Asymmetric Synthesis of 4′-Ethoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides by Palladium-Catalyzed Kinetic Discrimination between the Corresponding Diastereoisomeric Lactol Acetates

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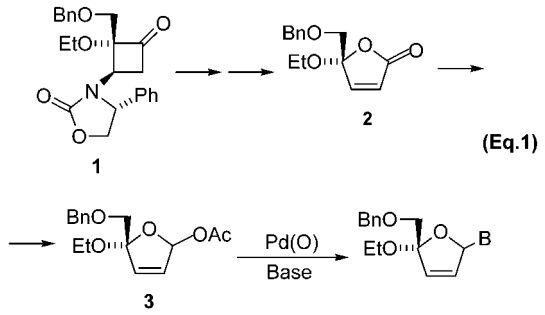
4′-Substituted nucleoside analogues have been synthesized using palladium-catalyzed asymmetric allylic amination conditions. A kinetic discrimination between the diastereomeric lactol acetates (**3**) produced the desired aminated products (**6a**−**d**) and recovered acetate (α-**3**) in high yields and <97:3 diastereoselectivity. Epimerization of the recovered lactol acetate (α-**3**) produced a 60:40 α/β mixture of (**3**), which could be resubjected, in principle, to the palladium-catalyzed asymmetric allylic amination conditions.

Introduction

Modified nucleoside analogues having substituents at the 4′-position are of interest as antiviral agents because some members of this class can act both as reverse transcriptase inhibitors as well as DNA chain terminators, with a mechanism of action different from AZT.[1] In addition, some 4′-substituted nucleoside analogues act as selective agonists or antagonists at adenosine receptors.[2] Most syntheses of 4′-substituted nucleosides involve 4′ functionalizations of intact nucleosides,[3] although de novo syntheses[4] offer more flexibility in regards to both functionality and stereochemistry.

Research in these laboratories has centered on the development of de novo synthetic approaches to nucleoside analogues[5] from optically active butenolides,[6] derived from chromium carbene complex photochemistry.[7] This chemistry can provide either enantiomer of the butenolide bearing the incipient quaternary nucleoside 4′ position, a feature of some significance in light of recent evidence suggesting that unnatural L-enantiomers of nucleoside analogues often maintain high levels of antiviral activity but have reduced toxicity.[8] The approach envisioned (eq 1) involved conversion of the butenolide to a lactol acetate and the use of π-allylpalladium chemistry for introduction of the nucleoside bases.



Palladium-catalyzed amination of allyl acetates has been extensively developed as a synthetic tool.[9] The process is very general and is efficient for a broad range of substrates and amines. The ability to induce asymmetry into these reactions by use of chiral ligands[10] has greatly expanded the utility of this process. By far the bulk of this work has been directed toward the desymmetrization of meso substrates,[11] or of meso-π-allyl

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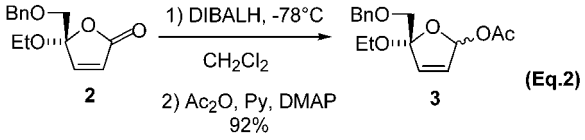
complex intermediates.[12] Kinetic[13] and dynamic kinetic[14] resolution of racemic allyl acetates and carbonates can also be efficiently achieved using appropriate chiral ligands.

Allylic geminal dicarboxylates[15] (acylals) and 4-carboxybutenolides[16] (5-acyloxy-2(5*H*)-furanones) are special cases in that the reacting allylic terminus is in the aldehyde oxidation state and bears two enantiotopic leaving groups. These also are reactive toward palladium-catalyzed nucleophilic attack, and high asymmetric induction has recently been achieved with the former class of compounds.[17] Given this extensive background, lactol acetate **3** seemed a promising candidate for palladium-catalyzed introduction of nucleoside bases with some degree of stereocontrol. Below are described experiments addressing this issue.

Results and Discussion

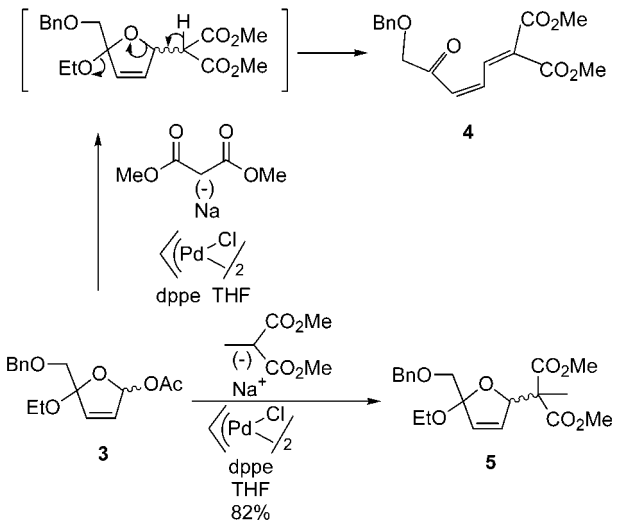
Lactol acetate **3** was made by reduction of butenolide **2**[6] using diisobutylaluminum hydride. Because of the leaving group (OEt) at the 4-position of butenolide **2**, the lactol itself was unstable and underwent a facile ring opening to the open-chain keto aldehyde. The procedure of Rhychnovsky,[18] which involves low-temperature trapping of the incipient lactol, proved effective, giving **3** in reproducible yields of 85−95%. The resident chiral quaternary center had *no* influence on the stereochemical outcome of this reduction, and an inseparable ≈1:1 mixture of α- and *β*- acetoxy diastereoisomers was obtained (eq 2).

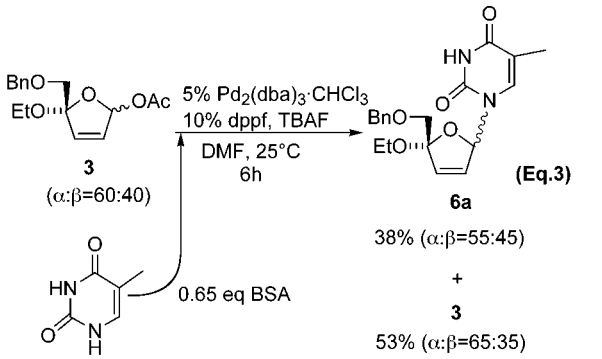


To probe the general reactivity of **3** toward *π*-allylpalladium chemistry, reaction with dimethyl malonate was attempted (Scheme 1). Only ring-opened product **4**, from overall loss of ethanol was observed.[19] Use of dimethyl methylmalonate led to the expected alkylation product **5** (eq 3), as a 1:1 mixture of C-1 epimers.

Next, the viability of nucleoside bases as nucleophiles was examined. Since solubility of these in organic solvents is low, they were first silylated in situ to bring them into solution and then released by treatment with TBAF after addition to the substrate/catalyst mixture. The effect of the resident chiral quaternary center on selectivity between the two diastereoisomeric α and *β* acetates was probed by using the achiral ligand dppf. As anticipated, the inherent lack of conformational rigidity of five membered rings coupled with the 1,3 disposition of the chiral centers resulted in little if any diastereoselectivity (eq 3). Because the diastereoisomers of both **3** and **6** are inseparable and our interest lies with the *β*-anomer of for nucleoside analogue chemistry,[20] diastereoselective amination of **3** was next examined.

Scheme 1





Induction of asymmetry into palladium-catalyzed reactions of allylic substrates is a highly active field, with new chiral ligands being reported almost on a daily basis.[21] One of the most extensively studied and broadly useful ligands for these processes is the *trans*-1,2-cyclohexanediamine-based ligand **7** of Trost,[10] which is highly effective in very wide range of reaction types. In

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(19) A similar elimination was observed in the reaction of dimethyl malonate with the gem diacetate of cinnamaldehyde. See ref 15b.

(20) It has been shown that both α and *β* anomers of nucleoside analogues are of biological interest. Pélicano, H.; Pierra, C.; Eriksson, S.; Gosselin, G.; Imbach, J. L.; Maury, G.; *J. Med. Chem.* **1997**, *40*, 3969−3973. (b). Van Draanen, N. A.; Tisdale, M.; Parry, N. R.; Jansen, R.; Dornsife, R. E.; Tuttle, J. V.; Averett, D. R.; Koszalka, G. W. *Antimicrob. Agents Chemother.* **1994**, *38*, 868−871. (c) Migawa, M, T.; Girardet, J.-L.; Walker, J. A., II; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242−1251.

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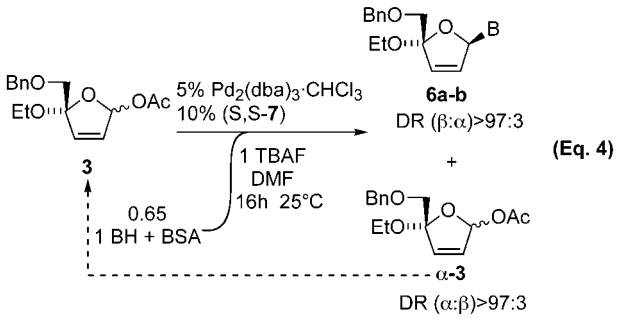
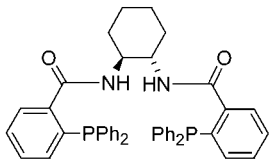
Table 1. Kinetic Diastereodifferentiations of α/β-3 To Produce 4′-Ethoxy Nucleoside Analogs 6a−d (eq 4)

base	product	yield (%)[a]	**3**α yield (%)[a]
thymine	**6a**[b]	49	41
cytosine	**6b**	51	44
uracil[c]	**6c**	49	44
adenine[d]	**6d**	38	39

[a] Yields are for isolated product purified by silica gel column chromatograph. [b] Stereochemistry was confirmed by an X-ray crystal structure. See Supporting Information for details. [c] The reaction was run at 0 °C. [d] The α:β ratio of **3** was 45:55.

contrast to these *enantioselective* processes, what is needed in the context of these studies is kinetic *diastereoselectivity* for the β-acetate, coupled with equilibration of the unreacted α-acetate (eq 4).





(*S*,*S*) Ligand **7** proved highly effective in promoting selective amination of β-**3** by a range of purine and pyrimidine bases, to produce β-4′-substituted nucleoside analogues. Excellent yields of recovered α-**3** were also obtained (Table 1).

Both the products **6a**−**d** and recovered starting material α-**3** were diastereoisomerically pure by H^1 NMR spectroscopy. Only guanine failed to react effectively. Although β-**3** was completely consumed and α-**3** was recovered in excellent yield, the base-containing products were obtained as an inseparable mixture of several components. Of the bases, uracil was by far the most reactive, converting β-**3** to **6c** in less than 3h at 0 °C. (When run at room temperature, some conversion of α-**3** to α-**6c** was noted.)

Because α- and β-**3** are diastereoismers rather than enantiomers, the selectivity of *R*,*R*-**7** need not mirror the selectivity of *S*,*S*-**7**. Indeed in the reaction of **3** with thymine, *R*,*R*-**7** was much less selective for α-**3** than *S*,*S*-**7** was for β-**3**. Well before complete consumption of α-**3**, the β-diastereoisomer began to convert, giving a mixture of α- and β-**6a**.

Equilibration of α-**3** back to a mixture of α- and β-isomers would allow recycling of **3** with the eventual conversion of both isomers to β-**6**. If this equilibration could be carried out concurrent with the coupling, a one-pot conversion of both diastereomeric acetates to the β-nucleoside analogue would be possible. Unfortunately, this could not be achieved. Subsequent epimerization of the remaining α-acetate also proved difficult, with a wide range of conditions[22] resulting either in no reaction or in decomposition. Finally, treatment of α-**3** with zinc acetate in acetic acid at 35 °C produced a 60:40 mixture of α/β anomers, which could be, in principle, resubjected to the amination procedure to produce more β-nucleoside, allowing the complete conversion of a 1:1 mixture of α- and β-**3** to the exclusively β-nucleoside.

Conclusion

In summary, a synthesis of 4′-ethoxy-2′,3′-unsaturated nucleoside analogues via diastereoselective, palladium-catalyzed amination of the corresponding lactol acetate has been developed. Equilibration of the undesired diastereoisomer of the lactol acetate allowed the conversion of a 1:1 mixture of α- and β-anomeric lactol acetates to a single β-anomer of the nucleoside analogue.

Experimental Section

General Methods and Materials. THF was distilled from sodium−benzophenone ketyl, and DMF was distilled from $MgSO_4$. Commercially available reagents were used as received. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ unless otherwise noted and chemical shifts are given in ppm relative to $CDCl_3$ (7.27 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR). Column chromatography was performed with ICN 32−66 nm, 60 Å silica gel using flash column techniques. All reactions were performed in flame-dried glassware under an atmosphere of Ar unless otherwise noted.

Acetate 3. Butenolide (−)-**2** (66 mg, 0.27 mmol) was placed into a 100 mL round-bottom flask and dissolved in CH_2Cl_2 (20 mL). The mixture was cooled to −78 °C, and DIBALH (0.4 mL, 0.4 mmol) was added dropwise via syringe. The reaction was stirred at −78 °C for 1.5 h or until the disappearance of starting material was noted by TLC (silica gel, 3:1 hexanes/ethyl acetate). Pyridine (0.06 mL, 0.8 mmol), DMAP (65 mg, 0.53 mmol) in a minimal amount of CH_2Cl_2, and acetic anhydride (0.1 mL, 1.0 mmol) were added respectively, and the solution was warmed to 0 °C for 4 h. The reaction mixture was quenched with a saturated solution of Rochelle's salt (50 mL), extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (10:1 hexanes/ethyl acetate) to yield acetate **3** (66 mg, 0.23 mmol, 85%) as a clear oil and as a 1:1 mixture of diastereomers: R_f 0.46 (25% ethyl acetate in hexanes); IR (neat) ν 1734 cm^{-1}; ^{1}H NMR δ 7.29 (m, 10H, both diast.), 6.84 (s, 1H), 6.66 (s, 1H), 6.11 (m, 4H, both diast.), 4.59 (s, 2H), 4.56 (s, 2H), 3.71 (m, 2H), 3.55 (m, 2H) 3.42 (m, 4H, both diast.), 2.06 (s, 3H), 1.99 (s, 3H), 1.15 (t, J = 6.9 Hz, 6H, both diast.); ^{13}C NMR δ 170.5, 170.1, 138.3, 138.1, 136.6, 134.4, 133.7, 130.2, 128.4, 128.4, 127.7, 127.6, 115.2, 114.1, 100.6, 99.0, 74.0, 73.9, 73.7, 73.5, 58.8, 58.4, 21.4, 15.6, 15.5.

Ring-Opened Product 4. Dimethyl malonate (36 μL, 0.319 mmol) was added via syringe to a slurry of NaH (7.3 mg, 0.183 mmol, 60% in mineral oil) in THF (0.10 mL) in a 25 mL round-bottom flask. The suspension bubbled for 2 min and then subsided. Acetate **3** (30 mg, 0.103 mmol), allylpalladium chloride (2.1 mg, 0.006 mmol, 5.5%), 1,2-bis(diphenylphosphino)ethane (dppe) (6.4 mg, 0.016 mmol, 15.6%), and THF (0.1 mL) were placed into a second 25 mL flask and stirred for 5 min. The contents of the second flask were transferred to the flask containing the NaH suspension via cannula needle, using THF (0.2 mL) to rinse. The yellow/orange mixture turned a dark orange after a few min. The reaction was monitored using TLC (silica gel, 4:1 hexanes/ethyl acetate) and was finished with the disappearance of starting material. After 3.5 h, the reaction solution was diluted with CH_2Cl_2 (10 mL) and then distilled H_2O (10 mL). The aqueous layer was extracted with

(22) See Table 6, Supporting Information, for details.

CH_2Cl_2 (3 × 20 mL), and the organic layers were combined, dried with Mg_2SO_4, and concentrated to give a brown oil. Analysis of the crude ^{1}H NMR spectrum showed no starting material present and no indication of the desired product.

Alkylation with Dimethyl Methylmalonate (5). Dimethyl methylmalonate (23 μL, 0.172 mmol) was added via syringe to a slurry of NaH (7.0 mg, 0.287 mmol, 60% in mineral oil) in THF (0.10 mL) in a 25 mL round-bottom flask. After 5 min a mixture of the acetate **3** (25 mg, 0.086 mmol, dr 55:45, α:*β*), allylpalladium chloride (3.12 mg, 0.009 mmol, 10%), and dppe (6.8 mg, 0.017 mmol, 20%) in THF (0.3 mL) were transferred via cannula needle to the flask. The reaction mixture turned orange, and then dark red after 5 min. After being stirred at room temperature for 3 h, the reaction mixture was diluted with CH_2Cl_2 and distilled H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (10:1 hexanes/ethyl acetate) gave **5** as a clear oil as a 55:45 (α:*β*) mixture of diastereomers (26 mg, 0.069 mmol, 82%.): R_f 0.42 (25% ethyl acetate in hexanes); IR (neat) ν 1734 cm^1; ^{1}H NMR δ 7.34 (m, 10H, both diast.), 6.31 (dd, J = 6.0, 1.2 Hz, 1H), 6.26 (dd, J = 6.0, 1.2 Hz, 1H), 5.99 (dd, J = 6.3, 2.4 Hz, 1H), 5.91 (dd, J = 6.0, 2.4 Hz, 1H), 5.47 (dd, J = 2.4, 1.5 Hz, 1H), 5.29 (t, J = 2.1 Hz, 1H), 4.59 (m, 4H, both diast.), 3.78 (d, J = 5.1 Hz, 1H), 3.76 (d, J = 4.8 Hz, 1H), 3.72 (s, 12H, both diast.), 3.67 (d, J = 6.0 Hz, 1H), 3.65 (d, J = 4.2 Hz, 1H), 3.43 (m, 4H, both diast.), 1.45 (s, 3H), 1.34 (s, 3H), 1.19 (t, J = 6.9 Hz, 3H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 171.2, 170.1, 138.3, 134.4, 133.7, 130.2, 128.4, 128.4, 127.7, 127.6, 115.2, 114.1, 100.6, 99.0, 74.0, 73.9, 73.8, 73.5, 60.6, 58.8, 58.4, 21.4, 21.3, 15.6, 15.5, 14.4.

Palladium-Catalyzed Amination of 3. Amination with Thymine and dppf (α,*β*-6a). Tetra-*n*-butylammonium fluoride hydrate (TBAF·3H_2O) (21 mg, 0.068 mmol) was weighed into a 10 mL round-bottom flask and dried under vacuum for approximately 1 h. It was then dissolved in dry DMF (0.10 mL) and transferred via syringe to a 15 mL round-bottom flask containing 4 Å MS and stirred for 45 min at room temperature. A second 15 mL round-bottom flask was charged with the thymine base (11 mg, 0.085 mmol) and *N*,*O*-bis(trimethylsilyl)-methane (BSA) (11 μL, 0.044 mmol) in DMF (0.10 mL) and stirred for 10 min. A 25 mL Schlenk tube was equipped with a stir bar and charged with tris(dibenzylideneacetone)−dipalladium(0)−chloroform adduct ($Pd_2(dba)_3$·$CHCl_3$) (3.5 mg, 0.0034 mmol, 5.0%) and 1,1-bis(diphenylphosphino)ferrocene (dppf) (3.8 mg, 0.0068 mmol, 10%). First, acetate **3** (15.4 mg, 0.068 mmol) in DMF (0.10 mL) was added to the Schlenk tube via syringe. Next, the silylated base was transferred via syringe to the reaction tube. Last, the TBAF in DMF was transferred via syringe to the reaction flask. The reaction mixture was light yellow in color and gradually darkened to a deep red upon completion. The reaction's progress was monitored by the consumption of the starting material by TLC (silica gel, 3:1 hexanes/ethyl acetate) and of aliquots taken from the reaction mixture. After the reaction was completed, the DMF was removed under reduced pressure leaving a dark brown oil. The oil was taken up in ethyl acetate and washed with brine. The brine was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (10:1 hexanes/ethyl acetate; 4:1 hexanes/ethyl acetate; 1:1 hexanes/ethyl acetate) to yield the allylated thymine product **6a** as a 55:45 (α:*β*) mixture of diastereomers (7.0 mg, 38%) and as a white solid (mp 107−109 °C). **3** was recovered as a 65:35 (*β*:α) mixture of diastereomers in 53% yield (8.2 mg, 0.028 mmol): Spectral data for **6a**: R_f 0.45 (5% CH_3OH in CH_2Cl_2); IR (neat) ν 1695 cm^{-1}; ^{1}H NMR δ 8.01 (bs, 2H, both diast.), 7.53 (s, 1H), 7.32 (m, 11 H, both diast.), 7.11 (s, 1H), 6.91 (s, 1H), 6.39 (dd, J = 5.7, 1.5 Hz, 1H), 6.13 (s, 2H), 6.03 (dd, J = 5.7, 1.5 Hz, 1H), 4.60 (d, J = 2.4 Hz, 2H), 4.57 (s, 2H), 3.84 (d, J = 10.2 Hz, 1H), 3.75 (s, 2H), 3.62 (m, 2H), 3.50 (d, J = 10.2 Hz, 1 H), 3.41 (m, 2H), 1.92 (s, 3H), 1.27 (s, 3H) 1.20 (t, J = 6.9 Hz, 3H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 164.2, 151.3, 151.1, 137.7, 137.4, 136.5, 136.2, 135.4, 134.0, 131.3, 129.0, 128.7, 128.6, 128.2, 128.0, 127.9, 127.9, 114.2, 112.5, 111.4, 111.2, 88.7, 87.9, 73.7, 73.7, 72.9, 70.7, 58.9, 57.9, 15.5, 15.3, 12.6, 11.9. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.62; H, 6.07; N, 7.58.

Amination with Thymine and *S*,*S*-7 (*β*-6a). TBAF·3H_2O (54 mg, 0.171 mmol) was weighed into a 5 mL round-bottom flask and dried under vacuum for approximately 1 h. The TBAF was dissolved in DMF (0.10 mL) and transferred via syringe to a 10 mL round-bottom flask containing 4 Å MS and was stirred for 45 min at room temperature. Thymine (27 mg, 0.214 mmol) and BSA (27 μL, 0.11 mmol) were placed in a 15 mL round-bottom flask and stirred for 10 min. $Pd_2(dba)_3$·$CHCl_3$ (8.9 mg, 0.0086 mmol, 5.0%) and **7** (12 mg, 0.017 mmol, 10%) were weighed into a 15 mL Schlenk tube containing a stir bar. First, the contents of the flask containing silylated base were transferred via syringe to the reaction flask. The addition of acetate **3** (50.8 mg, 0.171 mmol) via syringe to the reaction tube followed. Last, the TBAF solution was transferred via syringe to the reaction tube. The reaction mixture was light yellow/orange in color and gradually darkened to a deep red upon completion. The reaction's progress was checked by the analysis of the crude ^{1}H NMR spectrum of isolated aliquots. After 16 h the reaction was complete. The DMF was removed under reduced pressure leaving a dark brown oil. The oil was taken up in ethyl acetate and washed with brine. The brine was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (20:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) producing **6a** as a white solid **(**mp 133−135 °C), with a diastereomeric ratio of <97:3 (*β*:α) in 49% (21 mg, 0.054 mmol) and recovering α-**3** with a diastereomeric ratio of <97:3 (α:*β*) in 41% (22 mg, 0.075 mmol): Spectral data for *β*-**6a**: R_f 0.45 (5% CH_3OH in CH_2Cl_2); $[\alpha]_D$ +43 (*c* 0.9, $CHCl_3$); IR (neat) ν 1694 cm^{-1}; ^{1}H NMR δ 8.19 (bs, 1H), 7.54 (s, 1H), 7.32 (m, 5H), 7.11 (s, 1H), 6.13 (s, 2H), 4.58 (s, 2 H), 3.75 (s, 2H), 3.49 (m, 1H), 3.39 (m, 1H), 1.48 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 163.8, 151.0, 137.5, 136.6, 134.2, 131.2, 128.8, 128.3, 128.0, 114.3, 111.2, 88.8, 73.8, 73.0, 58.0, 15.4, 12.0. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.48; H, 6.29; N, 7.76.

Amination with Cytosine and *S*,*S*-7 (*β*-6b). TBAF·3H_2O (55 mg, 0.174 mmol) was weighed into a 5 mL round-bottom flask and dried under vacuum for approximately 1 h. The TBAF was dissolved in DMF (0.10 mL) and transferred via syringe to a 10 mL round-bottom flask containing 4 Å MS which was stirred for 45 min at room temperature. Cytosine (24 mg, 0.218 mmol) and BSA (28 μL, 0.113 mmol) were placed in a 15 mL round-bottom flask and stirred for 40 min. $Pd_2(dba)_3$·$CHCl_3$ (12 mg, 0.017 mmol, 5.0%) and **7** (9 mg, 0.0087 mmol, 10%) were weighed into a 15 mL Schlenk tube containing a stir bar. First, acetate **3** (51 mg, 0.174 mmol) was added to the reaction tube via syringe followed by the contents of the flask containing the silylated base. Last, the TBAF solution was transferred via syringe to the reaction tube. The reaction mixture was light yellow/orange in color and gradually darkened to a deep red upon completion. The reaction's progress was checked by the analysis of the crude ^{1}H NMR spectrum of isolated aliquots. After 16 h the reaction was complete. The DMF was removed under reduced pressure leaving a dark brown oil. The oil was taken up in ethyl acetate and washed with brine. The brine was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (20:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate then 1% CH_3OH/CH_2Cl_2) and produced **6b** as a white solid (mp 164−166 °C) with a diastereomeric ratio of <97:3 (*β*:α) in 51% (30 mg, 0.087 mmol)-and recovered α-**3** as a diastereomeric ratio of <97:3 (α:*β*) in 44% (23.3 mg, 0.076 mmol): Spectral data for *β*-**6b**: R_f 0.27 (5% CH_3OH in CH_2Cl_2); $[\alpha]_D$ +38 (c 0.9, $CHCl_3$); IR (neat) ν 2923, 2853, 1650 cm^{-1}; ^{1}H NMR δ 7.87 (d, J = 7.2 Hz, 1H), 7.31 (m, 5H), 7.24 (s, 1H), 6.19 (d, J = 5.7 Hz, 1H), 6.02 (dd,

J = 6.0, 1.8 Hz, 1H), 5.30 (bs 2H) 5.15 (d, J = 7.5 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 4.52 (d, J = 11.1 Hz, 1H) 3.77 (s, 2H) 3.49 (m, 1H), 3.39 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 165.8, 156.4, 142.5, 137.7, 132.6, 132.5, 128.7, 128.2, 128.1, 114.3, 94.4, 90.0, 73.8, 73.1, 57.8, 15.4; HRFABMS (M + H) calculated for $C_{18}H_{22}N_3O_4$: 344.1622; found 344.1610.

Amination with Uracil and *S,S*-7 (*β*-6c). TBAF·3H_2O (55 mg, 0.171 mmol) was weighed into a 5 mL round-bottom flask and dried under vacuum for approximately 1 h. The TBAF was dissolved in DMF (0.10 mL) and transferred via syringe to a 10 mL round-bottom flask containing 4 Å MS which stirred for 45 min at room temperature. Uracil (24 mg, 0.218 mmol) and BSA (28 μL, 0.113 mmol) were placed in a 15 mL round-bottom flask and stirred for 10 min. $Pd_2(dba)_3$·$CHCl_3$ (12 mg, 0.017 mmol, 5.0%) and **7** (9 mg, 0.0087 mmol, 10%) were weighed into a 15 mL Schlenk tube containing a stir bar. The reaction tube was cooled to 0 °C before the addition of acetate **3** (51 mg, 0.174 mmol) via syringe. Next, the silylated base was added to the reaction tube via syringe followed by the addition of TBAF via syringe. The reaction mixture was light yellow/orange in color and gradually darkened to a deep red upon completion. The reaction's progress was checked by the analysis of the crude ^{1}H NMR spectrum of isolated aliquots. After 3 h the reaction was complete. The DMF was removed under reduced pressure leaving a dark brown oil. The oil was taken up in ethyl acetate and washed with brine. The brine was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (20:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate then 1% CH_3OH/CH_2Cl_2) and produced **6c** as a white solid (mp 146−148 °C) with a diastereomeric ratio of <97:3 (β:α) in 49% (29.6 mg, 0.086 mmol) and recovered α-**3** as a diastereomeric ratio of <97:3 (α:β) in 44% (22.5 mg, 0.077 mmol): Spectral data for β-**6c**: R_f 0.55 (5% CH_3OH in CH_2Cl_2); $[\alpha]_D$ +17 (c 0.6, $CHCl_3$); IR (neat) ν 1694, 2359 cm^{-1}; ^{1}H NMR δ 8.38 (bs, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.25 (m, 5H), 7.02 (s, 1H), 6.05 (dd, J = 5.7, 1.8 Hz, 1H), 6.01 (d, J = 5.7 Hz, 1H), 5.03 (d, J = 8.1 Hz, 1H), 4.47 (d, J = 11.1 Hz, 1H), 4.41 (d, J = 10.8 Hz, 1H), 3.72 (d, J = 9.9 Hz, 1H), 3.67 (d, J = 10.2 Hz, 1H), 3.42 (m, 1H), 3.31 (m, 1H), 1.10 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 163.1, 150.9, 141.2, 137.3, 134.4, 131.0, 128.8, 128.5, 128.4, 114.5, 102.4, 88.8, 74.0, 73.1, 58.0, 15.4. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.89; H, 5.65; N, 8.28.

Amination with Adenine and *S,S*-7 (*β*-6d). TBAF·3H_2O (60 mg, 0.190 mmol) was weighed into a 5 mL round-bottom flask and dried under vacuum for approximately 1 h. The TBAF was dissolved in DMF (0.10 mL) and transferred via syringe to a 10 mL round-bottom flask containing 4 Å MS which stirred for 45 min at room temperature. Adenine (32 mg, 0.238 mmol) and BSA (30 μL, 0.120 mmol) were placed in a 15 mL round-bottom flask and stirred for 45 min. $Pd_2(dba)_3$·$CHCl_3$ (9.8 mg, 0.0095 mmol, 5.0%) and **7** (13 mg, 0.019 mmol, 10%) were weighed into a 15 mL Schlenk tube containing a stir bar. First, acetate **3** (55 mg, 0.190 mmol) was added to the reaction tube via syringe, followed by the flask containing the silylated base. Last, the addition of the TBAF solution via syringe was added to the reaction flask. The reaction mixture was light yellow/orange in color and gradually darkened to a deep red upon completion. The reaction's progress was checked by the analysis of the crude ^{1}H NMR spectrum of isolated aliquots. After 16 h the reaction was complete. The DMF was removed under reduced pressure leaving a dark brown oil. The oil was taken up in ethyl acetate and washed with brine. The brine was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (20:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate then 1% CH_3OH/CH_2Cl_2 to 3%) and produced β-**6d** as a tan solid (mp 112−115 °C) with a diastereomeric ratio of <97:3 (β:α) in 38% (21 mg, 0.057 mmol) and recovered α-**3** as a diastereomeric ratio of <97:3 (α:β) in 39% (21 mg, 0.072 mmol): Spectral data for β-**6d**: R_f : 0.36 (5% CH_3OH in CH_2Cl_2); $[\alpha]_D$ +27 (c 0.8, $CHCl_3$); IR (neat) ν 1645, 1598 cm^{-1}; ^{1}H NMR δ 8.39 (s, 1H), 8.10 (s, 1H), 7.29 (m, 5H), 7.20 (s, 1H), 6.32 (d, J = 6.0 Hz, 1H), 6.22 (dd, J = 6.0, 1.8 Hz, 1H), 5.75 (bs, 2H), 4.58 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.72 (d, J = 10.2 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.58 (m, 1H), 3.44 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz) δ 155.6, 153.3, 139.5, 134.3, 130.3, 128.7, 128.2, 115.1, 94.6, 87.2, 73.7, 72.8, 58.1, 29.9, 15.4; Anal. Calcd for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 61.99; H, 5.64; N, 18.94.

Epimerization of α-3. A 10 mL round-bottom flask was equipped with a stir bar and dried under argon. α-**3** (21.1 mg, 0.072 mmol) was diluted with acetic acid (0.5 mL) and transferred via syringe to the reaction flask. Zinc acetate (13.2 mg, 0.072 mmol) was then added to the reaction flask. The reaction stirred at 35 ºC for 12 h. The acetic acid was removed under reduced pressure, and the resulting yellow oil was dissolved with CH_2Cl_2. The crude mixture was washed with brine, and then the brine was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, dried with Mg_2SO_4, and concentrated. The crude oil was purified by flash column chromatography (10:1 hexanes/ethyl acetate) to give **3** with a diastereomeric ratio of 60:40 (α:β) in 92% (19 mg, 0.065 mmol).

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Supporting Information Available: Tables 1−6, ^{1}H and ^{13}C NMR spectra of **3**, **5**, **6**, **6a**, **6b**, **6c**, **6d**, and full X-ray data for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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