H), 1.90 (s, 3H), 2.09 (ddd, 1H, J = 6.2, 7.6, 12.1 Hz, $H_{3'a}$), 2.15 (ddd, 1H, J = 9.1, 10.2, 12.1 Hz, $H_{3'b}$), 2.34 (s, 6H), 3.38 (ddd, 1H, J = 7.3,7.6, 10.2 Hz, $H_{2'}$), 3.70 (dd, 1H, J = 4.0, 11.0 Hz, $H_{5'}$), 3.77 (dd, 1H, J = 4.0, 11.0 Hz, $H_{5'}$), 4.40 (dddd, 1H, J = 4.0, 4.0, 6.2, 9.1 Hz, $H_{4'}$), 6.04 (d, 1H, J = 7.3 Hz, $H_{1'}$), 7.05 (s, 1H, H_6), 7.36−7.68 (m, 10H), 9.73 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5, 19.2, 26.8, 42.3, 65.7, 69.5, 79.4, 87.1, 110.9, 127.7, 129.7, 133.2, 133.3, 135.57, 135.62, 136.2, 150.3, 163.9. Anal. Calcd for $C_{28}H_{37}N_3O_4Si$: C, 66.24; H, 7.35; N, 8.28. Found: C, 66.30; H, 7.36; N, 8.29.

To a THF solution (5 mL) of **12a** (0.173 g, 0.34 mmol) was added TBAF (0.375 mL, 0.37 mmol; 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At the end of this time, the solvent was removed, and the residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 9:1) give **13a** (0.091 g, 99%) as a white solid: mp 129−133 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.94 (d, 3H, J = 1.2 Hz), 2.13 (ddd, 1H, J = 6.1, 6.2, 10.4 Hz, $H_{3'a}$), 2.17 (ddd, 1H, J = 6.2, 6.2, 10.4 Hz, $H_{3'b}$), 2.38 (s, 6H), 2.63 (bs, 1H), 3.13 (ddd, 1H, J = 3.9, 6.2, 6.2 Hz, $H_{2'}$), 3.56 (dd, 1H, J = 3.5, 12.3 Hz, $H_{5'}$), 3.85 (dd, 1H, J = 2.6, 12.3 Hz, $H_{5'}$), 4.62 (dddd, 1H, J = 2.6, 3.5, 6.1, 6.2 Hz, $H_{4'}$), 6.07 (d, 1H, J = 3.9 Hz, $H_{1'}$), 7.08 (d, 1H, J = 1.2 Hz, H_6), 9.07 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7, 29.3, 29.7, 43.2, 64.2, 70.4, 81.3, 89.1, 111.0, 135.6, 150.2, 163.8. Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 54.03; H, 7.14; N, 15.62.

1-[(2*RS*,3*RS*,5*RS*)-3-(Dimethylamino)-5-(hydroxymethyl)tetrahydro-2-furanyl]-thymine (13b). Under a nitrogen atmosphere, *O,O′-bis*(trimethylsilyl)thymine (0.820 g, 3.0 mmol) and **11b** (0.265 g, 0.6 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). This solution was cooled to 0 °C, and $SnCl_4$ (1.0 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 9:1) to afford

1-[(2*RS*,3*RS*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]-oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanyl]thymine (**12b**) (0.298 g, 98%) as a white foam: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 9H), 1.91 (d, 3H, J = 0.9 Hz), 2.15−2.28 (m, 2H, $H_{3'}$), 2.44 (s, 6H), 3.66−3.84 (m, 3H, $H_{2'}$ and $H_{5'}$), 4.47 (m, 1H, $H_{4'}$), 6.03 (d, 1H, J = 6.3 Hz, $H_{1'}$), 7.13 (q, 1H, J = 0.9 Hz, H_6), 7.34−7.69 (m, 10H), 9.99 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4, 19.2, 26.8, 29.6, 41.7, 65.2, 69.3, 80.1, 87.9, 111.0, 127.7, 129.8, 133.0, 135.5, 137.1, 150.6, 164.1. Anal. Calcd for $C_{28}H_{37}N_3O_4Si$: C, 66.24; H, 7.35; N, 8.28. Found: C, 66.42; H, 7.33; N, 8.24.

To a THF solution (5 mL) of **12b** (0.290 g, 0.34 mmol) was added TBAF (0.375 mL, 0.37 mmol; 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At the end of this time, the solvent was removed, and the residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 9:1) give **13b** (0.092 g, 99%) as a white solid: mp 177−178 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.90 (d, 3H, J = 1.2 Hz), 2.05 (ddd, 1H, J = 9.0, 9.4, 12.7 Hz, $H_{3'a}$), 2.33 (ddd, 1H, J = 5.8, 7.4, 12.7 Hz, $H_{3'b}$), 2.46 (s, 6H), 3.54 (ddd, 1H, J = 5.8, 5.9, 9.0 Hz, $H_{2'}$), 3.55 (dd, 1H, J = 4.5, 12.2 Hz, $H_{5'}$), 3.72 (dd, 1H, J = 3.4, 12.2 Hz, $H_{5'}$), 4.54 (dddd, 1H, J = 3.4, 4.5, 7.4, 9.4 Hz, $H_{4'}$), 6.09 (d, 1H, J = 5.9 Hz, $H_{1'}$), 7.53 (q, 1H, J = 1.2 Hz, H_6); ^{13}C NMR (CD_3OD, 125 MHz) δ 12.4, 30.9, 43.4, 64.6, 71.3, 81.8, 89.0, 112.3, 138.37, 152.5, 163.7. Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.68; H, 7.13; N, 15.55.

5-Acetyloxymethyl-2,3-dimethyl-3-methoxycarbonyl isoxazolidines (15). A solution of *C*-methoxycarbonyl-*C*,*N*-dimethyl nitrone (**14**) (2.25 g, 17 mmol) in allyl acetate (40 mL) was heated at 75 °C, in a sealed tube, for 48 h. The reaction mixture was evaporated, and the residue was purified by column chromatography (cyclohexane/ethyl acetate 7:3) to give **15** in a 1.2:1 epimeric ratio (3.81 g, 97%) as a colorless oil. Major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 3H), 2.10 (s, 3H), 2.22 (dd, 1H, J = 3.6, 12.8 Hz, H_4), 2.65 (s, 3H), 2.91 (dd, 1H, J = 8.3, 12.8 Hz, H_4), 3.76 (s, 3H) 4.15 (m, 2H), 4.31 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 38.6, 41.9, 52.0, 65.1, 69.6, 73.9, 170.8, 173.1. Minor isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.82 (dd, 1H, J = 7.0, 12.6 Hz, H_4), 2.09 (s, 3H), 2.63 (s, 3H), 2.64 (m, 1H, H_4), 3.75 (s, 3H), 4.13 (m, 2H), 4.28 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.3, 30.6, 38.8, 40.9, 52.3, 65.7, 70.4, 74.2, 170.8, 172.3; MS (FAB) *m*/*z* 232 (MH^+).

(3*RS*,5*SR*)- and (3*SR*,5*SR*)-5-({[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)-3-methyldihydro-2(3*H*)-furanone (18a and 18b). A solution of **15** (3.00 g, 13 mmol) and methyl trifluoromethanesulfonate (1.75 mL, 15.6 mmol) in dry CCl_4 was stirred at 0 °C for 3 h. At the end of this time, the reaction mixture was evaporated under reduced pressure, and the residue, identified as an epimeric mixture of 5-[(acetyloxy)methyl]-3-metoxycarbonyl-2,2,3-trimethylisoxazolidinium trifluoromethanesulfonates (**16**) (100% yield, sticky oil), was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.93 (s, 3H), 1.97 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.41 (m, 1H), 2.63 (m, 1H), 2.94 (m, 1H), 3.28 (m, 1H), 3.61 (s, 6H), 3.63 (s, 6H), 3.93 (s, 3H) 3.96 (s, 3H), 4.22−4.37 (m, 4H), 5.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 20.8, 35.1, 36.2, 51.4, 51,7, 54, 7, 54.9, 55.2, 61.6, 62.1, 81.9, 83.5, 168.2, 169.0, 171.6, 172.1.

A solution of **16** (3.93 g, 10 mmol) in 50 mL of methanol was stirred under hydrogen atmosphere with 10% Pd on activated carbon for 36 h at 70 °C. After removal of catalyst by Celite filtration, to the filtrate was added 10 mL of a 10% $NaHCO_3$ aqueous solution. The solvent was evaporated under reduced pressure, and the residue was than purified by column chromatography ($CHCl_3$/MeOH 97:3) to give an epimeric mixture of 3-(dimethylamino)-5-(hydroxymethyl)-3-methyldihydro-2(3*H*)-furanones (**17**) (1.66 g, 96%) as a light yellow oil. Major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 3H), 1.96 (dd, 1H, J = 8.5, 14.0 Hz, H_4), 2.32 (s, 6H), 2.43 (dd, 1H, J = 7.8, 14.0 Hz, H_4), 3.59 (dd, 1H, J = 4.0, 12.5 Hz), 3.90 (dd, 1H, J = 2.5, 12.5 Hz), 4.60 (dddd, 1H, J = 2.5, 4.0, 7.8, 8.5 Hz, H_5), 4.73 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9, 33.1, 39.3, 63.5, 64.5, 77.8, 177.6. Minor isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 3H), 2.01 (dd, 1H, J = 7.5, 13.5 Hz, H_4), 2.35 (s, 6H), 2.48 (dd, 1H, J = 6.7, 13.5 Hz, H_4), 3.64 (dd, 1H, J = 3.5, 12.5 Hz), 3.95 (dd, 1H, J = 3.5, 12.5 Hz), 4.55 (dddd, 1H, J = 3.5, 3.5, 6.7, 7.5 Hz, H_5), 4.71 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.6, 32.0, 39.0, 63.2, 64.4, 77.1, 177.3.

A mixture of **17** (2.73 g, 15.8 mmol), *tert*-butyldiphenylsilyl chloride (TBDPSCl, 4.53 mL, 17.4 mmol), and imidazole (2.37 g, 34.8 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 3 h at 0 °C. The solvent was evaporated, and the residue was purified by silica gel column (cyclohexane/ethyl acetate 1:1). First eluted fraction was **18a** (3.05 g, 47%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.37 (s, 3H), 2.06 (dd, 1H, J = 8.0, 13.5 Hz, H_{4a}), 2.32 (s, 6H), 2.40 (dd, 1H, J = 7.7, 13.5 Hz, H_{4b}), 3.66 (dd, 1H, J = 3.8, 11.8, Hz), 3.86 (dd, 1H, J = 3.5, 11.8 Hz), 4.54 (dddd, 1H, J = 3.5, 3.8, 7.7, 8.0 Hz, H_5), 7.38−7.68 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 20.2, 26.7, 33.6, 39.4, 64.3, 64.6, 77.1, 127.8, 129.8, 132.7, 133.0, 135.5, 135.6, 177.2. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.31; H, 8.07; N, 3.40. Further elution gave **18b** (2.79 g, 43%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.45 (s, 3H), 1.77 (dd, 1H, J = 6.9, 12.7 Hz, H_{4a}), 2.34 (s, 6H), 2.52 (dd, 1H, J = 10.1, 12.7 Hz, H_{4b}), 3.73 (dd, 1H, J = 4.3, 11.5, Hz), 3.91 (dd, 1H, J = 3.5, 11.5 Hz), 4.43 (dddd, 1H, J = 3.5, 4.3, 6.9, 10.1 Hz, H_5), 7.40−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 22.2, 26.7, 29.5, 39.4, 64.3, 65.3, 76.3, 127.8, 129.9, 132.7, 132.9, 135.56, 135.64, 177.9. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.09; H, 8.06; N, 3.40.

1-[(2*RS*,3*RS*,5*SR*)-3-(Dimethylamino)-5-(hydroxymethyl)-3-methyltetrahydro-2-furanyl]-thymine (22a). To a stirred solution of **18a** (2.06 g, 5 mmol) in anhydrous toluene (10 mL) at −78 °C under nitrogen was added DIBALH (10 mL, 1.0 M solution in toluene) dropwise while the reaction temperature was maintained below −70 °C. The reaction mixture was stirred for 3h and then was quenched with ethyl acetate (1 mL). The mixture was left to warm to room temperature, water (1 mL) was added, and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 9:1) to afford (2*SR*,3*RS*,5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanol (**19a**) (1.78 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03 (s, 3H), 1.06 (s, 9H), 1.66 (dd, 1H, J = 4.3, 12.3 Hz, H_{3a}) 2.07 (dd, 1H, J = 10.0, 12.3 Hz, H_{3b}), 2.24 (s, 6H), 3.66 (dd, 1H, J = 5.4, 10.6 Hz, H_5), 3.72 (dd, 1H, J = 4.7, 10.6 Hz, H_5), 4.42

(dddd, 1H, J = 4.3, 4.7, 5.4, 10.0 Hz, H_4), 4.90 (s, 1H, H_1), 5.08 (bs, 1H), 7.34−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.3, 19.2, 26.8, 37.8, 40.1, 65.9, 68.1, 77.8, 101.2, 127.6, 129.6, 133.3, 135.6.

To a solution of acetyl chloride (0.195 mL, 2.75 mmol) and pyridine (0.21 mL, 2.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added dropwise a dichloromethane solution (10 mL) of lactol **19a** (1.03 g, 2.5 mmol). The reaction mixture was stirred for 4 h; the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH 95:5) to give a colorless oil which was identified as (2*RS*,3*RS*,5*SR*)-5-([1-(*tert*-butyl)-1,1-diphenylsilyl]oxymethyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanyl acetate (**20a**) (1.00 g, 88%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 9H), 1.34 (s, 3H), 1.97 (dd, 1H, J = 4.6, 12.3 Hz, H_{3a}), 2.30 (s, 3H), 2.55 (s, 6H), 2.59 (dd, 1H, J = 9.3, 12.3 Hz, H_{3b}), 3.67 (dd, 1H, J = 4.0, 11.3 Hz, H_5), 3.77 (dd, 1H, J = 4.3, 11.3 Hz, H_5), 4.53 (dddd, 1H, J = 4.0, 4.3, 4.6, 9.3 Hz, H_4), 6.05 (s, 1H, H_1) 7.34−7.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 19.1, 21.5, 26.7, 35.6, 40.1, 64.4, 69.7, 79.1, 98.1, 127.7, 129.78, 129.82, 132.7, 135.5, 170.6; MS (FAB) m/z 456 (MH^+). Under a nitrogen atmosphere, *O*,*O*′-*bis*(trimethilsilyl)thymine (0.820 g, 3.0 mmol) and **20a** (0.273 g, 0.6 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). This solution was cooled to 0 °C, and $SnCl_4$ (1.0 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane/ethyl acetate 2:8) to afford 1-[(2*RS*,3*RS*,5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]-oxy}methyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanyl]-thymine (**21a**) (0.288 g, 92%) as a white solid: mp 68−70 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (s, 3H), 1.11 (s, 9H), 1.48 (d, 3H, J = 1.2 Hz), 1.78 (dd, 1H, J = 11.6, 13.7 Hz, $H_{3'}$), 2.23 (dd, 1H, J = 4.4, 13.7 Hz, $H_{3'}$), 2.38 (s, 6H), 3.85 (dd, 1H, J = 3.5, 11.6 Hz, $H_{5'}$), 4.14 (dd, 1H, J = 2.6, 11.6 Hz, $H_{5'}$), 4.35 (dddd, 1H, J = 2.6, 3.5, 4.4, 11.6 Hz, $H_{4'}$), 6.13 (s, 1H, $H_{1'}$), 7.33−7.45 (m, 6H), 7.54 (q, 1H, J = 1.2 Hz, H_6), 7.64−7.72 (m, 4H), 9.13 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.9, 19.5, 27.1, 36.7, 39.1, 64.2, 70.3, 79.2, 90.4, 110.3, 127.86, 127.90, 129.92, 130.0, 132.8, 133.4, 135.3, 135.4, 135.7, 150.6, 164.0. Anal. Calcd for $C_{29}H_{39}N_3O_4Si$: C, 66.76; H, 7.53; N, 8.05. Found: C, 66.58; H, 7.53; N, 8.06.

To a THF solution (5 mL) of **21a** (0.177 g, 0.34 mmol) was added TBAF (0.375 mL, 0.37 mmol; 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At the end of this time, the solvent was removed, and the residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 9:1) give **22a** (0.095 g, 99%) as a white solid: mp 135−138 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (s, 3H), 1.86 (dd, 1H, J = 11.8, 14.1 Hz, $H_{3'}$), 1.89 (d, 3H, J = 0.8 Hz), 2.21 (dd, 1H, J = 4.6, 14.1 Hz, $H_{3'}$), 2.39 (s, 6H), 2.86 (bs, 1H), 3.77 (dd, 1H, J = 3.4, 12.3 Hz, $H_{5'}$), 4.14 (dd, 1H, J = 2.4, 12.3 Hz, $H_{5'}$), 4.36 (dddd, 1H, J = 2.4, 3.4, 4.6, 11.8 Hz, $H_{4'}$), 6.14 (s, 1H, $H_{1'}$), 8.06 (q, 1H, J = 0.8 Hz, H_6), 9.27 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.8, 12.6, 35.5, 39.0, 61.9, 70.9, 79.4, 90.0, 110.0, 136.7, 150.7, 164.2. Anal. Calcd for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 54.99; H, 7.48; N, 14.80.

1-[(2*SR*,3*SR*,5*SR*)-3-(Dimethylamino)-5-(hydroxymethyl)-3-methyltetrahydro-2-furanyl]-thymine (22b). To a stirred solution of **18b** (2.06 g, 5 mmol) in anhydrous toluene (10 mL) at −78 °C under nitrogen was added DIBALH (10 mL, 1.0 M solution in toluene) dropwise while the reaction temperature was maintained below −70 °C. The reaction mixture was stirred for 3h and then was quenched with ethyl acetate (1 mL). The mixture was left to warm to room temperature, water (1 mL) was added, and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95:5) to afford (2*RS*,3*SR*, 5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanol (**19b**) (1.88 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 3H), 1.06 (s, 9H), 1.73 (dd, 1H, J = 9.5, 11.5 Hz, H_{3a}) 1.80 (dd, 1H, J = 6.8, 11.5 Hz, H_{3b}), 2.20 (s, 6H), 3.66 (dd, 1H, J = 6.5, 10.5 Hz, H_5), 3.85 (dd, 1H, J = 5.5, 10.5 Hz, H_5), 4.25 (dddd, 1H, J = 5.5, 6.5, 6.8, 9.5 Hz, H_4), 4.83 (s, 1H, H_1), 4.85 (bs, 1H), 7.35−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.7, 19.2, 26.8, 39.5, 39.7, 68.1, 68.1, 79.5, 100.9, 127.5, 129.5, 133.5, 133.6, 135.54, 135.56.

To a solution of acetyl chloride (0.195 mL, 2.75 mmol) and pyridine (0.21 mL, 2.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added dropwise a dichloromethane solution (10 mL) of lactol **19b** (1.03 g, 2.5 mmol). The reaction mixture was stirred for 4 h; the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:7) to give a colorless oil which was identified as (2*SR*,3*SR*,5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanyl acetate (**20b**) (0.968 g, 85%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 1.10 (s, 3H), 1.86 (dd, 1H, J = 10.5, 11.5 Hz, H_3), 1.94 (s, 3H), 1.97 (dd, 1H, J = 6.5, 11.5 Hz, H_3), 2.20 (s, 6H), 3.62 (dd, 1H, J = 5.5, 10.0 Hz, H_5), 3.75 (dd, 1H, J = 6.1, 10.0 Hz, H_5), 4.34 (dddd, 1H, J = 5.5, 6.1, 6.5, 10.0 Hz, H_4), 5.94 (s, 1H, H_1), 7.35−7.68 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2, 19.1, 21.6, 26.8, 39.2, 40.1, 67.3, 67.9, 80.6, 100.1, 127.6, 129.6, 133.3, 133.5, 135.47, 135.50, 170.6; MS (FAB) m/z 456 (MH^+). Under a nitrogen atmosphere, *O*,*O*′-*bis*(trimethilsilyl)thymine (0.820 g, 3.0 mmol) and **20b** (0.273 g, 0.6 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). This solution was cooled to 0 °C, and $SnCl_4$ (1.0 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95:5) to afford 1-[(2*SR*,3*SR*,5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)-3-methyltetrahydro-2-furanyl]-thymine (**21b**) (0.282 g, 90%) as a white solid: mp 165−167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (s,3H), 1.07 (s, 9H), 1.77 (dd, 1H, J = 7.5, 13.5 Hz, $H_{3'a}$), 1.94 (s, 3H), 2.27 (s, 6H), 2.42 (dd, 1H, J = 6.0, 13.5 Hz, $H_{3'b}$), 3.76 (dd, 1H, J = 5.0, 10.0 Hz, $H_{5'}$), 3.82 (dd, 1H, J = 5.0, 10.0 Hz, $H_{5'}$), 4.41

(dddd, 1H, J = 5.0, 5.0, 6.0, 7.5 Hz, $H_{4'}$), 616 (s, 1H, $H_{1'}$), 7.08 (s, 1H, H_6), 7.36−7.67 (m, 10H), 9.33 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7, 13.1, 19.2, 26.8, 37.1, 39.5, 65.9, 69.1, 79.4, 90.3, 110.1, 127.6, 129.7, 133.3, 135.5, 136.1, 150.5, 163.9. Anal. Calcd for $C_{29}H_{39}N_3O_4Si$: C, 66.76; H, 7.53; N, 8.05. Found: C, 66.90; H, 7.56; N, 8.08.

To a THF solution (5 mL) of **21b** (0.177 g, 0.34 mmol) was added TBAF (0.375 mL, 0.37 mmol; 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At the end of this time, the solvent was removed, and the residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 95:5) give **22b** (0.096 g, 100%) as a white solid: mp 185−188 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03 (s, 3H), 1.95 (d, 3H, J = 1.0 Hz), 1.96 (dd, 1H, J = 9.6, 14.4 Hz, $H_{3'a}$), 2.43 (s, 6H), 2.47 (dd, 1H, J = 2.2, 14.4 Hz, $H_{3'b}$), 3.56 (dd, 1H, J = 2.0, 12.0 Hz, $H_{5'}$), 3.88 (dd, 1H, J = 2.8, 12.0 Hz, $H_{5'}$), 4.73 (dddd, 1H, J = 2.0, 2.2, 2.8, 9.6 Hz, $H_{4'}$), 5.63 (bs, 1H), 6.43 (s, 1H, $H_{1'}$), 7.02 (q, 1H, J = 1.0 Hz, H_6), 10.17 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6, 12.8, 37.9, 39.2, 64.3, 70.5, 81.3, 90.7, 110.8, 134.9, 150.6, 164.1. Anal. Calcd for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.28; H, 7.47; N, 14.86.

1-[(2*SR*,5*RS*)-5-(Hydroxymethyl)-2,5-dihydro-2-furanyl]-thymine (24).[5b,9b] To an ice-cooled solution containing 0.092 g (0.2 mmol) of **12a** in 2 mL of CH_2Cl_2 was added a solution containing 0.050 g (0.29 mmol) of *m*-CPBA in 5 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred for 3 h at 25 °C and an additional 0.5 h at 50 °C, extracted with 10% Na_2CO_3 solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to leave behind a white foam which was subjected to silica gel chromatography (CH_2Cl_2/MeOH 95:5), giving a thick syrup identified as compound 1-[(2*SR*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-2,5-dihydro-2-furanyl]-thymine (**23**) (0.054 g, 60%) according to literature data.

Using a procedure similar to that used for **22b**, **23** (0.050 g, 0.11 mmol) was converted to a white solid (mp 155−157 °C) which was identified as **24** (0.023 g, 95%).[5b,9b]

1-[(2*RS*,5*SR*)-5-(Hydroxymethyl)-3-methyl-2,5-dihydro-2-furanyl]-thymine (26). To an ice-cooled solution containing 0.104 g (0.2 mmol) of **21a** in 2 mL of CH_2Cl_2 was added a solution containing 0.050 g (0.29 mmol) of *m*-CPBA in 5 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred for 3 h at 25 °C and an additional 0.5 h at 50 °C, extracted with 10% $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to leave behind a thick syrup which was subjected to silica gel chromatography (CH_2Cl_2/MeOH 97:3), giving a white foam identified as 1-[(2*RS*,5*SR*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-methyl-2,5-dihydro-2-furanyl]-thymine (**25**) (0.062 g, 65%) according to its spectral data: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 9H), 1.46 (d, 3H, J = 1.3 Hz), 1.70 (m, 3H), 3.84 (dd, 1H, J = 4.4, 11.3 Hz, $H_{5'}$), 3.87 (dd, 1H, J = 4.0, 11.3 Hz, $H_{5'}$), 4.86 (m, 1H, $H_{4'}$), 5.93 (m, 1H, $H_{3'}$), 6.83 (m, 1H, $H_{1'}$), 7.05 (q, 1H, J = 1.3 Hz, H_6), 7.32−7.68 (m, 10H), 8.57 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.6, 11.9, 19.4, 27.0, 65.9, 86.0, 91.1, 111.6, 127.8, 128.3, 129.9, 130.0, 132.9, 133.4, 135.0, 135.36, 135.40, 150.6, 163.5. Anal. Calcd for $C_{27}H_{32}N_2O_4Si$: C, 68.04; H, 6.77; N, 5.88. Found: C, 67.99; H, 6.79; N, 5.87.

Using a procedure similar to that used for **22b**, **25** (0.050 g, 0.105 mmol) was converted to a white foam which was identified as **26** (0.025 g, 99%).[9a]

***tert*-Butyl[(4-methyl-2-furyl)methoxy]diphenylsilane (29)**. To an ice-cooled solution containing 0.165 g (0.4 mmol) of **18a** in 2 mL of CH_2Cl_2 was added a solution containing 0.100 g (0.58 mmol) of *m*-CPBA in 5 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred for additional 3 h at 25 °C, extracted with 10% $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to leave behind a oil which was subjected to silica gel chromatography (cyclohexane/ethyl acetate 85:15), giving a colorless oil identified as (5*SR*)-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-methyl-2(5*H*)-furanone (**27**) (0.145 g, 99%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 9H), 1.92 (s, 3H), 3.86 (m, 2H), 4.92 (m, 4H), 6.95 (m, 1H), 7.36−7.66 (m, 10H); MS (FAB) m/z 367 (MH^+). Anal. Calcd for $C_{22}H_{26}O_3Si$: C, 72.09; H, 7.15. Found: C, 71.97; H, 7.13.

To a stirred solution of **27** (0.092 g, 0.25 mmol) in anhydrous toluene (2 mL) at −78 °C under nitrogen was added DIBALH (0.5 mL, 1.0 M solution in toluene) dropwise while the reaction temperature was maintained below −70 °C. The reaction mixture was stirred for 3h and then was quenched with ethyl acetate (0.2 mL). The mixture was left to warm to room temperature, water (0.2 mL) was added, and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (cyclohexane/ethyl acetate 8:2) to afford an anomeric mixture (1.5:1) of 5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]-oxy}methyl)-3-methyl-2,5-dihydro-2-furanol (**28**) (0.080 g, 87%) as a white solid: mp 102−104 °C. Major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 9H), 1.88 (s, 3H), 3.29 (d, 1H, J = 11.4 Hz, OH) 3.52 (dd, 1H, J = 2.1, 11.1 Hz, H_5), 3.82 (dd, 1H, J = 3.3, 11.1 Hz, H_5), 4.73 (dd, 1H, J = 2.1, 3.3 Hz, H_4), 5.46 (s, 1H, H_3), 5.65 (d, 1H, J = 11.4 Hz, H_1), 7.36−7.68 (m, 10H). Minor isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9H), 1.81 (s, 3H), 2.76 (d, 1H, J = 8.7 Hz, OH) 3.68 (m, 2H, H_5), 4.94 (m, 1H, H_4), 5.67 (m, 1H, H_3), 5.83 (dd, 1H, J = 3.9, 8.7 Hz, H_1), 7.36−7.68 (m, 10H).

To a solution of acetyl chloride (0.195 mL, 2.75 mmol) and pyridine (0.21 mL, 2.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added dropwise a dichloromethane solution (10 mL) of **28** (0.916 g, 2.5 mmol). The reaction mixture was stirred for 4 h; the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 95:5) to give a white foam which was identified as **29** (0.859 g, 98%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9H), 2.01 (s, 3H), 4.59 (s, 2H), 2.30 (s, 3H), 6.04 (s, 1H), 7.17 (s, 1H), 7.38−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 20.0, 27.5, 59.7, 110.7, 121.1, 128.4, 130.4, 134.1, 136.4, 139.4, 154.7; MS (FAB) m/z 351 (MH^+). Anal. Calcd for $C_{22}H_{26}O_2Si$: C, 75.38; H, 7.48. Found: C, 75.31; H, 7.51.

(2*SR*,3*SR*,5*RS*)- and (2*RS*,3*SR*,5*RS*)-5-({[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanyl acetate (32a and 32b). To a stirred solution of **9** (1.99 g, 5 mmol) in dry benzene was added 1.07 g (7.0 mmol) of DBU under nitrogen atmosphere, and the mixture was then heated at 80 °C for 4 h. Evaporation of the solvent left a residue which, purified by flash chromatography, gave a clear oil (1.79

g, 90%) identified as (3*SR*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)dihydro-2(3*H*)-furanone (**30**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 2.31 (m, 2H, H_4), 2.41 (s, 6H), 3.65 (dd, 1H, J = 2.7, 11.2 Hz), 3.88 (dd, 1H, J = 2.7, 11.2 Hz), 3.92 (dd, 1H, J = 9.1, 9.1 Hz, H_3), 4.55 (m, 1H, H_5) 7.38−7.66 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 25.6, 26.7, 41.5, 63.0, 65.7, 77.2, 127.8, 129.9, 132.2, 132.7, 135.4, 135.6, 175.3. Anal. Calcd for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.43; H, 7.89; N, 3.51.

To a stirred solution of **30** (1.99 g, 5 mmol) in anhydrous toluene (10 mL) at −78 °C under nitrogen was added DIBALH (10 mL, 1.0 M solution in toluene) dropwise while the reaction temperature was mantained below −70 °C. The reaction mixture was stirred for 3h and then was quenched with ethyl acetate (1 mL). The mixture was left to warm to room temperature, water (1 mL) was added, and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95:5) to afford an anomeric mixure (3:1) of (2*SR*,3*SR*,5*RS*)- and (2*RS*,3*SR*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}methyl)-3-(dimethylamino)tetrahydro-2-furanol (**31**) (1.80 g, 90%). Minor isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9H), 2.11 (m, 2H, H_3), 2.26 (s, 6H), 2.59 (ddd, 1H, J = 4.0, 7.5, 11.5 Hz, H_2), 3.70 (dd, 1H, J = 5.5, 10.5 Hz, H_5), 3.77 (dd, 1H, J = 4.5, 10.5 Hz, H_5), 4.19 (bs, 1H), 4.21 (m, 1H, H_4), 5.21 (d, 1H, J = 4.0 Hz, H_1), 7.39−7.69 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.8, 26.8, 43.4, 67.4, 70.0, 79.2, 96.1, 100.8, 127.7, 129.6, 133.3, 135.5. Major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 2.03 (m, 2H, H_3), 2.29 (s, 6H), 2.74 (ddd, 1H, J = 4.0, 8.5, 10.0 Hz, H_2), 3.60 (dd, 1H, J = 4.0, 11.0 Hz, H_5), 3.66 (dd, 1H, J = 4.5, 11.0 Hz, H_5), 4.18 (bs, 1H), 4.39 (m, 1H, H_4), 5.30 (d, 1H, J = 4.0 Hz, H_1), 7.37−7.68 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 26.8, 43.4, 65.8, 67.4, 78.1, 96.4, 100.5, 127.6, 129.9, 133.4, 135.6.

To a solution of acetyl chloride (0.195 mL, 2.75 mmol) and pyridine (0.21 mL, 2.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added dropwise a dichloromethane solution (10 mL) of lactols **31** (1.00 g, 2.5 mmol). The reaction mixture was stirred for 4 h; the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH 97:3). First eluted product was a colorless oil which was identified as **32b** (0.243 g, 22%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 2.00 (s, 3H), 2.18 (m, 2H, H_3), 2.30 (s, 6H), 2.74 (m, 1H, H_2), 3.66 (dd, 1H, J = 5.0, 10.5 Hz, H_5), 3.74 (dd, 1H, J = 4.5, 10.5 Hz, H_5), 4.31 (m, 1H, H_4), 6.25 (d, 1H, J = 3.5 Hz, H_1), 7.38−7.67 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0, 21.2, 26.8, 30.4, 42.4, 67.1 69.2, 81.8, 95.1, 127.6, 127.7, 129.6, 133.4, 135.5, 170.5. MS (FAB) m/z 442 (MH^+). Further eluted product was **32a** (0.729 g, 66%), as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9H), 2.15 (s, 3H), 2.20 (m, 2H, H_3), 2.34 (s, 6H), 2.98 (m, 1H, H_2), 3.62 (dd, 1H, J = 3.0, 11.0 Hz, H_5), 3.74 (dd, 1H, J = 2.5, 11.0 Hz, H_5), 4.43 (m, 1H, H_4), 6.32 (d, 1H, J = 4.0 Hz, H_1) 7.37−7.67 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 21.4, 26.8, 29.3, 44.8, 65.7, 68.5, 79.5, 95.5, 127.6, 127.7, 129.7, 133.0, 133.2, 135.5, 170.8; MS (FAB) m/z 442 (MH^+).

1-[(2*SR*,3*SR*,5*RS*)-3-(Dimethylamino)-5-(hydroxymethyl)tetrahydro-2-furanyl]-thymine (34a). Under a nitrogen atmosphere, *O*,*O*′-*bis*(trimethilsilyl)thymine (0.820 g, 3.0 mmol) and **32a** (0.265 g, 0.6 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). This solution was cooled to 0 °C, and $SnCl_4$ (1.0 mmol) was added. The mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was extracted further with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95:5) to afford (1-[(2*SR*,3*SR*,5*RS*)-5-({[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy}-methyl)-3-(dimethylamino)tetrahydro-2-furanyl]-thymine (**33a**) (0.265 g, 87%) as a white foam: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (s, 9H), 1.60 (d, 3H, J = 1.0 Hz), 2.22 (m, 2H, $H_{3'}$), 2.38 (s, 6H), 3.29 (m, 1H, $H_{2'}$), 3.68 (dd, 1H, J = 2.8, 11.4 Hz, $H_{5'}$), 3.99 (dd, 1H, J = 2.5, 11.4 Hz, $H_{5'}$), 4.26 (m, 1H, $H_{4'}$), 6.13 (d, 1H, J = 6.4 Hz, $H_{1'}$), 7.34−7.70 (m, 10H), 7.38 (q, 1H, J = 1.0 Hz, H_6), 9.35 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.0, 19.4, 27.0, 27.5, 42.5, 65.7, 68.9, 78.0, 85.6, 111.3, 127.7, 127.9, 129.9, 130.0, 132.5, 133.1, 135.3, 135.5, 150.4, 163.8. Anal. Calcd for $C_{28}H_{37}N_3O_4Si$: C, 66.24; H, 7.35; N, 8.28. Found: C, 65.99; H, 7.33; N, 8.28.

To a THF solution (5 mL) of **33a** (0.173 g, 0.34 mmol) was added TBAF (0.375 mL, 0.37 mmol; 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At the end of this time, the solvent was removed, and the residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 9:1) give **34a** (0.091 g, 99%) as a white foam: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90 (d, 3H, J = 1.0 Hz), 2.18 (m, 2H, $H_{3'}$), 2.32 (s, 6H), 3.03 (bs, 1H), 3.31 (m, 1H, $H_{2'}$), 3.66 (dd, 1H, J = 3.2, 12.2 Hz, $H_{5'}$), 3.91 (dd, 1H, J = 2.6, 12.2 Hz, $H_{5'}$), 4.28 (m, 1H, $H_{4'}$), 5.93 (d, 1H, J = 5.6 Hz, $H_{1'}$), 7.45 (q, 1H, J = 1.0 Hz, H_6), 9.63 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.5, 27.8, 42.6, 63.9, 69.0, 79.3, 88.7, 111.0, 137.2, 150.5, 164.0. Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.31; H, 7.10; N, 15.59.

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