

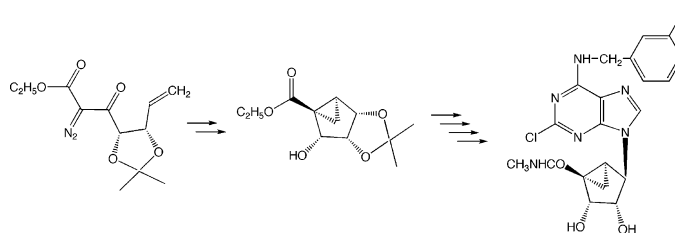
A New Synthetic Route to (North)-Methanocarba Nucleosides Designed as A₃ Adenosine Receptor Agonists

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Activation of the A₃ adenosine receptor (AR) is associated with cerebroprotective, cardioprotective, and anticancer effects. Among potent and selective A₃ AR agonists are novel methanocarba adenosine analogues in which the conformation of a pseudo-ribose moiety is locked in the North (N) hemisphere of the pseudorotational cycle. 5'-Uronamide (N)-methanocarba nucleosides, such as MRS1898 and MRS2346, are examples of full agonists of the human A₃ AR. An improved convergent approach from easily accessible 2,3-*O*-isopropylidene-D-erythrose (**2b**), and the combination of a strategic intramolecular cyclopropanation step plus the acid-catalyzed isomerization of an isopropylidene group, provided a suitable pseudosugar precursor (**23**) for the synthesis of MRS1898, MRS2346, and related analogues. This new synthetic route uses readily available building blocks and opens the way for the preparation of a variety of targets on a reasonable scale.

Introduction

Activation of the A₃ adenosine receptor (AR)^{1–3} is associated with cerebroprotective,⁴ cardioprotective,^{5,6} and anticancer⁷ effects. Agonists of this receptor are

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nearly always purine nucleoside analogues, mostly synthetic adenosine derivatives that activate the receptor at nanomolar concentrations.^{8–12} Among potent and selective A₃ AR agonists are some novel methanocarba adenosine analogues, in which the furanose moiety has been replaced by a bicyclo[3.1.0]hexane scaffold.^{13–16} With

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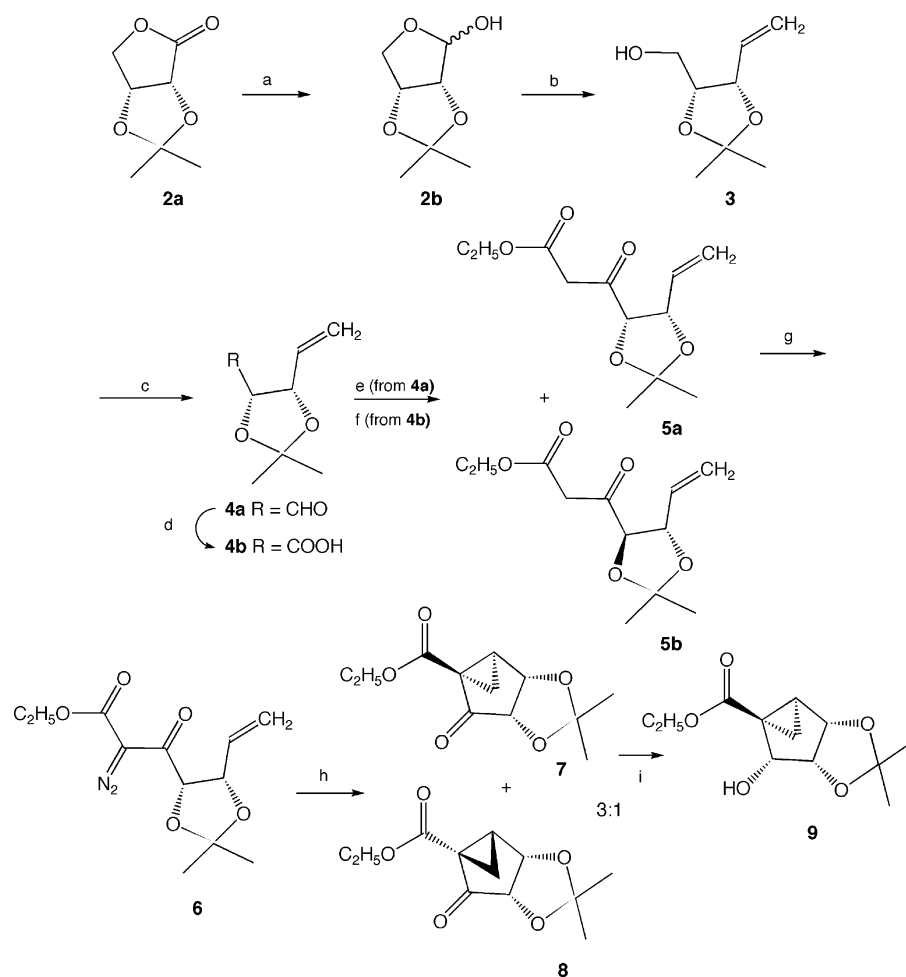
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SCHEME 1. Synthesis of 9^a

^a Reagents and conditions: (a) DIBAL-H, CH₂Cl₂, -78 °C; (b) methyltriphenylphosphonium bromide, KOBu^t, THF, -78 °C to room temperature; (c) DMSO, (COCl)₂, CH₂Cl₂, -78 °C; (d) NaOCl; (e) N₂CHCOOEt, SnCl₂, CH₂Cl₂, room temperature; (f) 1,1'-carbonyldiimidazole, LDA, CH₃COOEt, THF, -78 °C; (g) TsN₃, CH₃CN, TEA, room temperature; (h) CuI, toluene, reflux; (i) NaBH₄, MeOH, room temperature.

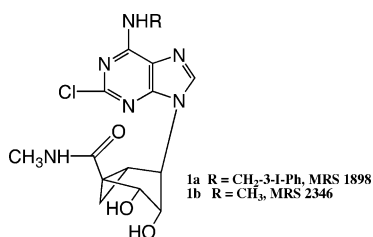


FIGURE 1. Structure of A₃ AR agonists containing a (N)-methanocarba ring system.

an appropriate substitution pattern, this methanocarba template is able to lock the conformation of the pseudofuranose moiety into either the North (N) or South (S) hemisphere of the pseudorotational cycle. We have shown that the (N)-methanocarba analogues are substantially more potent in receptor binding than their isomeric (S)-methanocarba analogues,¹⁷ suggesting that the N con-

formation of the ribose, or ribose-like moiety, more closely corresponds to the biologically active, receptor bound conformation. Specifically, the structurally optimized agonists (N)-methanocarba-2-chloro-5'-N-methyluronamide analogues of adenosine, e.g., (1'S,2'R,3'S,4'R,5'S)-[4'-(2-chloro-6-[(3-iodophenyl)methyl]amino}purin-9-yl)-2',3'-dihydroxybicyclo[3.1.0]hexyl]-N-methylcarboxamide (MRS1898, **1a**), and the 6-methylamino derivative (MRS2346, **1b**), were found to fully activate the human A₃ AR with EC₅₀ values of 3.3 and 1.4 nM, respectively (Figure 1).^{18,19}

Unfortunately, currently available synthetic methods^{13–18} are not amenable to perform the extensive probing at the N⁶ and C2 positions that is required for a systematic analysis of the structure activity relationship (SAR) of this (N)-methanocarba-5'-N-methyluronamide series.^{13–17} In addition, more efficient synthetic proce-

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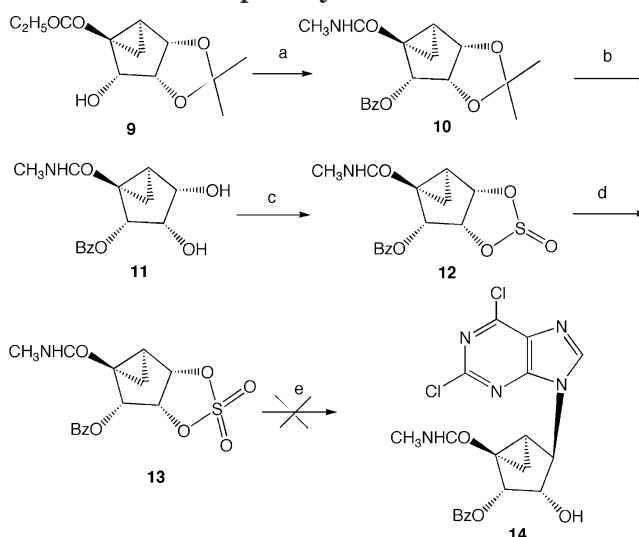
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dures are needed to provide sufficient material for continuing biological studies.²⁰ We have devised an improved convergent synthetic route for this class of compounds that introduces the purine ring in one step. This feature is ideally suited for the use of parallel synthetic methods designed to explore chemical diversity. Furthermore, the readily available building blocks for this synthesis would allow the preparation of target compounds on a reasonably large scale. The approach is based on two key steps: (1) an intramolecular cyclopropanation reaction performed on an appropriately substituted carbohydrate chiral synthon and (2) a key acid-catalyzed isomerization of an isopropylidene group. The biological characterization at ARs of a large series of these analogues will be described later.²¹

Our initial approach for a convergent strategy was to utilize either a cyclic sulfite or a cyclic sulfate as pseudoglycosyl donors (compounds **12** and **13**, Scheme 2) to introduce the purine moiety in one step.²² The synthesis started with commercially available 2,3-*O*-isopropylidene-D-erythronolactone (**2a**), which was reduced with DIBAL-H to provide 2,3-*O*-isopropylidene-D-erythrose (**2b**) according to published methods (Scheme 1).²³ This lactol underwent Wittig olefination with the corresponding methylenetriphenylphosphine ylide to afford the ring-opened alcohol **3** in 60% yield. At this stage, a Swern oxidation protocol was chosen among several methods tested to oxidize **3** to the corresponding aldehyde **4a**. The resulting aldehyde was found to be unstable and therefore it was utilized immediately for the next reaction. Oxidation of the aldehyde to the acid (**4b**) with sodium chlorite, followed by Dieckmann condensation of the activated acid with ethyl 2-lithioacetate, afforded the desired β -keto ester **5a** (59%) plus an unwanted epimerized derivative **5b** (9%) as a mixture of separable diastereoisomers. This epimerization problem was surmounted by treating aldehyde **4a** directly with ethyl diazoacetate in the presence of tin(II) chloride to provide the keto ester **5a** as the sole product in 36% overall yield from alcohol **3**. Using a standard protocol, the unsaturated keto ester **5a** was converted to the diazo compound **6**, which underwent a thermally induced intramolecular cyclopropanation to give the bicyclo[3.1.0]hexan-2-one derivatives **7** and **8** in a combined 48% yield with a favorable diastereoisomeric ratio (3:1) for the desired isomer **7**. The bicyclo derivative **7** was isolated chromatographically and reduced stereospecifically with NaBH₄ to give alcohol **9** as a single product in 72% yield. The structure of **9** was confirmed by X-ray analysis, which unambiguously validated the suitability of our synthetic approach to construct (N)-methanocarba carbocyclic nucleosides.

The ester group in **9** was converted to the corresponding *N*-methyl amide, and protection of the free hydroxyl group afforded **10** in 55% overall yield (Scheme 2). Removal of the acetonide group in aqueous TFA provided

SCHEME 2. Attempted Synthesis of **14**^a



^a Reagents and conditions: (a) (i) CH₃NH₂, room temperature; (ii) BzCl, pyridine, CH₂Cl₂, room temperature; (b) 10% CF₃COOH in MeOH, H₂O, room temperature; (c) SOCl₂, TEA, CH₂Cl₂, 0 °C; (d) NaIO₄, RuCl₃, CCl₄, H₂O, room temperature; (e) NaH, CH₃CN, 2,6-dichloropurine, room temperature.

diol **11**, which readily reacted with thionyl chloride to give cyclic sulfite **12**. Further oxidation of **12** with NaIO₄ afforded cyclic sulfate **13**. After achieving the syntheses of **12** and **13**, our plan was to couple these bicyclo derivatives with a suitable purine base. Accordingly, we initially attempted the regioselective opening of sulfite **12** with 2,6-dichloropurine. However, several attempts with this reaction failed to give the requisite pseudonucleoside derivative **14**. Also, the sodium salt of 2,6-dichloropurine reacted with cyclic sulfate **13** and the resulting isolated product obtained on further treatment with an excess of CH₃NH₂ did not give the expected, previously reported compound **1b**.¹⁸

The failure of the cyclic sulfite/sulfate approach in a convergent methodology contrasts with its utility in linear approaches, which appear to be better suited for accessing pyrimidine targets. Indeed, the set of analogous cyclic sulfite/sulfate derivatives **18** and **19**, prepared in a similar fashion as illustrated in Scheme 3, reacted well with sodium azide to give the azido derivative **20** in 82% yield, along with a small amount of its regioisomer **21**. Reduction of azide **20** to the corresponding amine **22** provides a useful starting material for the synthesis of 5'-hydroxymethyl (N)-methanocarba nucleosides, which are also targets of interest for ARs¹⁷ as well as other biological receptors. The bicyclic amine **22** (to which synthetic approaches were presented at a recent Roundtable Conference¹⁶) can therefore be used as a direct precursor of purine and pyrimidine analogues by using well-established linear approaches.²² However, our need to develop parallel methods to explore diversity is not well served by this approach where each complex multisubstituted purine has to be individually assembled on the requisite bicyclo[3.1.0]hexane scaffold.

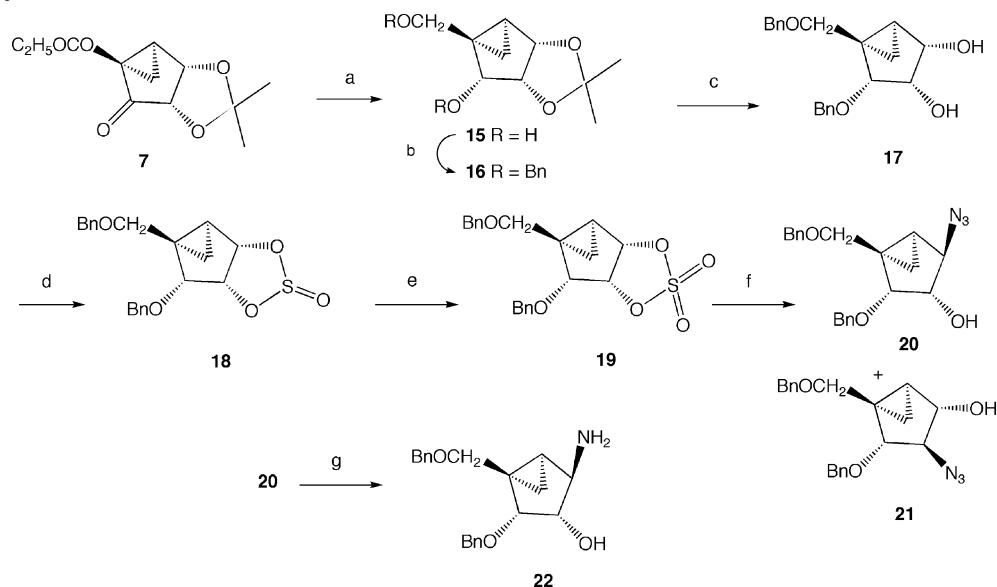
The problems described above prompted us to look for an alternative strategy to nucleobase coupling via a Mitsunobu reaction (Scheme 4). Accordingly, alcohol **9** was subjected to an acid-catalyzed equilibration to pro-

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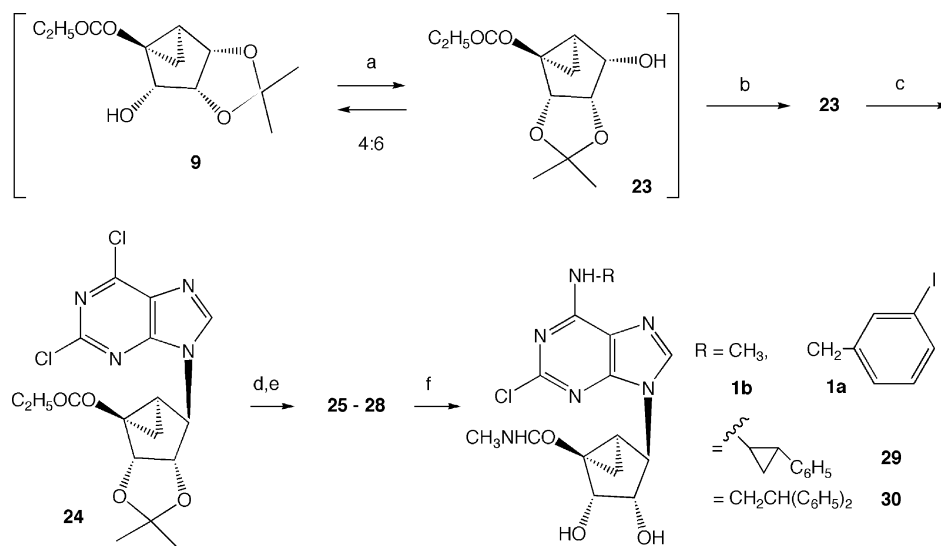
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SCHEME 3. Synthesis of **24**^a

^a Reagents and conditions: (a) DIBAL-H, -78°C to room temperature; (b) BnBr, NaH, DMF, 0°C to room temperature; (c) Dowex ion exchange resin, MeOH, room temperature; (d) SOCl_2 , TEA, CH_2Cl_2 , 0°C ; (e) NaIO_4 , RuCl_3 , CCl_4 , H_2O , room temperature; (f) NaN_3 , DMF, 100°C ; (g) Lindlar catalyst, H_2 .

SCHEME 4. Synthesis of **A₃ AR Agonists**^a

^a Reagents and conditions: (a) *p*-TsOH, acetone, reflux; (b) crystallization; (c) 2,6-dichloropurine, DIAD, TPP, THF, room temperature; (d) 3-iodobenzylamine·HCl, TEA (for **1a**), 40% aq MeNH_2 (for **1b**), *trans*-2-phenylcyclopropylamine·HCl, TEA (for **29**), 2,2-diphenylethylamine (for **30**), in MeOH, room temperature; (e) 40% aq MeNH_2 ; (f) 10% CF_3COOH in MeOH, H_2O , 70°C .

duce the isomeric acetonide **23**, which was isolated in 90% yield (based on recovery of alcohol **9**) by careful crystallization from cyclohexane. The requisite alcohol **23** when subjected to a Mitsunobu coupling reaction with 2,6-dichloropurine afforded the condensed product **24** in 36% yield. Treatment of **24** with an excess of CH_3NH_2 followed by deprotection of the acetonide group afforded authentic (N)-methanocarba nucleoside **1b** (MRS 2346), whose spectral properties matched those reported in the literature.¹⁸ In addition, reaction of **24** with 3-iodobenzylamine in the presence of Et_3N , followed by reaction with an excess of CH_3NH_2 , provided compound **26**. Removal of the acetonide by standard methods produced the other target **1a** (MRS 1898) in 74% yield. The spectral proper-

ties of **1a** matched those of the identical compound reported in the literature.¹⁸ To demonstrate the generality of this route, other novel *N*⁶-substituted (N)-methanocarba nucleosides, e.g., **29** and **30**, were prepared in reasonable yields. The detailed biological characterization of this series of nucleosides as selective *A₃* AR agonists will be reported separately.²¹ The experimental use of *A₃* AR agonists in models of cardiac ischemia and other medical conditions provides a promising approach for therapeutics.^{5-7,24}

Experimental Section

General Experimental Details. ¹H NMR spectra were obtained with a Varian Gemini-300 spectrometer (300 MHz)

with D₂O, CDCl₃, CD₃OD, and DMSO-*d*₆ as solvents. Low-resolution mass spectra were measured with a Finnigan-Thermoquest LCQ with APCI (Atmospheric Pressure Chemical Ionization) interface. Low-resolution and high-resolution FAB (fast atom bombardment) mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix.

2,3-O-Isopropylidene-D-erythrose (2b). **2b** was prepared from commercially available 2,3-O-isopropylidene-D-erythro-nolactone (**2a**) by the procedure of Cohen et al.²³ in 90% yield.

(4R,5S)-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)methan-1-ol (3). To a solution containing methyltriphenylphosphonium bromide (7.85 g, 22 mmol) in dry THF (60 mL) was added potassium *tert*-butoxide (2.2 g, 20 mmol). The resulting reaction mixture was stirred at room temperature for 1 h under nitrogen. The lactol **2** (1.60 g, 10 mmol) in dry THF (20 mL) was added at -78 °C, and the reaction was allowed to reach room temperature. After being stirred for an additional 3 h, it was treated with saturated brine (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated. Purification by column chromatography (silica gel; EtOAc:hexanes, 25:75) gave **3** (0.94 g, 60%) as an oil; [α]_D²⁵ +41.2 (c 2.5 CHCl₃) [lit.²⁵ [α]_D²⁵ +40.1] with identical spectral properties as reported in the literature.²⁵

Ethyl (4S,5S)-3-[2,2-Dimethyl-5-vinyl(1,3-dioxolan-4-yl)]-3-oxopropanoate (5a). **Method A.** From compound **3**, the acid **4b** was prepared according to the work of Rao and Lahiri.²⁵ A stirred solution of **4b** (0.35 g, 2.03 mmol) in THF (3 mL) maintained at 0 °C was treated with 1,1'-carbonyldiimidazole (0.43 g, 2.64 mmol). After 30 min, the temperature was raised to 30 °C and additional stirring was continued for 2 h. After being cooled to room temperature, this solution was added via cannula to a -78 °C solution of LiCH₂CO₂CH₂CH₃ obtained from EtOAc (0.6 mL, 6.14 mmol) and LDA (0.48 g, 6.1 mmol) in anhydrous THF (5 mL) during 1.5 h at -78 °C. The reaction was quenched at the same temperature with 1 N HCl (6.1 mL), stirred further at -78 °C for 10 min, allowed to warm to 0 °C, adjusted to pH 3, and extracted with EtOAc (80 mL). The combined organic extract was washed with brine, dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc, 95:5) to give the desired β-keto ester **5a** (0.293 g, 59%) as a clear oil. A small amount of the (4R,5S)-isomer **5b** (0.038 g, 8%) was also obtained as a clear oil.

Ethyl (4R,5S)-3-[2,2-dimethyl-5-vinyl(1,3-dioxolan-4-yl)]-3-oxopropanoate (5a): IR (neat) 1748, 1722 cm⁻¹; [α]_D²⁵ -42.7 (c 0.26, CHCl₃); ¹H NMR (CDCl₃) δ 12.08 (s, 0.1 H, D₂O exchangeable, enolic OH), 5.92–6.06 (m, 1 H), 5.37–5.56 (m, 2 H), 4.51–4.62 (m, 1 H), 4.20–4.38 (m, 3 H), 3.75 (AB q, 2 H, *J* = 16.4 Hz), 1.54–1.57 (m, 6 H, 2), 1.34–1.41 (m, 3 H); ¹³C NMR (CDCl₃) δ 202.72, 166.98, 131.80, 119.35, 111.06, 83.00, 78.81, 61.41, 47.56, 26.81, 24.79, 14.23 ppm; FAB MS *m/z* (rel intensity) 185 (7.2), 243 (MH⁺, 2).

5b: IR (neat) 1750, 1721 cm⁻¹; [α]_D²⁵ +29.9 (c 1.23 CHCl₃); ¹H NMR (CDCl₃) δ 12.00 (s, 1 H, D₂O exchangeable, enolic OH), 5.72–5.90 (m, 1 H), 5.30–5.57 (m, 2 H), 4.85–4.99 (m, 1 H), 4.22–4.33 (m, 2 H), 3.69 (d, 1 H, *J* = 16.4 Hz), 3.43 (d, 1 H, *J* = 16.4 Hz), 1.70 (s, 3 H), 1.48 (s, 3 H), 1.32–1.40 (m, 3 H); FAB MS *m/z* (rel intensity) 185 (98), 243 (MH⁺, 38).

Method B. A solution of dry DMSO (1.75 g, 22.4 mmol) in dry CH₂Cl₂ (20 mL) was added to a solution of (COCl)₂ (1.52 g, 12 mmol) in dry CH₂Cl₂ (40 mL), which had been cooled to -78 °C under a nitrogen atmosphere. The resulting reaction mixture was further stirred at the same temperature for another 15 min before a solution of alcohol **3** (1.27 g, 8 mmol) in dry CH₂Cl₂ (15 mL) was added carefully over 10 min, while the temperature was kept at -78 °C. The stirring was

continued for 30 min and then dry Et₃N (8.0 g, 80 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature, CH₂Cl₂ (100 mL) was subsequently added, and again the mixture was cooled to -78 °C. The solution was treated with saturated NaCl (40 mL) and then the reaction mixture was allowed to warm to room temperature. The organic layer was separated, dried (Na₂SO₄), and concentrated under reduced pressure. The crude aldehyde **4a** (3.0 g) was dissolved in CH₂Cl₂ (40 mL) and treated with SnCl₂ (5.10 g, 24 mmol) and ethyl diazoacetate (1.14 g, 10 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a pad of Celite (20.0 g), and the resulting organic layer was concentrated. The desired keto ester was purified by column chromatography (silica gel; hexanes:EtOAc, 95:5) to furnish **5a** as oil (0.69 g, 36%) with identical spectroscopic properties as those reported under Method A.

Ethyl (4S,5S)-3-[2,2-Dimethyl-5-vinyl(1,3-dioxolan-4-yl)]-2-diazo-3-oxopropanoate (6). To a stirred solution of keto ester **5a** (4.84 g, 20 mmol) in acetonitrile (40 mL) was successively added tosyl azide (4.13 g, 21 mmol) and Et₃N (4.4 g, 40 mmol). The resulting reaction mixture was concentrated after being stirred for 30 min at room temperature. The diazo derivative was purified by column chromatography (silica gel; hexanes:EtOAc, 95:5) to furnish **6** (3.75 g, 70%) as an oil; IR (neat) 2141, 1713 cm⁻¹; [α]_D²⁵ +81.0 (c 2.02, CHCl₃); ¹H NMR (CDCl₃) δ 5.77 (ddd, 1 H, *J* = 17.3, 10.1, 7.3 Hz), 5.70 (d, 1 H, *J* = 7.6 Hz), 5.45 (dm, 1 H, *J* = 17.1 Hz), 5.30 (dm, 1 H, *J* = 10.2 Hz), 5.05 (t, 1 H, *J* = 7.5 Hz), 4.36 (q, 2 H, *J* = 7.1 Hz), 1.74 (s, 3 H), 1.51 (s, 3 H), 1.41 (t, 3 H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃) δ 188.16, 161.13, 132.79, 119.61, 110.74, 80.45, 78.97, 61.80, 51.63, 26.87, 25.47, 14.12 ppm. FAB MS *m/z* (rel intensity) 269 (MH⁺, 86). This compound was used for the next step without further purification.

Ethyl (1S,3S,4S,5S)-3,4-O-Isopropylidene-2-oxobicyclo-[3.1.0]hexanecarboxylate (7). To a stirred solution of diazo compound **6** (5.36 g, 20 mmol) in dry toluene (15 mL) was added CuI (0.190 g, 1 mmol) at room temperature and the reaction mixture was refluxed for 8 h. The reaction mixture was cooled to room temperature, concentrated, and purified by column chromatography (silica gel; hexanes:EtOAc, 75:25) to provide bicyclic compound **7** (1.72 g, 36%) and compound **8** (0.57 g, 12%).

7: IR (neat) 1751, 1719 cm⁻¹; [α]_D²⁵ +33.6 (c 1.69, CHCl₃); ¹H NMR (CDCl₃) δ 5.12 (ddd, 1 H, *J* = 8.3, 5.4, 1.0 Hz), 4.45 (d, 1 H, *J* = 8.3 Hz), 4.29 (q, 2 H, *J* = 7.1 Hz), 2.84 (dt, 1 H, *J* = 8.3, 5.3 Hz), 2.18 (dd, 1 H, *J* = 8.1, 5.1 Hz), 1.89 (t, 1 H, *J* ≈ 5.2 Hz), 1.59 (s, 3 H), 1.39 (s, 3 H), 1.36 (t, 3 H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃) δ 199.95, 167.12, 115.12, 80.63, 73.68, 61.95, 33.19, 25.85, 24.39, 20.88, 14.19 ppm; FAB MS *m/z* (rel intensity) 241 (MH⁺, 100). Anal. Calcd for C₁₂H₁₆O₅: C, 59.99; H, 6.71. Found: C, 59.95; H, 6.80.

Ethyl (1R,3S,4S,5R)-3,4-O-isopropylidene-2-oxobicyclo-[3.1.0]hexanecarboxylate (8): IR (neat) 1755, 1722 cm⁻¹; [α]_D²⁵ +67.9 (c 1.12, CHCl₃); ¹H NMR (CDCl₃) δ 4.81 (d, 1 H, *J* = 5.1 Hz), 4.38 (dd, 1 H, *J* = 4.8, 1.7 Hz), 4.32 (dq, 2 H, *J* = 7.1, 1.5 Hz), 2.96 (dd, 1 H, *J* = 8.7, 5.7 Hz), 2.21 (ddd, 1 H, *J* = 8.8, 5.7, 1.7 Hz), 1.53 (s, 3 H), 1.45 (s, 3 H), 1.37 (t, 3 H, *J* = 4.1 Hz), 1.35 (irregular t, 1 H); ¹³C NMR (CDCl₃) δ 204.00, 168.89, 115.87, 81.10, 77.23, 63.40, 37.36, 29.20, 27.39, 22.34, 15.84 ppm; FAB MS *m/z* (rel intensity) 241 (MH⁺, 100). Anal. Calcd for C₁₂H₁₆O₅·0.45H₂O: C, 58.03; H, 6.86. Found: C, 57.96; H, 6.76.

Ethyl (1S,2R,3S,4S,5S)-3,4-O-isopropylidene-2-hydroxybicyclo[3.1.0]hexanecarboxylate (9). To a stirred solution of **7** (1.20 g, 5 mmol) in methanol (20 mL) at room temperature was added NaBH₄ (0.19 g, 5 mmol) while stirring was continued for an additional 1 h. The reaction mixture was then treated with acetone (2 mL) and concentrated to dryness. The residue was purified by column chromatography (silica gel; hexanes:EtOAc, 70:30) to give compound **9** (0.87 g, 72%) as a white solid; mp 109 °C (cyclohexane); [α]_D²⁵ +72.0 (c 0.15, CH₂-

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Cl₂); ¹H NMR (CDCl₃) δ 4.95 (t, 1 H, *J* = 7.5 Hz), 4.88 (t, 1 H, *J* = 6 Hz), 4.60 (t, 1 H, *J* = 7 Hz), 4.12–4.24, (m, 2 H), 2.48 (d, 1 H, *J* = 12 Hz, OH), 2.16–2.26 (m, 1 H), 1.48–1.61 (m, 5 H), 1.32 (s, 3 H), 1.26 (t, 3 H, *J* = 6.5 Hz); ¹³C NMR (CDCl₃) δ 172.13, 113.20, 79.77, 79.41, 70.35, 61.24, 41.03, 32.74, 26.33, 24.80, 16.07, 14.42 ppm; FAB MS *m/z* (rel intensity) 243 (MH⁺, 100). Anal. Calcd for C₁₂H₁₈O₅: C, 59.49; H, 7.49. Found: C, 59.36; H, 7.54.

(1S,2R,3S,4S,5S)-3,4-O-Isopropylidene-1-(N-methylcarbamoyl)bicyclo[3.1.0]hex-2-yl Benzoate (10). Compound **9** (0.240 g, 1 mmol) was stirred with aqueous CH₃NH₂ (1 mL, 40%) for 8 h. The mixture was concentrated to dryness under reduced pressure and the residue was dissolved in pyridine (2 mL). Benzoyl chloride (0.168 g, 1.2 mmol) was added and the resulting reaction mixture was stirred at room temperature for 4 h. After being reduced to dryness under vacuum the residue was dissolved in CHCl₃ (25 mL) and washed with water, and the organic layer was dried (Na₂SO₄). Purification by column chromatography (silica gel; CHCl₃:MeOH, 90:10) furnished **10** (0.175 g, 55%) as a solid, mp 75 °C; [α]²⁵_D +90.0 (*c* 0.1, CH₂Cl₂); ¹H (CDCl₃) δ 8.12–8.22 (m, 2 H), 7.42–7.65 (m, 3 H), 6.82 (br s, 1 H), 5.82–5.89 (m, 1 H), 4.78–5.05 (m, 2 H), 2.82 (br s, 3 H), 2.25–2.42 (m, 1 H), 1.42–1.81 (m, 5 H), 1.24 (s, 3H); FAB MS *m/z* (rel intensity) 332.1 (MH⁺, 62). Anal. Calcd for C₁₈H₂₁NO₅·H₂O: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.18; H, 6.39; N, 4.07.

(1S,2R,3S,4S,5S)-3,4-Dihydroxy-1-(N-methylcarbamoyl)-bicyclo[3.1.0]hex-2-yl Benzoate (11). A mixture of amide **10** (0.319 g, 1 mmol) containing 10% trifluoroacetic acid/MeOH (5 mL) and H₂O (0.5 mL) was stirred at room temperature for 10 h. The solvent was removed, and the residue was dried by coevaporation with toluene. Purification by column chromatography (silica gel; CHCl₃:MeOH, 90:10) afforded **11** (0.165 g, 57%) as a white solid; mp 112 °C; [α]²⁵_D +100.0 (*c* 0.1, CH₂-Cl₂); ¹H NMR (CDCl₃) δ 8.14 (d, 2 H, *J* = 6 Hz), 7.22–7.65 (m, 3 H), 7.18 (br s, 1 H), 5.62 (d, 1 H, *J* = 4.5 Hz), 4.48 (t, 1 H, *J* = 3.5 Hz), 4.24 (t, 1 H, *J* = 3.1 Hz), 2.83 (d, 3 H, *J* = 6.6 Hz), 2.43–2.74 (m, 3 H), 1.78 (t, 1 H, *J* = 2.5 Hz), 1.22–1.38 (m, 1 H); FAB MS *m/z* (rel intensity) 292.1 (MH⁺, 50). Anal. Calcd for C₁₅H₁₇NO₅: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.53; H, 6.12; N, 4.68.

Methyl (1S,2R,3S,4S,5S)-3,4-Sulfinyldioxy-2-phenyl-carbonyloxybicyclo[3.1.0]hexanecarboxamide (12). A solution of **11** (0.29 g, 1 mmol) in CH₂Cl₂ (4 mL) at 0 °C was stirred with Et₃N (0.61 g, 6 mmol) and SOCl₂ (0.24 g, 2 mmol) for 10 min. Ether (40 mL) and H₂O (20 mL) were added. The organic layer was washed with brine, dried (Na₂SO₄), and then reduced to dryness. The residue was purified by column chromatography (silica gel; CHCl₃:MeOH, 95:5) to furnish a sulfite **12** (0.249 g, 74%) as a solid; ¹H NMR (CDCl₃) δ 8.18 (dd, 2 H, *J* = 3.2, 2.5 Hz), 7.42–7.58 (m, 3 H), 7.14 (br s, 1 H), 5.95 (dd, 1 H, *J* = 2.7, 2.4 Hz), 5.61–5.76 (m, 1H), 5.54 (t, 1 H, *J* = 3.5 Hz), 5.36 (t, 1 H, *J* = 4.2 Hz), 2.82 (d, 3 H, *J* = 1.5 Hz), 2.52–2.61 (m, 1 H), 1.62–1.81 (m, 2 H); FAB MS *m/z* (rel intensity) 338.1 (MH⁺, 64).

Methyl (1S,2R,3S,4S,5S)-3,4-Sulfonyldioxy-2-phenyl-carbonyloxybicyclo[3.1.0]hexanecarboxamide (13). A solution of **12** (0.34 g, 1 mmol) in a mixture of CCl₄ (2 mL), CH₃-CN (2 mL), and H₂O (2 mL) was treated with NaIO₄ (0.27 g, 1.25 mmol) and RuCl₃·3H₂O (0.002 g). After 1 h of stirring, the reaction mixture was partitioned between ether (40 mL) and H₂O (20 mL). The organic layer was washed with brine, dried (Na₂SO₄), and evaporated. The residue was purified by column chromatography (silica gel; CHCl₃:MeOH, 95:5) to furnish sulfone **13** (0.240 g, 67%) as a solid; [α]²⁵_D +16.0 (*c* 0.1, CH₂Cl₂); ¹H NMR (CDCl₃) δ 8.14 (dd, 2 H, *J* = 1.4 Hz, 1.2 Hz), 7.42–7.76, (m, 3 H), 7.18 (br s, 1 H), 6.08 (d, 1 H, *J* = 3.2 Hz), 5.55 (t, 1 H, *J* = 3.6 Hz), 5.35 (t, 3 H, *J* = 4.1 Hz), 2.83 (d, 3 H, *J* = 3.6 Hz), 2.61–2.67 (m, 1 H), 1.82–1.89 (m, 1 H), 1.63–1.76, (m, 1 H); FAB MS *m/z* (rel intensity) 354.1 (MH⁺, 50).

(1S,2R,3S,4S,5S)-3,4-O-Isopropylidene-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2-ol (15). A stirred solution of

7 (2.0 g, 8.32 mmol) in toluene (30 mL) cooled to –78 °C was treated dropwise with diisobutylaluminum hydride (DIBAL-H, 21.1 mL, 1.5 M solution in THF) and stirred at that temperature for 1 h. Methanol (15 mL) and EtOAc (70 mL) were added and the resulting mixture was stirred for 5 h allowing it to reach room temperature. The generated gel was filtered off through a pad of Celite, and the filtrate collected was evaporated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH₂Cl₂:MeOH, 95:5) to give diol **15** (0.923 g, 55%) as an oil; IR (neat) 3419 cm⁻¹; [α]²⁵_D +19.6 (*c* 0.75, MeOH); ¹H NMR (CDCl₃) δ 4.95 (t, 1 H, *J* = 5.6 Hz), 4.60–4.70 (m, 2 H), 3.86 (d, 1 H, *J* = 11.5 Hz), 3.60 (d, 1 H, *J* = 11.5 Hz), 2.25 (br s, 2 H, 2 × OH), 1.71 (irregular quintet, 1 H), 1.63 (s, 3 H), 1.3 (s, 3 H), 1.27 (irregular t, 1 H), 0.77 (dd, 1 H, *J* = 8.3, 5.4 Hz); FAB MS *m/z* (rel intensity) 79 (100), 95 (33), 125 (91), 201 (MH⁺, 64). Anal. Calcd for C₁₀H₁₆O₄·0.1CH₃OH: C, 59.63; H, 8.13. Found: C, 59.48; H, 8.21.

(1S,2R,3S,4S,5S)-3,4-O-Isopropylidene-1-[(phenylmethoxy)methyl]-2-(phenylmethoxy)bicyclo[3.1.0]hexane (16). A stirred solution of diol **15** (0.46 g, 2.31 mmol) in DMF (14 mL) at 0 °C was treated portionwise with NaH (0.23 g, 60% dispersion in mineral oil, 5.78 mmol). Stirring was continued for 30 min allowing the temperature to reach ambient conditions. Benzyl bromide (0.61 mL, 5.13 mmol) was added and after warming to 75 °C the reaction was stirred for 3 h. After reaching room temperature, the mixture was partitioned between Et₂O (250 mL) and water (50 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered, and reduced to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc, 80:20) to give fully protected compound **16** (0.542 g, 62%) as an oil plus recovered starting material **15** (0.126 g).

16: IR (neat) 1076 cm⁻¹; [α]²⁵_D +81.2 (*c* 1.2, CHCl₃); ¹H NMR (CDCl₃) δ 7.18–7.37 (m, 10 H), 4.78 (d, 1 H, *J* = 5.8 Hz), 4.74 (d, 1 H, *J* = 12.1 Hz), 4.50 (d, 1 H, *J* = 12.1 Hz), 4.48 (m, 1 H), 4.36 (m, 3 H), 3.77 (d, 1 H, *J* = 10.3 Hz), 2.94 (d, 1 H, *J* = 10.3 Hz), 1.54 (s, 3 H), 1.50 (m, 1 H), 1.25 (s, 3 H), 1.43 (irregular t, 1 H), 0.58 (m, 1 H); FAB MS *m/z* (rel intensity) 91 (100), 381 (MH⁺, 2). Anal. Calcd for C₂₄H₂₈O₄: C, 75.76; H, 7.42. Found: C, 75.50; H, 7.37.

(1S,2R,3S,4S,5S)-1-[(Phenylmethoxy)methyl]-2-(phenylmethoxy)bicyclo[3.1.0]hexane-3,4-diol (17). A solution of **16** (0.54 g, 1.42 mmol) in MeOH (30 mL) was stirred at room temperature for 3 days in the presence of DOWEX ion-exchange resin (3 g, 50WX8-100). After the resin was filtered off, the filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc:hexanes, 30:70) to give diol **17** (0.438 g, 91%) as an oil, plus recovered starting material **16** (0.049 g).

17: IR (neat) 3421 cm⁻¹; [α]²⁵_D +44.9 (*c* 1.2, CHCl₃); ¹H NMR (MeOH-*d*₄) δ 7.20–7.35 (m, 10 H), 4.64 (d, 1 H, *J* = 11.7 Hz), 4.46 (d, 1 H, *J* = 11.7 Hz), 4.38 (AB q, 2 H, *J* = 11.7 Hz), 4.19–4.22 (m, 2 H), 3.92 (t, 1 H, *J* = 6.1 Hz), 3.75 (d, 1 H, *J* = 10.5 Hz), 3.08 (d, 1 H, *J* = 10.5 Hz), 1.43–1.49 (m, 2 H), 0.41 (m, 1 H); FAB MS *m/z* (rel intensity) 91 (100), 341 (MH⁺, 5). Anal. Calcd for C₂₁H₂₄O₄: C, 74.09; H, 7.11. Found: 73.39; H, 7.10.

(1S,2R,3S,4S,5S)-3,4-O-Sulfinyl-1-[(phenylmethoxy)methyl]-2-(phenylmethoxy)bicyclo[3.1.0]hexane (18). In the presence of triethylamine (0.71 mL, 5.10 mmol), a stirred solution of diol **17** (0.43 g, 1.27 mmol) in CH₂Cl₂ (8 mL) at 0 °C was treated with SOCl₂ (0.14 mL, 1.92 mmol). After 10 min, the reaction was partitioned between Et₂O (80 mL) and water (10 mL), and the organic layer was washed with brine (10 mL), dried (MgSO₄), and filtered. The filtrate was reduced to dryness under reduced pressure and residue was purified by silica gel column chromatography (hexanes:EtOAc, 80:20) to give the cyclic sulfite **18** (0.436 g, 89%) as an oil; IR (neat) 1027 cm⁻¹; ¹H NMR (CDCl₃) δ (m, 10 H), 5.56 (t, 1 H, *J* = 5.9 Hz), 5.19 (irregular t, 1 H), 4.73 (d, 1 H, *J* = 11.7 Hz), 4.61 (d, 1 H, *J* = 6.2 Hz), 4.52 (d, 1 H, *J* = 11.7 Hz), 4.44 (AB q, 2 H,

$J = 11.7$ Hz), 3.84 (d, 1 H, $J = 10.3$ Hz), 3.10 (d, 1 H, $J = 10.3$ Hz), 1.72 (irregular quintet, 1 H), 1.18 (dd, 1 H, $J = 5.9$, 4.4 Hz), 0.72 (irregular t, 1 H); FAB MS m/z (rel intensity) 91 (100), 387 (MH^+ , 3). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_5\text{S}$: C, 65.27; H, 5.74; S, 8.30. Found: C, 65.33; H, 5.81; S, 8.20.

(1S,2R,3S,4S,5S)-3,4-O-Sulfonyl-1-[(phenylmethoxy)methyl]-2-(phenylmethoxy)bicyclo[3.1.0]hexane (19). A stirred solution of cyclic sulfite **18** (0.25 g, 0.64 mmol) in CCl_4 (2.5 mL), CH_3CN (2.5 mL), and water (3.75 mL) was cooled to 0 °C and treated with NaIO_4 (0.204 g, 0.95 mmol) and RuCl_3 (0.005 g). After 30 min, the reaction mixture was partitioned between Et_2O (100 mL) and water (20 mL). The organic layer was washed with brine (10 mL), dried (MgSO_4), filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes: EtOAc , 75:25) to give the cyclic sulfate **19** (0.254 g, 99%) as an oil; (IR) 1718 cm^{-1} ; $[\alpha]^{25}_{\text{D}} +76.6$ (c 1.14, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 7.20–7.36 (m, 10 H), 5.40 (t, 1 H, $J = 5.9$ Hz), 4.96 (irregular t, 1 H), 4.68 (d, 1 H, $J = 11.7$ Hz), 4.58 (dd, 1 H, $J = 6.2$, 1.5, Hz), 4.48 (d, 1 H, $J = 11.7$ Hz), 4.42 (AB q, 2 H $J = 11.7$ Hz), 4.10 (q, traces of EtOAc), 3.88 (d, 1 H, $J = 10.6$ Hz), 3.00 (d, 1 H, $J = 10.6$ Hz), 1.81 (irregular quintet, 1 H), 1.62 (dd, 1 H, $J = 6.6$, 4.0 Hz), 1.25 (t, traces of EtOAc), 0.87 (br t, 1 H); FAB MS m/z (rel intensity) 91 (100), 403 (MH^+ , 2). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_6\text{S}$: C, 62.33; H, 5.66; S, 7.63. Found: C, 62.10; H, 5.67; S, 7.72.

(1S,2R,3S,4R,5S)-4-Azido-2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexan-3-ol (20). **Method 1.** A stirred solution of cyclic sulfite **18** (0.25 g, 0.34 mmol) and NaN_3 (0.044 g, 0.68 mmol) in DMF (2 mL) was heated at 100 °C for 12 h. After reaching room temperature, the reaction mixture was partitioned between Et_2O (60 mL) and water (20 mL). The organic layer was washed with brine (10 mL), dried (MgSO_4), filtered, and evaporated. The residue was purified by silica gel flash column chromatography (hexanes: EtOAc , 70:30) to give the desired azido compound **20** (0.102 g, 82%) and its regiosomer **21** (0.012 g, 10%) as oils. **Method 2.** A solution of cyclic sulfite **19** (0.023 g, 0.06 mmol) and NaN_3 (0.011 g, 0.17 mmol) in CH_3CN (2 mL) was stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc (20 mL) and water (5 mL), and the organic layer was washed with brine (2 mL), dried (MgSO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes: EtOAc , 70:30) to give exclusively the desired azido compound **20** (0.014 g, 70%) as an oil; (IR) 2096 cm^{-1} ; $[\alpha]^{25}_{\text{D}} -58.4$ (c 1.06, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 7.25–7.33 (m, 10 H), 4.63 (d, 1 H, $J = 11.3$ Hz), 4.51 (AB d, 2 H, $J = 11.7$ Hz), 4.45 (d, 1 H, $J = 11.3$ Hz), 4.36 (br d, 1 H, $J = 6.2$ Hz), 3.90 (dm, 1 H, $J = 6.2$ Hz), 3.71 (br d, 1 H, $J = 2$ Hz), 3.61 (d, 1 H, $J = 10.5$ Hz), 3.28 (d, 1 H, $J = 10.5$ Hz), 2.53 (br s, 1 H, OH), 1.38 (dd, 1 H, $J = 8.8$, 4.1 Hz), 1.24 (dd, 1 H, $J = 5.3$, 4.1 Hz), 0.70 (ddd, 1 H, $J = 8.6$, 5.5, 1.2 Hz). This compound was used without further purification for the next step.

(1S,2R,3S,4R,5S)-3-Azido-4-(benzyloxy)-5-[(benzyloxy)methyl]bicyclo[3.1.0]hexan-2-ol (21): (IR) 2098 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.19–7.33 (m, 10 H), 5.54 (irregular t, 1 H), 5.17 (irregular t, 1 H), 4.70 (d, 1 H, $J = 11.7$ Hz), 4.58 (d, 1 H, $J = 5.5$ Hz), 4.48 (d, 1 H, $J = 11.7$ Hz), 4.40 (AB q, 2 H, $J = 11.7$ Hz), 3.81 (d, 1 H, $J = 10.5$ Hz), 2.91 (d, 1 H, $J = 10.5$ Hz), 1.66 (irregular quintuplet, 1 H), 1.13 (dd, 1 H, $J = 5.9$, 4.3 Hz), 0.69 (br t, 1 H).

(1S,2R,3S,4R,5S)-4-Amino-2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexan-3-ol (22). A solution of azido compound **20** (0.012 g, 0.03 mmol) in a mixture of CH_2Cl_2 (1.2 mL) and MeOH (1.2 mL) was stirred for 3 days under a balloon filled with a hydrogen atmosphere in the presence of Lindlar's catalyst (0.002 g). The catalyst was filtered off with Celite as a filtering aid, and the filtrate was reduced to dryness under vacuum. The residue was purified by silica gel flash column chromatography (CH_2Cl_2 :MeOH, 90:10) to give amine **22** (0.009 g, 81%) as a clear oil; (IR) (neat)

3346, 3278 cm^{-1} ; $[\alpha]^{25}_{\text{D}} +13.1$ (c 0.78, MeOH); $^1\text{H NMR}$ ($\text{CH}_3\text{OH}-d_4$) δ 7.28–7.40 (m, 10 H), 4.61 (AB q, 2 H, $J = 11.7$ Hz), 4.48 (AB s, 2 H), 4.33 (d, 1 H, $J = 6.2$ Hz), 3.81 (dd, 1 H, $J = 6.2$, 3.3 Hz), 3.68 (d, 1 H, $J = 10.3$ Hz), 3.33 (d, 1 H, $J = 10.3$ Hz), 3.05 (d, 1 H, $J = 3.3$ Hz), 1.28 (irregular t, 1 H), 1.20 (dd, 1 H, $J = 8.6$, 4.2 Hz), 0.73 (dd, 1 H, $J = 8.6$, 4.9 Hz); FAB MS m/z (rel intensity) 91 (100), 340 (MH^+ , 75). Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_3 \cdot 0.5\text{H}_2\text{O}$: C, 72.39; H, 7.52; N, 4.02. Found: C, 72.23; H, 7.28; N, 3.95.

Ethyl (1S,2R,3S,4S,5S)-2,3-O-(isopropylidene)-4-hydroxybicyclo[3.1.0]hexanecarboxylate (23). A solution of **9** (0.48 g, 2.0 mmol) and $p\text{-TsOH} \cdot \text{H}_2\text{O}$ (0.19 g, 1 mmol) in acetone (20 mL) was refluxed for 8 h. Following the addition of NET_3 (1 mL), the solution was concentrated under reduced pressure. Flash column chromatography (silica gel; CHCl_3 :MeOH, 90:10) of the residue furnished a mixture of isomerized alcohols **25** and **9** in a 6:4 ratio based on NMR. This crude mixture was further purified by careful crystallization from cyclohexane to obtain the requisite pure **23** (0.196 g, 41%) as colorless crystals. The remaining alcohol **9** was recycled.

23: mp 80 °C; $[\alpha]^{25}_{\text{D}} +124.0$ (c 0.15, CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3) δ 5.38 (d, 1 H, $J = 5.5$ Hz), 4.42–4.64 (m, 2 H), 4.08–4.21 (m, 2 H), 2.39–2.45 (m, 2 H), 1.42–1.62 (m, 5 H), 1.35 (s, 3 H), 1.12 (t, 2 H, $J = 3.2$ Hz); FAB MS m/z (rel intensity) 243.1 (MH^+ , 100); $^{13}\text{C NMR}$ (CDCl_3) δ 172.21, 113.42, 79.97, 79.65, 70.20, 61.29, 39.25, 26.27, 24.74, 16.93, 14.43 ppm. Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_5$: C, 59.49; H, 7.49. Found: C, 59.46; H, 7.59.

Ethyl (1'S,2'R,3'S,4'R,5'S)-4'-(2,6-Dichloropurin-9-yl)-2',3'-O-(isopropylidene)bicyclo[3.1.0]hexanecarboxylate (24). A mixture of triphenyl phosphine (0.104 g, 0.4 mmol) and 2,6-dichloropurine (0.076 g, 0.4 mmol) in dry THF (2 mL) was treated with diisopropylazodicarboxylate (0.080 g, 0.4 mmol) at room temperature. After 20 min of stirring, a solution of **23** (0.048 g, 0.2 mmol) in THF (1 mL) was added and the mixture was stirred further for 8 h. Concentration and purification of the residue by column chromatography (silica gel; CHCl_3 :MeOH, 90:10) furnished **24** (0.029 g, 36%) as a white solid; mp 104 °C; $[\alpha]^{25}_{\text{D}} +34$ (c 0.1, CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3) δ 8.09 (s, 1 H), 5.85 (d, 1 H, 6.5 Hz), 4.91 (s, 1 H), 4.72 (d, 1 H, $J = 5.5$ Hz), 4.05–4.38 (m, 2 H), 2.14–2.2 (m, 1 H), 1.75–1.82 (m, 1 H), 1.52–1.62 (m, 4 H), 1.15–1.38 (m, 6 H); $^{13}\text{C NMR}$ (CDCl_3) δ 171.41, 153.39, 152.53, 144.90, 131.56, 112.97, 89.12, 80.83, 61.93, 61.38, 40.22, 36.78, 26.10, 24.35, 18.86, 14.48 ppm; FAB MS m/z (rel intensity) 413.1 (MH^+ , 100). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_4$: C, 49.41; H, 4.39; N, 13.56. Found: C, 49.14; H, 4.64; N, 13.26.

(1'S,2'R,3'S,4'R,5'S)-{4'-[2-Chloro-6-(methylamino)purin-9-yl]-2',3'-O-(isopropylidene)bicyclo[3.1.0]hexyl}-N-methylcarboxamide (25). A stirred solution of **24** (0.041 g, 0.1 mmol) in MeOH (2 mL) was treated with aqueous CH_3NH_2 (0.5 mL, 40%) for 8 h at room temperature. The reaction mixture was concentrated to dryness and the product was purified by preparative TLC, using CHCl_3 :MeOH (90:10) as the mobile phase, to afford **25** (0.022 g, 60%) as white solid; mp 221 °C; $[\alpha]^{25}_{\text{D}} +10.0$ (c 0.05, MeOH); $^1\text{H NMR}$ (CDCl_3) δ 7.71 (s, 1 H), 6.92 (br s, 1 H), 6.08 (s, 1 H), 5.65 (d, 1 H, $J = 5.4$ Hz), 4.63–4.84 (m, 2 H), 3.11 (br s, 3 H), 2.95 (d, 3 H, $J = 3.8$ Hz), 1.95–2.06 (m, 1 H), 1.61–1.66 (m, 1 H), 1.56 (s, 3 H), 1.08–1.24 (m, 4 H); FAB MS m/z (rel intensity) 393.1 (MH^+ , 100). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{ClN}_6\text{O}_3$: C, 51.98; H, 5.39; N, 21.39. Found: C, 51.71; H, 5.86; N, 20.82.

(1'S,2'R,3'S,4'R,5'S)-{4'-[2-Chloro-6-(methylamino)purin-9-yl]-2',3'-dihydroxybicyclo[3.1.0]hexyl}-N-methylcarboxamide (1b). A mixture of amide **25** (0.016 g, 0.04 mmol) containing 10% trifluoroacetic acid/MeOH (5 mL) and H_2O (0.5 mL) was heated at 70 °C for 3 h. The solvent was removed and the residue was dried by coevaporation with toluene. The residue was purified by using preparative TLC (CHCl_3 :MeOH, 90:10) to afford **1b** (0.010 g, 71%) as a white solid; mp 248 °C dec; $[\alpha]^{25}_{\text{D}} +16.0$ (c 0.05, CH_2Cl_2); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 8.22 (br s, 1 H), 8.05 (s, 1 H), 7.55 (br s, 1H),

5.38 (d, 1 H, $J = 2.5$ Hz), 4.80–4.94 (m, 2 H), 4.61 (s, 1 H), 3.76–3.86 (m, 2 H), 3.30 (br s, 3 H), 2.74 (d, 3 H, $J = 2.5$ Hz), 1.74–1.83 (m, 1 H), 1.61 (t, 1 H, $J = 2.4$ Hz), 1.21–1.32 (m, 1 H); FAB MS m/z (rel intensity) 353.07 (MH⁺, 100). Anal. Calcd for C₁₄H₁₇ClN₆O₃·0.25H₂O: C, 47.06; H, 4.94; N, 23.52. Found: C, 47.06; H, 5.24; N, 23.98.

(1'S,2'R,3'S,4'R,5'S)-(4'-[2-Chloro-6-[(3-iodophenyl)amino]purin-9-yl]-2',3'-O-(isopropylidene)bicyclo[3.1.0]hexyl)-N-methylcarboxamide (26). A solution of 24 (0.042 g, 0.1 mmol) in MeOH (2 mL) was treated with 3-iodobenzylamine hydrochloride (0.078 g, 0.15 mmol) and Et₃N (0.5 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated to dryness and the resulting residue was purified by flash column chromatography (silica gel; CHCl₃:MeOH, 90:10). The intermediate product was dissolved in MeOH (3 mL), treated with an excess of aqueous CH₃NH₂ (0.5 mL, 40%), and stirred at room temperature for 6 h. After being evaporated to dryness and preparative TLC purification (CHCl₃:MeOH, 90:10) 26 (0.028 g, 46%) was obtained as a white solid; mp 156 °C; [α]_D²⁵ +7.50 (c 0.04, MeOH); ¹H NMR (CDCl₃) δ 7.61–7.78 (m, 3 H), 7.38 (d, 1 H, $J = 5.4$ Hz), 7.09 (t, 1 H, $J = 5.7$ Hz), 6.82 (br s, 1 H), 6.35 (br s, 1 H), 5.63 (d, 1 H, $J = 6.3$ Hz), 4.65–4.82 (m, 3 H), 2.91 (d, 3 H, $J = 2.5$ Hz), 2.02–2.11 (m, 1 H), 1.11–1.92 (m, 8 H); FAB MS m/z (rel intensity) 595.1 (MH⁺, 100). Anal. Calcd for C₂₃H₂₄ClIN₆O₃·0.5H₂O: C, 45.75; H, 4.17; N, 13.92. Found: C, 45.92; H, 4.16; N, 13.89.

(1'S,2'R,3'S,4'R,5'S)-(4'-[2-Chloro-6-[(3-iodophenyl)methyl]amino]purin-9-yl)-2',3'-dihydroxybicyclo[3.1.0]hexyl]-N-methylcarboxamide (1a). A mixture of amide 26 (0.024 g, 0.04 mmol) containing 10% trifluoroacetic acid in MeOH (5 mL) and H₂O (0.5 mL) was heated at 70 °C for 3 h. The solvent was removed, and the residue was dried by coevaporation with toluene. The residue was purified with preparative TLC (CHCl₃: MeOH, 90:10) to afford 1a (0.016 g, 74%) as a white solid; mp 230 °C; [α]_D²⁵ +7.0 (c 0.1, MeOH); ¹H NMR (DMSO-*d*₆) δ 8.84 (br s, 1 H), 8.11 (s, 1 H), 7.78 (s, 1 H), 7.42–7.62 (m, 2 H), 7.36 (d, 1 H, $J = 3.5$ Hz), 7.14 (t, 1 H, $J = 4.5$ Hz), 5.44 (d, 1 H, $J = 4.8$ Hz), 4.75–4.91 (m, 2 H), 4.56–4.69 (m, 2 H), 3.86–3.92 (m, 1 H), 2.67 (d, 1 H, $J = 2.5$ Hz), 1.81–1.89 (m, 1 H), 1.61–1.65 (m, 1 H), 1.23–1.29 (m, 1 H); ¹³C NMR (DMSO-*d*₆) δ 171.06, 154.79, 152.95, 149.46, 141.96, 139.44, 136.05, 135.56, 130.54, 126.85, 94.76, 76.11, 71.05, 61.19, 42.50, 38.12, 37.82, 27.63, 26.13, 13.71 ppm; FAB MS m/z (rel intensity) 555.1 (MH⁺, 100). Anal. Calcd for C₂₀H₂₀ClIN₆O₃·0.5H₂O: C, 42.61; H, 3.75; N, 14.91. Found: C, 42.54; H, 3.76; N, 14.52.

(1'S,2'R,3'S,4'R,5'S)-(4'-[2-Chloro-6-[(*trans*-2-phenylcyclopropyl)amino]purin-9-yl]-2',3'-O-(isopropylidene)bicyclo[3.1.0]hexyl)-N-methylcarboxamide (27). With the same procedure described for the synthesis of 26, except for the use of *trans*-2-phenylcyclopropylamine hydrochloride, compound 27 (0.023 g, 48%) was obtained as a solid; mp 168 °C; [α]_D²⁵ +4.0 (c 0.1, MeOH); ¹H NMR (CDCl₃) δ 7.71 (s, 1 H), 7.19–7.38 (m, 5 H), 6.98 (br s, 1 H), 6.18 (br s, 1 H), 5.68 (d, 1 H, $J = 5.2$ Hz), 5.76–5.82 (m, 3 H), 2.91 (d, 1 H, $J = 3.6$ Hz), 2.18–2.23 (m, 1 H), 1.97–2.08 (m, 1 H), 1.54–1.78 (m, 5 H), 1.22–1.34 (m, 5 H); FAB MS m/z (rel intensity) 495.3 (MH⁺, 100). Anal. Calcd for C₂₅H₂₇ClN₆O₃·0.25H₂O: C, 58.02; H, 5.75; N, 16.24. Found: C, 58.17; H, 5.46; N, 15.85.

(1'S,2'R,3'S,4'R,5'S)-(4'-[6-[(2,2-Diphenylethyl)amino]-2-chloropurin-9-yl]-2',3'-O-(isopropylidene)bicyclo[3.1.0]hexyl)-N-methylcarboxamide (28). With the same procedure described for the synthesis of 26, except for the use of 2,2-diphenylethylamine, compound 28 (0.023 g, 42%) was obtained as a solid; mp 145 °C; [α]_D²⁵ +8.0 (c 0.1, MeOH); ¹H NMR (CDCl₃) δ 7.21–7.78 (m, 11 H), 6.83 (br s, 1 H), 6.26 (br s, 1 H), 5.66 (d, 1 H, $J = 5.6$ Hz), 4.21–4.83 (m, 5 H), 2.91 (d, 3 H, $J = 4.8$ Hz), 1.97–2.03 (m, 1 H), 1.23–1.78 (m, 8 H); FAB MS m/z (rel intensity) 559.3 (MH⁺, 100). Anal. Calcd for C₃₀H₃₁ClN₆O₃·H₂O: C, 63.43; H, 5.68; N, 14.79. Found: C, 63.19; H, 5.71; N, 15.05.

(1'S,2'R,3'S,4'R,5'S)-(4'-[2-Chloro-6-[(*trans*-2-phenylcyclopropyl)amino]purin-9-yl]-2',3'-dihydroxybicyclo[3.1.0]hexyl)-N-methylcarboxamide (29). Starting from compound 27 and following the same procedure described for the synthesis of 1a, compound 29 (0.013 g, 72%) was obtained as a solid; mp 230 °C dec; [α]_D²⁵ +19.0 (c 0.1, MeOH); ¹H NMR (CDCl₃) δ 7.82 (s, 1 H), 7.23–7.38 (m, 5 H), 6.92 (br s, 1 H), 6.31 (br s, 1 H), 4.98 (d, 1 H, $J = 4.8$ Hz), 4.83 (s, 1 H), 4.08–4.29 (m, 2 H), 2.92 (d, 3 H, $J = 4.8$ Hz), 2.08–2.23 (m, 1 H), 1.62–1.96 (m, 2 H), 1.21–1.44 (m, 3 H); ¹³C NMR (CDCl₃) δ 171.98, 156.37, 140.15, 139.25, 128.59, 127.32, 126.57, 119.68, 72.66, 62.31, 39.28, 26.88, 26.56, 25.75, 14.31 ppm; FAB MS m/z (rel intensity) 455.2 (MH⁺, 100). Anal. Calcd for C₂₂H₂₃ClN₆O₃·0.5H₂O: C, 56.96; H, 5.21; N, 18.12. Found: C, 57.17; H, 4.93; N, 16.47.

(1'S,2'R,3'S,4'R,5'S)-(4'-[6-[(2,2-Diphenylethyl)amino]-2-chloropurin-9-yl]-2',3'-dihydroxybicyclo[3.1.0]hexyl)-N-methylcarboxamide (30). Starting from compound 28 and following the same procedure described for the synthesis of 1a, compound 30 (0.014 g, 70%) was obtained as a solid; mp 232 °C dec; [α]_D²⁵ +6.0 (c 0.1, MeOH); ¹H NMR (CDCl₃) δ 7.76 (s, 1 H), 7.21–7.38 (m, 10 H), 6.83 (br s, 1 H), 5.97 (br s, 1 H), 4.96 (d, 1 H, $J = 4.8$ Hz), 4.80 (br s, 1H), 4.02–4.38 (m, 4 H), 2.91 (d, 3 H, $J = 4.8$ Hz), 2.12–2.21 (m, 1 H), 1.21–1.39 (m, 2 H); ¹³C NMR (CDCl₃) δ 171.87, 155.42, 141.70, 139.14, 129.04, 128.34, 127.23, 119.23, 72.75, 62.41, 50.69, 45.36, 39.35, 26.86, 26.55, 14.30 ppm; FAB MS m/z (rel intensity) 519.3 (MH⁺, 100). Anal. Calcd for C₂₇H₂₇ClN₆O₃·H₂O: C, 60.39; H, 5.44; N, 15.65. Found: C, 60.61; H, 5.34; N, 15.64.

X-ray Crystallographic Structure Determination. A colorless plate with approximate orthogonal dimensions 0.346 × 0.213 × 0.120 mm³ was placed and optically centered on a Bruker SMART CCD system at –80 °C. The initial unit cell was indexed by using a least-squares analysis of a random set of reflections collected from three series of 0.3° wide ω -scans, 10 s per frame, and 25 frames per series that were well distributed in reciprocal space. Data frames were collected [Mo K α] with 0.2° wide ω -scans, 30 s per frame, and 909 frames per series. Five complete series were collected at varying φ angles ($\varphi = 0^\circ, 72^\circ, 144^\circ, 216^\circ, 288^\circ$). Additionally, 300 frames, a partial repeat of the first series, were also collected for redundancy and decay purposes. The crystal to detector distance was 4.913 cm, thus providing a complete sphere of data to $2\theta_{\max} = 55.0^\circ$. A total of 37686 reflections were collected and corrected for Lorentz and polarization effects and absorption, using Blessing's method as incorporated into the program SADABS^{26,27} with 5784 unique $|R(\text{int})| = 0.0350$.

Crystallographic calculations were performed on a personal computer (PC) with a Pentium 1.80 GHz processor and 512MB of extended memory. The SHELXTL²⁸ program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences, and intensity statistics indicated the unique chiral orthorhombic space group $P2_12_12_1$ (no. 19). The structure was determined by direct methods with the successful location of nearly all non-hydrogen atoms, using the program XS.²⁹ The structure was refined with XL.³⁰ One least-squares difference Fourier cycle was required to locate the remaining non-hydrogen atoms. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were initially placed in calculated positions but allowed to refine freely during the final refinement stages. The absolute structure parameter, Flack (x),³¹

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was found to be 0.0(9), indicating, additionally from the known precursor, that the correct enantiomorph has been chosen. The final structure was refined to convergence [$\Delta/\sigma \leq 0.001$] with $R(F) = 4.06\%$, $wR(F^2) = 8.04\%$, $GOF = 1.123$ for all 2753 unique reflections [$R(F) = 3.23\%$, $wR(F^2) = 7.66\%$ for those 2424 data with $F_o > 4\sigma(F_o)$]. The final difference Fourier map was featureless, indicating that the structure is both correct and complete.

The function minimized during the full-matrix least-squares refinement was $\sum w(F_o^2 - F_c^2)$, where $w = 1/[\sigma^2(F_o^2) + (0.0366P)^2 + 0.1908P]$ and $P = (\max(F_o^2, 0) + 2F_c^2)/3$. An empirical correction for extinction was also attempted but found to be negative and therefore not applied.

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Supporting Information Available: X-ray structural coordinates and 3D representation of compound **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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