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Preparation of Both C5′ Epimers of 5′-*C*-Methyladenosine: Reagent Control Trumps Substrate Control

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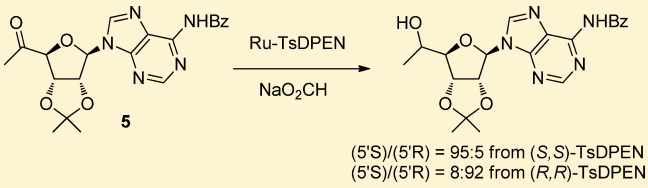
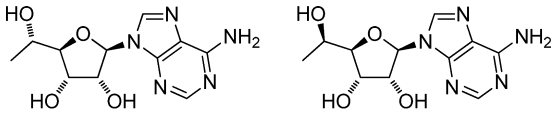
Supporting Information

ABSTRACT: Adenosine-derived ketone **5** was subjected to Noyori asymmetric transfer hydrogenation (ATH) using aqueous sodium formate as a stoichiometric reductant. Despite the well-known sensitivity of ATH to stereoelectronic effects from a contiguous stereogenic center, the 5′ stereochemistry was overwhelmingly controlled by the chirality of the catalyst. Both the (5′*S*,4′*R*) and the (5′*R*,4′*R*) diastereomers could be prepared selectively in good yields. An efficient three-step route that provides ketone **5** in 75% overall yield was developed.



(5′*S*)-*C*-Methyladenosine (**1a**) and its (5′*R*) diastereomer **1b** have been of interest to medicinal chemists for over 50 years.[1] These nucleosides and their phosphoric esters typically remain functionally competent analogues of adenosine, ADP, and ATP that allow systematic variation of their solution conformations.[2] Consequently, they have long played an important role as structural probes in molecular biology and enzymology.[3]

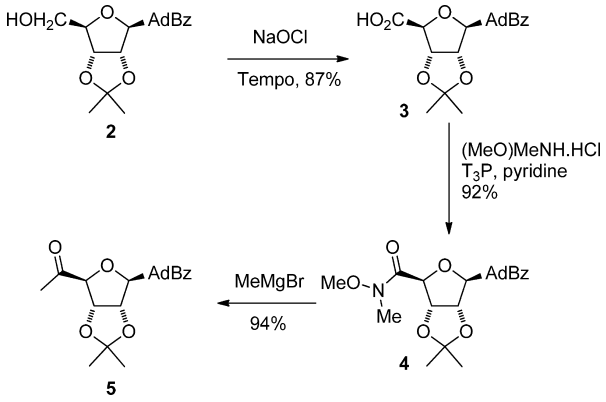


Existing routes[1−5] to **1a** and **1b** require chromatography, which complicates scale-up. In this paper, we report a novel approach to **1a** and **1b** in which a protected adenosine derivative is converted to methyl ketone **5** in three straightforward steps[6] and is then subjected to stereoselective reduction.[7]

Our approach to ketone **5** is summarized in Scheme 1 (AdBz = 6-*N*-benzoyladenine).[8] TEMPO-catalyzed oxidation of the readily available[9] protected adenosine derivative **2** does not stop at the aldehyde oxidation stage but proceeds directly to the known[10] carboxylic acid **3**. This observation is extensively precedented[11] and presumably reflects the tendency of the electron-deficient aldehyde intermediate to exist as a readily oxidizable hydrate. Carboxylic acid **3** was conveniently isolated as its sodium salt and was then converted to the known[12] Weinreb amide **4** using T_3P/pyridine[13] as a coupling reagent.

The conversion of **4** to the known[14] ketone **5** requires 2 equiv of methylmagnesium bromide: 1 equiv to deprotonate the amide N−H and 1 equiv for the nucleophilic substitution of the Weinreb amide. It proved advantageous to delay the addition of the second equivalent of Grignard reagent, allowing time for the deprotonation of the amide nitrogen to proceed to completion. Presumably this protocol avoids premature protonolysis of the Weinreb addition product, which would generate ketone **5** and allow addition of a second equivalent of Grignard reagent.[15]

Scheme 1. Synthesis of Ketone 5 from Protected Adenosine 2



Several approaches to the reduction of ketone **5** were explored. As previously reported,[14] reduction with sodium borohydride proved unselective, producing a 2:1 mixture of diastereomeric alcohols at the 5′ position. Attempted Meerwein−Pondorf reduction with either aluminum isopropoxide or indium isopropoxide[16] instead resulted in removal of the benzamide protecting group. Reduction with L-Selectride proved unselective, while the attempted reduction using the CBS catalyst[17] resulted in partial decomposition of ketone **5**.

Better results were obtained using lithium tri-*tert*-butoxyaluminum hydride as the reductant. As shown in Scheme 2, the enantioselectivity—and even the predominant absolute configuration of the product—showed an unusual temperature dependence.[18] The major product obtained at room temper-

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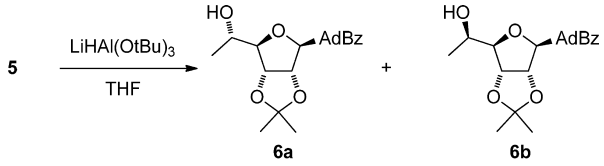
Scheme 2. Effect of Temperature on the Reduction of Ketone 5

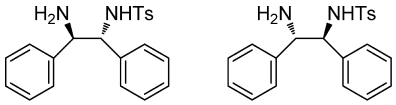


Temp. (deg C)	6a:6b
25	82:18
-25	76:24
-78	39:61

ature could be enriched to 98% diastereomeric purity after a single crystallization from heptane/ethyl acetate.

In order to determine the absolute stereochemistry at C4′ and C5′ of the major product at room temperature (**6a**), X-ray crystal structure analysis was carried out. The molecular structure clearly shows that **6a** has the (5′*S*,4′*R*) configuration (see the Supporting Information).

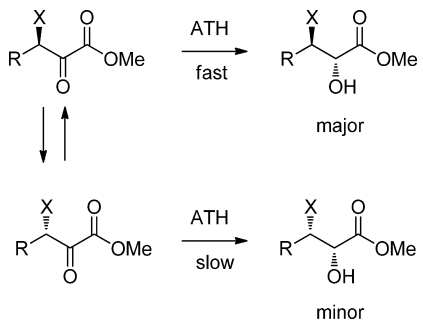
We turned our attention to asymmetric transfer hydrogenation (ATH) using Noyori's *N*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) ligands.[19] In recent years, the replacement of formic acid/triethylamine with aqueous sodium formate as a stoichiometric reductant has significantly improved the operational simplicity of ATH reactions.[20]



Most of the published examples of ATH reactions using TsDPEN-type ligands involve differentiation between saturated and unsaturated ketone groups. The unsaturated substituent has most often been an aromatic ring, but examples involving alkene[21] and alkyne[22] substituents are also known. Moreover, during the past decade examples have begun to appear in which heteroatoms attached to the α-carbon of the ketone carbonyl serve as effective control elements.[23] While we are unaware of examples in which a nonaromatic heterocycle serves in this role,[24] 2-acetylfuran is an excellent substrate for ATH, and this reaction has been utilized in organic synthesis.[25]

The presence of pre-existing chirality in ketone **5** was a concern since ATH is usually[26] sensitive to such chiral centers. As illustrated in Scheme 3, when this sensitivity is combined with a dynamic kinetic resolution (DKR) process, it provides highly useful ATH/DKR reactions that allow control of the absolute stereochemistry at contiguous stereogenic centers.[27] Such reactions depend on the fact that ATH for one enantiomer is significantly slower than interconversion between the enantiomers. Since we wished to retain the biologically relevant (4′*R*) stereochemistry, it was essential to avoid such a DKR process.

Scheme 3. Typical ATH/DKR Reaction



A small (3 × 3) combinatorial study[28] was undertaken to identify a suitable combination of ligand and metal precursor for the ATH of ketone **5**. Under the conditions of this screen (25 °C, 28:1 substrate/catalyst ratio, sodium formate as the stoichiometric reductant, two-phase water/ethyl acetate solvent system), the highest enantioselecitivity was observed using (*p*-cymene)ruthenium(II) dichloride dimer as the metal precursor. Using this precursor in combination with (*S*,*S*)-TsDPEN predominantly afforded the (5′*S*) alcohol **6a** (**6a**/**6b** = 94:6), while using (*R*,*R*)-TsDPEN gave the reverse selectivity (**6a**/**6b** = 8:92).

Diastereoselectivity in the reduction of ketone **5** was expected to reflect both reagent control stemming from the chirality of the catalyst and substrate control resulting from the inherent chirality of the rigid furanose substrate. Thus, the minor difference in stereoselectivity when the results for (*S*,*S*)-TsDPEN and (*R*,*R*)-TsDPEN were compared was unexpected. In contrast to the reduction by $LiAlH(OtBu)_3$, substrate control apparently had little impact on the stereochemical course of ATH. Consistent with this proposal, reduction of ketone **5** using the corresponding Ru catalyst bearing an achiral (*N*-tosyl)ethylenediamine ligand afforded a 52:48 mixture of **6a** and **6b**.

The absolute configuration of the products obtained in the reduction of ketone **5** is the same as that observed for the Ru-TsDPEN-catalyzed ATH of aromatic substrates such as acetophenone. For the ATH of acetophenone, several theoretical studies have established that a key control element is an attractive π-interaction between the aryl group of the ketone and the electron-deficient metal arene moiety.[29] By analogy, we tentatively ascribe our results to an attractive interaction between the negative electron density around the lone electron pairs of the tetrahydrofuran oxygen atom and the partial positive charge surrounding the η^6 aromatic ring (Scheme 4).[30,31] Similar arguments have been put forth to rationalize the ATH of other heteroatom-containing ketones.[32]

We employed the Ru−TsDPEN catalyst system for the synthesis of both **6a** and **6b**. In the case of the (5′*S*) alcohol **6a**, complete conversion was observed in 24 h at room temperature using a 1% catalyst loading. The resulting 95:5 mixture of diastereomers could be freed of **6b** and catalyst residues by trituration in hot 60:40 ethyl acetate/heptane. Upon cooling, the product was collected by filtration to afford **6a** in 82% yield with 99% diastereomeric purity.

Similar reaction conditions were successfully applied to prepare **6b**. However, the trituration protocol described above could not be applied to this lower-melting product. Consequently, an alternative isolation was developed that takes advantage of the tendency of **6b** to reversibly form a poorly soluble hydrate in the presence of bulk water. The crude product was dissolved in 20 volumes of ethyl acetate and was stirred with 10 volumes of water at room temperature. The amorphous product was collected by filtration and after drying afforded **6b** in 72% yield with 98% diasteromeric purity.

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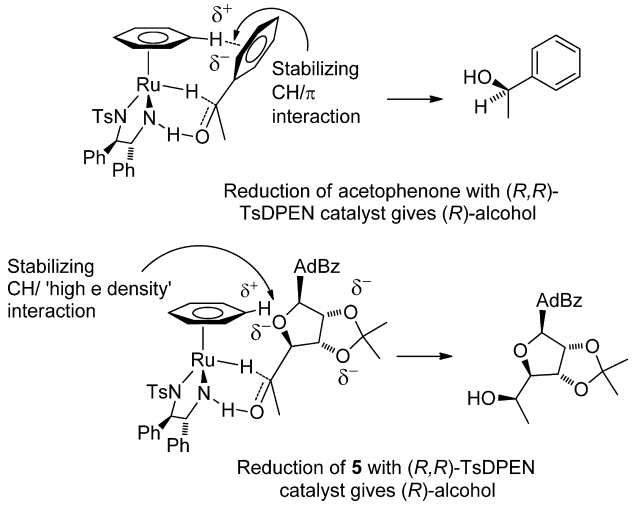
Scheme 4. Proposed Model for the Absolute Stereochemistry in ATH of Ketone 5



In conclusion, ATH of ketone **5** using the appropriate enantiomer of the Ru−TsDPEN catalyst allows straightforward synthesis of either diastereomer of protected 5′-*C*-Me-adenosine. Compounds **6a** and **6b** can be deprotected using known protocols[14] to afford the adenosine derivatives **1a** and **1b**, respectively. In addition, we have developed an efficient three-step synthesis of the ketone **5** starting material from protected adenosine **2** in 75% overall yield.

It is perhaps not surprising that, under the mild conditions of the ATH reaction using aqueous sodium formate, epimerization at C4′ is not observed. Nevertheless, given the general observation that ATH is sensitive to stereoelectronic effects from contiguous stereogenic centers, and particularly in view of the considerable steric bulk of the protected nucleoside in **5**, we were surprised to find that ATH proceeds readily with either enantiomer of the catalyst. Finally, our successful use of an ether oxygen atom as a control element provides another example of the rapidly growing list of substrate classes that undergo selective ATH reactions.

EXPERIMENTAL SECTION

General Information. NMR spectra were determined at 25 °C at a field strength of 400 MHz (^{1}H spectra) or 100 MHz (^{13}C spectra). The chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane, and coupling constants (J) are given in hertz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. The starting material, 2′,3′-isopropylidene-6-*N*-benzoyladenosine (**2**), was prepared by the procedure of van Delft and co-workers[9a] or was purchased from commercial sources. Anhydrous tetrahydrofuran and all of the synthetic reagents were commercial materials and were used as received. Flash chromatography was performed on 220−400 mesh silica following the standard procedure of Still.[33] The reactions reported below were run under an atmosphere of dry nitrogen. Melting points were determined on an automated apparatus employing digital image processing technology. The following HPLC method was employed in all of the work reported below: Agilent Poroshell SB-C18 column, 4.6 mm × 150 mm (2.7 μm particle size); mobile phase A = water with 0.1% TFA, mobile phase B = methanol with 0.1% TFA, gradient 30−70% B in 20 min, total 29 min; flow rate = 0.8 mL/min; 70:30 water/methanol as the diluent; column temperature 40 °C; UV detection at 260 nm. Retention times were as follows: carboxylic acid **3** = 14.8 min, Weinreb amide **4** = 16.5 min, ketone **5** = 15.4 min, alcohol **6a** = 16.7 min, alcohol **6b** = 16.9 min. The initial catalyst screen for the ATH reactions was carried out with in situ-generated catalysts, while synthetic runs utilized commercial samples of pregenerated catalysts.

Synthetic Details. *Preparation of Carboxylic Acid **3** as Its Sodium Salt Monohydrate.* A 3 L jacketed round-bottom flask was equipped with an overhead stirrer, nitrogen inlet, and temperature probe. The flask was charged with technical grade alcohol **2** (48.75 g, 92 wt %, 109.0 mmol) and dichloromethane (270 mL). A solution of sodium hydrogen carbonate (12.81 g, 152.5 mmol) in water (240 mL) was added, and the mixture was cooled to 5 °C with stirring. TEMPO (3.476 g, 21.80 mmol) was added all at once, after which a 9.42 wt % solution of sodium hypochlorite (206.7 g, 261.6 mmol) was added dropwise over 2 h, keeping the internal temperature below 7 °C. After about half of the bleach was added, solids began to separate from solution. Additional dichoromethane (180 mL) was added, and the temperature was allowed to rise to 15 °C, at which time the solids were collected by filtration. The flask and filter cake were rinsed with water (90 mL), and the solids were pulled dry for 1 h. The resultant red/brown solids were suspended in dichloromethane (225 mL) and stirred overnight. The resulting material was collected by filtration, rinsed with dichloromethane (90 mL), and dried for 3 days in a vacuum oven at 55 °C to afford the sodium salt of **3** (44.35 g, 87% yield) as an off-white solid that was 98.7% pure by HPLC and contained 1.0 molar equiv of water as determined by NMR analysis.

It proved convenient to use this sodium salt directly in the subsequent Weinreb amide formation. However, in order to allow comparison with literature data, the salt was converted to the free carboxylic acid **3** for purposes of characterization. This was accomplished by dissolving 2.00 g of the sodium salt in 20 mL of water and acidifying resulting solution to pH 1 with 3 N HCl. The precipitated solid was removed by filtration, washed with water, and dried overnight in a 60 °C vacuum oven to afford the acid **3** (1.60 g, 87%) as a white solid. The product could be recrystallized from 98:2 ethanol/water. Mp: 216.8−219.9 °C (lit.[10b] 208−209 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (s, 3H), 1.54 (s, 3H), 4.77 (d, 1H, J = 0.9 Hz), 5.58 (s, 2H), 6.47 (s, 1H), 7.55 (m, 2H), 7.65 (m, 1H), 8.04 (m, 2H), 8.59 (s, 1H), 8.69 (s, 1H), 11.18 (br s, 1H), 12.39 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.0, 26.4, 83.4, 83.8, 85.7, 89.8, 112.7, 125.3, 128.1, 128.41, 128.45, 132.4, 133.4, 144.0, 150.2, 151.3, 152.0, 165.5, 170.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}N_5O_6^+$ 426.1408, found 426.1428. The spectroscopic data match those previously reported.[10b]

*Preparation of Weinreb Amide **4**.* A 1 L jacketed reactor was equipped with an overhead stirrer, temperature probe, and nitrogen inlet. The reactor was charged with the sodium salt monohydrate of carboxylic acid **3** (20.0 g, 45.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (5.04 g, 52 mmol), ethyl acetate (60 mL), and pyridine (20 mL). The resultant thick slurry was cooled with stirring to 0 °C. A 50 wt % solution of T_3P in ethyl acetate (56 mL, 94 mmol) was slowly added by syringe over the course of 30 min, keeping the internal temperature below 5 °C. Stirring was continued for an additional 2 h at 0 °C, at which time the reaction was quenched by addition of 20% aqueous citric acid (80 mL). The product was extracted into ethyl acetate (200 mL then 100 mL), and the combined organic layers were washed with half-saturated sodium bicarbonate (80 mL) and then water (80 mL). The solvent was distilled at reduced pressure to afford crude **4**, which was twice azeotropically dried by addition of dichloromethane (120 mL) followed by distillation at reduced pressure. This afforded **4** (19.4 g, 92%) as a pale-yellow foam that retained a small amount of ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.51 (s, 3H), 3.02 (s, 3H), 3.60 (s, 3H), 5.16 (m, 2H), 5.33 (m, 1H), 6.16 (m, 1H), 7.33 (m, 2H), 7.42 (m, 1H), 8.00 (m, 2H), 8.48 (s, 1H), 8.62 (s, 1H), 9.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 27.0, 32,3, 61.9, 83.2, 83.7, 85.1, 91.7, 114.2, 122.9, 127.9, 128.8, 132.7, 133.8, 142.3, 149.5, 151.8, 152.6, 164.7, 169.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{25}N_6O_6^+$ 469.1830, found 469.1853. The ^{1}H NMR data match those previously reported.[12]

*Preparation of Ketone **5**.* A 250 mL jacketed reactor was equipped with a magnetic stirrer, a nitrogen inlet, and a temperature probe. The reactor was charged with Weinreb amide **4** (18.5 g, 39.5 mmol) and

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tetrahydrofuran (266 mL), and the stirred mixture was cooled to −5 °C. A 3.0 M solution of methylmagnesium chloride in THF (13.2 mL, 39.6 mmol) was added at a rate such that the internal temperature did not rise above −2 °C, after which the mixture was stirred for an additional 1 h at −18 °C. A second portion of 3.0 M methylmagnesium chloride in THF (17.1 mL, 51.3 mmol) was added at a rate such that the internal temperature did not rise above −4 °C, and the mixture was again stirred for 1 h at −18 °C. The reaction was carefully quenched (*caution*: gas evolution) by addition of half-saturated aqueous ammonium chloride (260 mL), and the product was extracted into ethyl acetate (185 mL and then 90 mL). The combined organic layers were washed with water (185 mL) and dried over magnesium sulfate. The solvent was removed on a rotary evaporator initially at 50 °C and 300 mbar to promote azeotropic distillation of water. Completion of the distillation at full vacuum resulted in a gooey residue that retained considerable ethyl acetate. MTBE (100 mL) was added, and the flask was spun on the rotary evaporator in a 50 °C bath for 1 h. Distillation of the solvent at reduced pressure then afforded ketone **5** (15.7 g, 94%) as a crisp white foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (s, 3H), 1.56 (s, 3H), 1.86 (s, 3H), 4.78 (d, 1H, J = 2.3 Hz), 5.46 (d, 1H, J = 6.4 Hz), 5.56 (dd, 1H, J = 6.4, 2.3 Hz), 6.51 (s, 1H), 7.55 (m, 2H), 7.65 (m, 1H), 8.06 (m, 2H), 11.24 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.0, 26.8, 82.7, 84.2, 91.4, 93.2, 123.3, 128.0, 128.8, 132.9, 133.5, 142.6, 149.9, 151.0, 152.5, 164.8, 205.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{22}N_5O_5^+$ 424.1615, found 424.1633. The spectroscopic data match those previously reported.[14]

In the original literature report on ketone **5**,[14] it was noted that this compound epimerized to the extent of 80% upon attempted chromatography on "silicic acid". We did not observe any degradation upon flash chromatography using ethyl acetate as the eluent. In fact, flash chromatography was found to be a useful method for purifying compound **5** and could remove minor impurities that otherwise would make the downstream purification of alcohols **6a** and **6b** less efficient.

ATH Catalyst Screening. The screen was conducted as a small (3 × 3) combinatorial study. Ligand inputs were (*S*,*S*)-TsDPEN, (*R*,*R*)-TsDPEN, and (*S*,*S*,*S*)-CsDPEN.[28] Metal precursor inputs were (*p*-cymene)ruthenium(II) dichloride dimer, (pentamethylcyclopentadienyl)rhodium(III) dichloride dimer, and (pentamethylcyclopentadienyl)iridium(III) dichloride dimer. A set of borosilicate glass tubes equipped with Teflon screw caps were taken into a nitrogen-filled glovebox. Each tube was charged with transition metal precursor (0.0090 mmol of the dimer, delivering 0.018 mg-atom of metal), ligand (0.021 mmol), and deaerated water (10 mL). The resulting mixture was stirred at 40 °C for 1 h to afford a homogeneous solution. To each tube was added a solution of ketone **5** (211 mg, 0.500 mmol) in ethyl acetate (2 mL) followed by sodium formate (1.70 g, 25 mmol), and the two-phase mixture was stirred under nitrogen for 24 h at room temperature. The contents of each tube was transferred to a separatory funnel with ethyl acetate (15 mL). The organic phase was separated, and the aqueous phase was further washed with ethyl acetate (5 mL). HPLC analysis of the combined organic phases was used to determine the conversion and yield of alcohols **6a** and **6b**. In all cases, the conversion was >99%. A tabulation of the observed stereoselectivities is given in the Supporting Information.

*2′,3′-O,O-Isopropylidene-6-N-benzoyl-(5′S)-5′-C-methyladenosine (**6a**).* A 100-mL round-bottom flask equipped with a septum-covered side arm was charged with η^6-(*p*-cymene)-(*S*,*S*)-*N*-toluenesulfonyl-1,2-diphenylethylenediamine(1−)ruthenium(II) chloride (15 mg, 0.024 mmol, 1%) and ketone **5** (1.00 g, 2.4 mmol), and the system was flushed with nitrogen. A solution of sodium formate (6.8 g, 100 mmol) in water (40 mL) was added, followed by ethyl acetate (10 mL). The resulting two-phase mixture was stirred for 24 h at room temperature, during which time some of the solid product separated from solution. The solids were redissolved with additional ethyl acetate (20 mL). The organic phase was separated, and the aqueous phase was extracted with another 10 mL of ethyl acetate. The solvent was removed from the combined organic layers at reduced pressure on a rotary evaporator. The solid residue (5′*S*/5′*R* = 95:5) was suspended in a mixture of 12 mL of ethyl acetate and 8 mL of heptane. The mixture was heated to 80 °C for 15 min, and the still-heterogeneous mixture was allowed to cool to room temperature with stirring. The solids were collected by filtration and dried in a vacuum oven overnight at 60 °C to afford **6a** as an off-white solid. HPLC analysis indicated that the 5′*S*/5′*R* diastereomeric ratio was 99:1. Mp 165.7−166.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (d, 3H, J = 6 Hz), 1.35 (s, 3H), 1.58 (s, 3H), 3.83 (m, 1H), 4.09 (dd, 1H, J = 4, 3 Hz), 4.98 (dd, 1H, J = 6, 3 Hz), 5.16 (br s, 1H), 5.34 (dd, 1H, J = 6, 3 Hz), 6.30 (d, 1H, J = 3 Hz), 7.56 (m, 2H), 7.65 (m, 1H), 8.06 (m, 2H), 8.77 (s, 1H), 8.78 (s, 1H), 11.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.3, 27.6, 68.4, 82.6, 82.8, 88.9, 93.5, 114.2, 124.3, 128.0, 128.8, 132.9, 133.5, 142.6, 150.3, 150.6, 152.3, 164.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N_5O_5^+$ 426.1772, found 426.1793.

*2′,3′-O,O-Isopropylidene-6-N-benzoyl-(5′R)-5′-C-methyladenosine (**6b**).* A 100 mL round-bottom flask equipped with a septum-covered side arm was charged with η^6-(*p*-cymene)-(*R*,*R*)-*N*-toluenesulfonyl-1,2-diphenylethylenediamine(1−)ruthenium(II) chloride (15 mg, 0.024 mmol, 1%), and ketone **5** (1.00 g, 2.4 mmol), and the system was flushed with nitrogen. A solution of sodium formate (6.8 g, 100 mmol) in water (40 mL) was added, followed by ethyl acetate (10 mL). The resulting two-phase mixture was stirred for 30 h at room temperature, during which time some of the solid product separated from solution. Sufficient dichloromethane (ca. 30 mL) to redissolve the product was added, and the two homogeneous phases were transferred to a separatory funnel. The organic layer was separated, and the solvent was distilled using a rotary evaporator. The residue (5′*R*/5′*S* = 92:8) was transferred to a straight-walled vessel and dissolved in ethyl acetate (20 mL), after which water (10 mL) was added. The mixture was stirred overnight at room temperature, during which time a white solid separated and the colored catalyst residue remained dissolved in the organic phase. The solid was collected by filtration, washed with MTBE (2 × 10 mL), and finally dried at 15 Torr to afford **6b** (723 mg, 72%) as an amorphous snow-white powder. HPLC analysis indicated that the 5′*R*/5′*S* diastereomeric ratio was 98:2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, 3H, J = 6 Hz), 1.36 (s, 3H), 1.57 (s, 3H), 3.75 (m, 1H), 3.99 (dd, 1H, J = 5, 2 Hz), 5.10 (dd, 1H, J = 6, 2 Hz), 5.18 (br s, 1H), 5.42 (dd, 1H, J = 6, 3 Hz), 6.27 (d, 1H, J = 3 Hz), 7.56 (m, 2H), 7.65 (m, 1H), 8.06 (m, 2H), 8.69 (s, 1H), 8.77 (s, 1H), 11.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 25.2, 27.5, 67.3, 79.4, 83.0, 89.7, 93.6, 114.5, 124.4, 127.9, 128.9, 132.9, 133.4, 142.5, 150.3, 150.5, 152.3, 164.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N_5O_5^+$ 426.1772, found 426.1778.

*Reduction of Ketone **5** with Lithium Tri-tert-butoxyaluminum Hydride.* A three-neck round-bottom flask was equipped with a temperature probe, an addition funnel, and a nitrogen inlet. To the flask was added a solution of crude ketone **5** (10.0 g, 80 wt % purity, 18.9 mmol) in anhydrous THF (170 mL), and the system was flushed with nitrogen. A 1.0 M solution of lithium tri-*tert*-butoxyaluminum hydride in THF (47.2 mL, 47.2 mmol) was added dropwise over the course of 5 min, during which time the internal temperature rose from 17.4 to 22.4 °C. The mixture was stirred for 1 h at room temperature and was then subjected to an inverse quench by addition to 5% aqueous oxalic acid (100 mL). The mixture was concentrated at 50 °C on a rotary evaporator until most of the THF had distilled over. The aqueous residue was extracted with ethyl acetate (100 mL), and the organic phase was stirred for 30 min with aqueous sodium bicarbonate (100 mL), after which the organic phase was dried over sodium sulfate. In order to azeotrope off any remaining water, the solution was distilled on a rotary evaporator at 50 °C bath temperature and 300 mbar pressure. Two additional 100 mL portions of ethyl acetate were added and distilled off to further dry the residue (5′*S*/5′*R* = 88:12). The crude product (9.86 g) was suspended in ethyl acetate (60 mL) and heated to reflux to produce a clear solution. Heptane (35 mL) was added, keeping the temperature above 60 °C. The heating mantle was unplugged, and the mixture was allowed to slowly cool to room temperature, during which time a white solid separated. The solid was collected by filtration and dried at 60 °C for 3 h in a vacuum oven with a nitrogen sweep to afford **6a** (3.96 g, 49%) as an off-white solid.

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HPLC analysis indicated that the 5′*S*/5′*R* diastereomeric ratio was 98:2. The spectroscopic properties were identical to those reported above for alcohol **6a**.

■ ASSOCIATED CONTENT

Supporting Information

Tabulated results for the ATH catalyst screen, details of the structure assignment for **6a** and **6b**, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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