JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

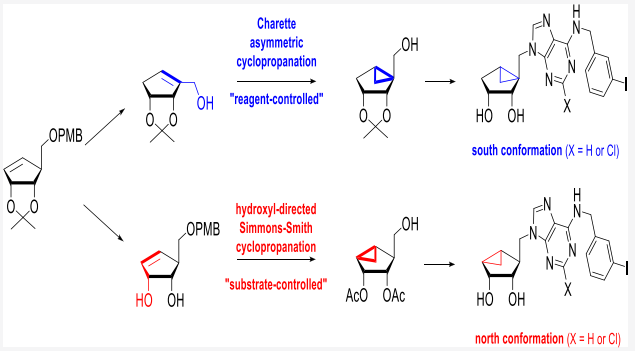
Stereoselective Synthesis of (*S*)- and (*N*)-Cyclopropyl-Fused Carbocyclic Nucleosides Using Stereoselective Cyclopropanation

Young Eum Hyun, Hong-Rae Kim, and Lak Shin Jeong*

Cite This: *J. Org. Chem.* 2021, 86, 9828−9837 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: To determine which sugar conformation is favorable in binding to peroxisome proliferator-activated receptors, the conformationally locked south (*S*) and north (*N*) analogues were asymmetrically synthesized using a bicyclo[3.1.0]hexane template. The (*S*)-conformer was synthesized by employing "reagent-controlled" Charette asymmetric cyclopropanation in a 100% stereoselective manner, whereas the (*N*)-conformer was stereoselectively synthesized by using "substrate-controlled" hydroxyl-directed Simmons−Smith cyclopropanation as a key step.



Conformational restriction is a useful strategy for medicinal chemists to increase potency and selectivity against physiological targets by limiting flexible conformations.[1] Since only certain conformations are expected to be optimal for effective binding with the target enzyme, nucleos(t)ides with a fixed conformation are desirable for further and accurate study of the role of conformation in biological interactions. It is well-known that the normal ribose ring of nucleosides is in a dynamic north (*N*)/south (*S*) equilibrium in the solution state. Since the energy barrier between this equilibrium is less than 4 kcal/mol, it has been very difficult to confirm whether the *N* or *S* conformation is suitable for proper binding to the target enzyme or receptor for maximal biological activity.[2] As a notable approach to resolving this problem, it is also widely known that bicyclo[3.1.0]hexane nucleosides locked in either north or south conformations were utilized to confirm which conformation was favorable for target proteins. One representative case is a discernment in the optimal ribose pucker of them, zidovudine (AZT) and its active form AZT 5′-triphosphate, and consequently, the *S* conformation was required for phosphorylation, and the *N* conformation for a better interaction with HIV reverse transcriptase.[3a−c] On the basis of this conformational analysis, a prodrug approach to the *N* conformation might be a practical application in that phosphorylation is the rate-determining step for antiviral agents. Other noteworthy cases were exemplified by herpes thymidine kinase,[3d,e] adenosine kinase,[3f] and several subtypes of adenosine receptors.[3g]

We recently reported that novel peroxisome proliferator-activated receptor (PPAR) γ/δ dual modulators (**1** and **2**), which function as both PPARγ partial agonists and PPARδ antagonists, have therapeutic potential against cancer and metabolic diseases associated with hypoadiponectinemia. Those 1′-homologated nucleosides abolished typical binding to adenosine receptors and polymerases, making them inactive.[4] In view of medicinal chemistry, this finding looks important in that it opened up a novel scaffold for the development of pure PPAR modulators.

On the basis of the interesting biological activity of **1** and **2** acting as PPARγ/δ dual modulators (Figure 1), we wanted to

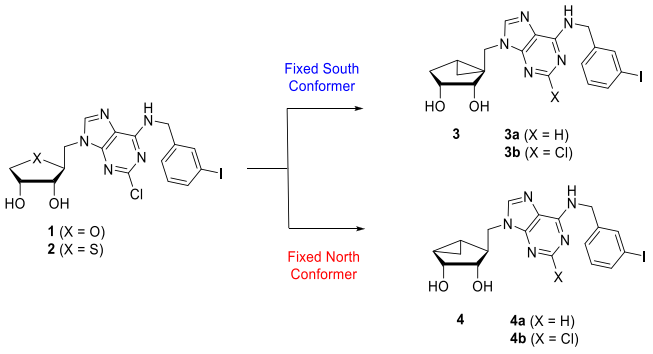


Figure 1. Truncated 1′-homologated adenosine derivatives as PPARγ/δ dual modulators **1** and **2**, and their conformationally rigid analogues **3** and **4**.

Received: March 25, 2021
Published: June 29, 2021

identify which conformation is more favorable for binding to PPARγ/δ. To achieve this goal, we adopted a bicyclo[3.1.0]-hexane template to restrict sugar puckering. Thus, we designed conformationally rigid southern C3′-exo conformer **3** and northern C3′-endo conformer **4**, using a bicyclo[3.1.0]hexane carbasugar. These target nucleosides are expected to mimic normal furanose ring puckering in the classical north and south conformations. Although several groups have reported the elegant syntheses of (*N*)-methanocarba nucleosides,[5] only very few syntheses of (*S*)-methanocarba nucleosides have been reported with a low diastereoselective ratio under intramolecular cyclopropanation of a γ,δ-unsaturated diazocarbonyl compound, and extremely low overall yields (Figure 2).[6] Thus,

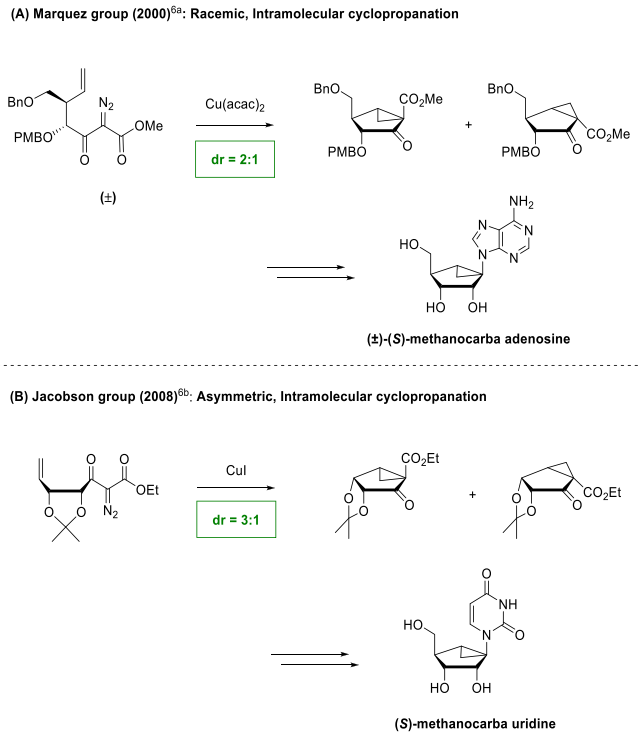
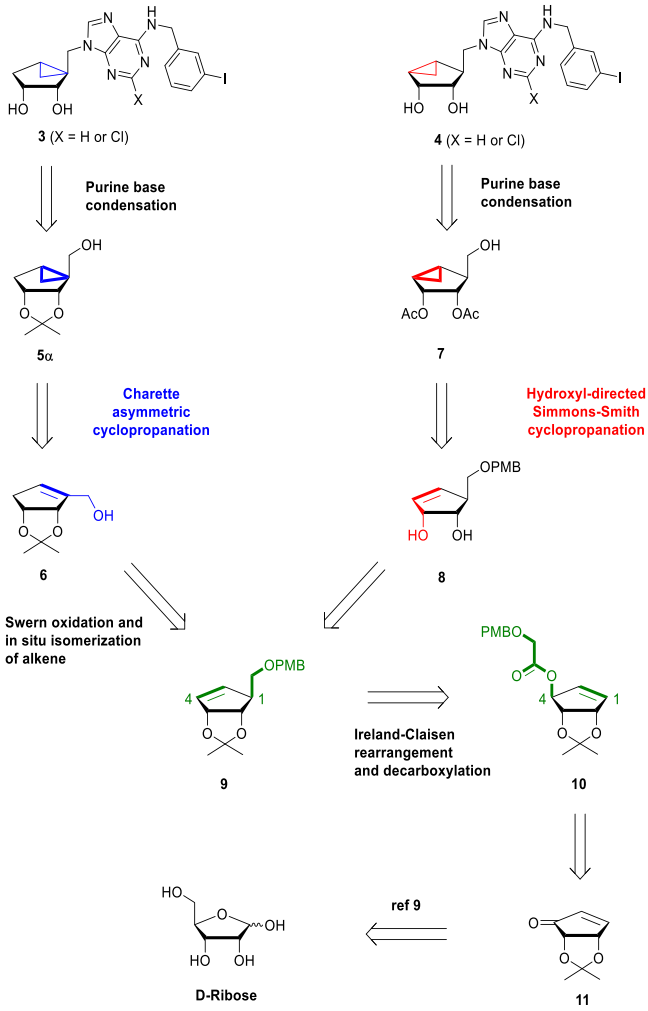


Figure 2. Previous syntheses of (*S*)-methanocarba nucleosides.

it intrigued us to develop an efficient synthetic strategy, employing highly diastereoselective cyclopropanation. Herein, we describe the asymmetric synthesis of truncated 1′-homologated (*S*)- and (*N*)-methanocarba nucleosides **3a**, **3b** and **4a**, **4b** with highly diastereoselective cyclopropanation.

Scheme 1 illustrates the retrosynthetic analysis of target nucleosides **3** and **4**. It was envisioned that desired (*S*)-nucleosides **3** and (*N*)-nucleosides **4** could be obtained by the Mitsunobu condensation of (*S*)-alcohol ***5α*** and (*N*)-alcohol **7** with a purine base, respectively. It was thought that (*S*)-alcohol ***5α*** could be achieved by the Charette asymmetric cyclopropanation of allylic alcohol **6**.[7] On the other hand, (*N*)-alcohol **7** could be derived from **8**, using hydroxyl-directed Simmons–Smith cyclopropanation[8] to achieve the desired α-cyclopropane. The allylic alcohol **6** could be prepared from **9** through the Swern oxidation and in situ isomerization of alkene, while another substrate **8** could be easily synthesized from the same intermediate **9**. It was envisaged that common intermediate **9** could be derived from **10** via Ireland–Claisen rearrangement and Barton's decarboxylation, in which the chirality of C4 in **10** would be transferred to C1 in **9**.

Scheme 1. Retrosynthetic Analysis of Truncated 1′-Homologated (*S*)- and (*N*)-Methanocarba Nucleosides 3 and 4

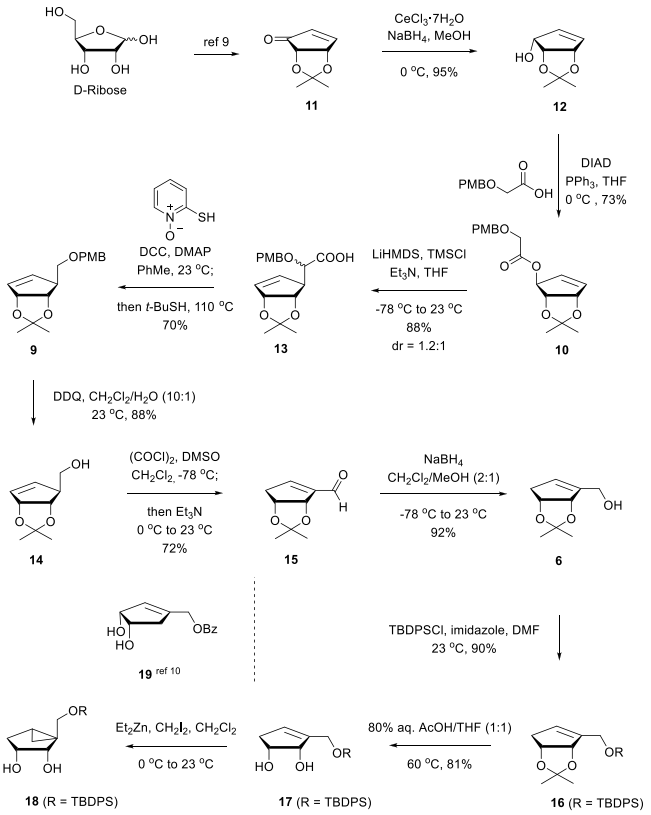


Compound **10** would be derived from known cyclopentenone **11** using stereoselective reduction and the Mitsunobu reaction. Compound **11** was efficiently derived from D-ribose.

Our initial approach to build a cyclopropane ring in truncated 1′-homologated (*S*)-methanocarba nucleosides **3** employed "substrate-controlled" hydroxyl-directed cyclopropantion, as shown in Scheme 2. D-Ribose was converted to known cyclopentenone **11** according to our previously reported procedure.[9] Stereoselective Luche reduction of **11** afforded alcohol **12** in 95% yield, which was subjected to the Mitsunobu reaction using 4-methoxyphenylacetic acid, DIAD, and PPh_3 to afford ester **10** in 73% yield. The Ireland–Claisen rearrangement of **10** produced inseparable diastereomeric mixture **13** (1.2:1, determined by ^1H NMR) in 88% yield. Barton's decarboxylation of carboxylic acid **13** in the presence of *tert*-butylthiol provided common intermediate **9**, which can also serve as the substrate for the synthesis of the (*N*)-conformer. Deprotection of the PMB group of **9** with DDQ yielded primary alcohol **14** in 88% yield. Oxidation of **14** yielded a β,γ-unconjugated aldehyde, which was spontaneously isomerized to α,β-conjugated aldehyde **15** in 72% yield under Swern oxidation conditions. Reduction of **15** with $NaBH_4$ afforded allylic alcohol **6**, which was subjected to TBDPS protection and acetonide deprotection to give diol **17**.

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828–9837

Scheme 2. Initial "Substrate-Controlled" Cyclopropanation Approach to Construct the Cyclopropane Ring of (*S*)-Conformer 18

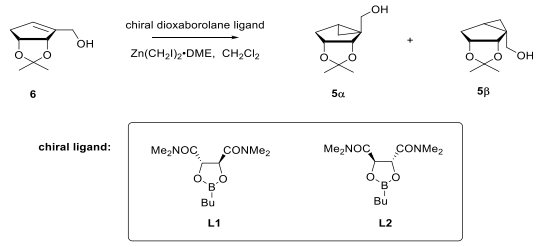


Compound **17** was expected to act as a good substrate for hydroxyl-directed Simmons–Smith cyclopropanation for the synthesis of the (*S*)-conformer since Marquez and co-workers reported successful Simmons–Smith cyclopropanation with desired diastereoselectivity using a similar diol substrate **19**.[10] However, cyclopropanation of diol **17** under various Simmons–Smith reaction conditions produced desired (*S*)-conformer **18** in negligible amounts.

Thus, we changed our strategy to construct the (*S*)-cyclopropane ring, opting for the Charette asymmetric cyclopropanation of allylic alcohol **6** (Table 1). The introduction of a cyclopropane ring to **6** in the desired α face was the key for the synthesis of (*S*)-methanocarba nucleosides **3**. It was thought that, under Simmons–Smith cyclopropanation, undesired β-cyclopropane **5*β*** would be more dominant than desired α-cyclopropane **5*α*** because of the bulky acetonide and the hydroxymethyl group in the sp^2 geometry lacking facial selectivity. Interestingly, cyclopropanation of **6** with diethylzinc and diiodomethane afforded a 2:1 diastereomeric mixture in favor of the **5*α*** isomer unlike our expectation (entry 1). This result could be explained by previous reports on a directing effect of acetonide oxygens.[11] It was speculated that the electronic effect of directing zinc carbenoid overwhelmed a steric effect of the acetonide group.

To increase the formation of α-cyclopropanation, we turned our attention to Charette asymmetric cyclopropanation, in which the chiral controller determines the stereochemical outcome of cyclopropanation. Although there have been many reports on the use of Charette asymmetric cyclopropanation in acyclic systems,[12] only a few cyclic systems have been reported.[7b,13] Delightfully, Charette cyclopropanation of **6**

Table 1. Charette Asymmetric Cyclopropanation of Allylic Alcohol 6



entry	chiral ligand	time (h)	temp (°C)	ratio (5*α*:5*β*)	yield[e] (%)
1[a]		46	0 to 23	2:1[c]	52
2[b]	**L1**	38	−15 to 23	**5*α*** only[d]	88
3[b]	**L2**	70	−15 to 23	**5*β*** only[d]	65

[a]Reactions were carried out by mixing 2.0 equiv of the preformed zinc reagent ($Zn(CH_2I)_2$) with **6** at 0 °C and finally warming to 23 °C ($Zn(CH_2I)_2$ was added at 24 h intervals). [b]Reactions were carried out by mixing 2.0 equiv of preformed zinc reagent ($Zn(CH_2I)_2$·DME) with 1.2 equiv of chiral ligand (**L1** or **L2**) at −15 °C, then adding **6** at −15 °C, and finally warming to 23 °C ($Zn(CH_2I)_2$·DME was added at 24 h intervals). [c]Determined by crude ^{1}H NMR. [d]Only a single diastereomer was observed. [e]Isolated total yields after silica gel chromatography.

with chiral dioxaborolane ligand **L1** resulted in cyclopropanation on the more sterically congested side to afford desired glycosyl donor **5*α*** as a single stereoisomer in excellent yield (entry 2). In contrast, chiral enantiomeric ligand **L2** produced **5*β*** as a single diastereomer in 65% yield (entry 3). The stereochemistry of **5*α*** and **5*β*** was easily confirmed by ^{1}H NOE experiments (see the Supporting Information). The proposed transition state for the Charette asymmetric cyclopropanation is depicted in Figure 3. It was conjectured

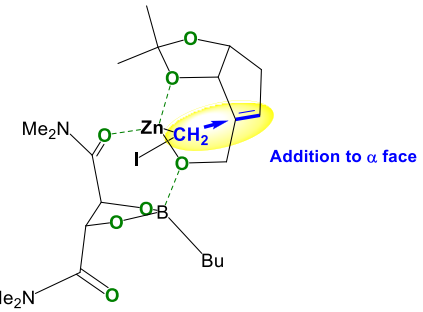


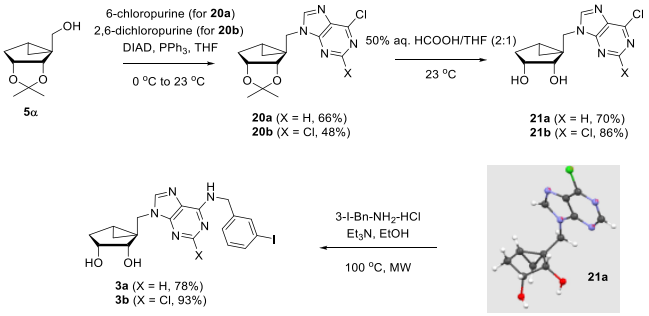
Figure 3. Proposed transition state for the Charette asymmetric cyclopropanation of allylic alcohol **6**.

that the zinc carbenoid was complexed simultaneously with both the carbonyl amide of **L1** and the oxygen of the allylic alkoxide **6**, in coordination with the acetonide oxygen. This coordination seems to play a key role for delivering methylene to alkene from the α phase, resulting in asymmetric α-cyclopropanation.

5*α* was condensed with 6-chloropurine and 2,6-dichloropurine under the Mitsunobu conditions to give protected nucleosides **20a** and **20b** in moderate yields, respectively (Scheme 3). Treatment of **20a** and **20b** with 50% aqueous formic acid yielded **21a** and **21b**, respectively. The stereochemistry of **5*α*** was further confirmed by the X-ray crystal structure of **21a** (see the Supporting Information). Nucleophilic substitution of **21a** and **21b** with 3-iodobenzylamine

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837

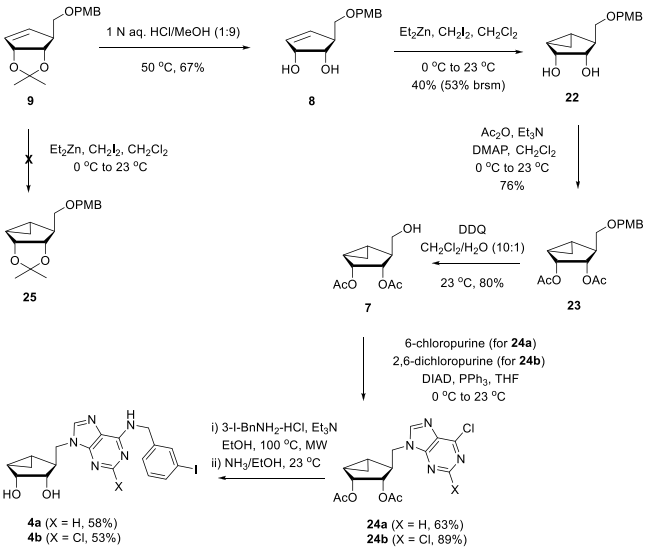
Scheme 3. Synthesis of Truncated 1′-Homologated (*S*)-Methanocarba Nucleosides 3a and 3b



under microwave irradiation afforded the final truncated 1′-homologated (*S*)-methanocarba nucleosides **3a** and **3b**, respectively.

The synthesis of truncated 1′-homologated (*N*)-methanocarba nucleosides **4** commenced with common intermediate **9**, as shown in Scheme 4. First, we applied the Simmons–Smith

Scheme 4. Synthesis of Truncated 1′-Homologated (*N*)-Methanocarba Nucleosides 4a and 4b



cyclopropanation performed in entry 1 (Table 1). It was thought that compound **9** whose primary alcohol was protected with a bulky PMB group to prevent zinc carbenoid coordination,[14] would produce the desired α-cyclopropane as a major product by the directing effect of oxygen in the acetonide group.[11c,d] However, Simmons–Smith cyclopropanation of **9** did not give **25**. Other noncomplexing protecting groups such as TBDPS,[11c,d,15a] Bn,[15b] and MOM,[11c] or other more reactive zinc carbenoids such as $CF_3COOZnCH_2I$,[16] 2,4,6-$Cl_3C_6H_2OZnCH_2I$,[17] and $Zn(CH_2Cl)_2$[18] gave the same results. Next, we tried "substrate-controlled" hydroxyl-directed cyclopropanation which has a stronger coordination effect than ether oxygen.[19] Compound **9** was treated with 1 N HCl to give diol **8**, which was subjected to hydroxyl-directed Simmons–Smith cyclopropanation to yield desired (*N*)-cyclopropane derivative **22** in moderate yield. Acetylation of **22** gave diacetate **23** in 76% yield, which was treated with DDQ to provide another glycosyl donor **7** in 80% yield. Condensation of **7** with 6-chloropurine and 2,6-dichloropurine under the Mitsunobu conditions produced protected nucleosides **24a** and **24b**, respectively. Treatment of **24a** and **24b** with 3-iodobenzylamine, followed by further treatment with ethanolic ammonia, afforded the final truncated 1′-homologated (*N*)-methanocarba nucleosides **4a** and **4b**, respectively.

The biological assay of final compounds is in progress and will be reported elsewhere.

In summary, we designed and synthesized truncated 1′-homologated conformationally rigid (*S*)- and (*N*)-methanocarba nucleosides **3a**, **3b** and **4a**, **4b** to determine which sugar conformation is essential for binding to PPARs. For the synthesis of (*S*)-conformers **3a** and **3b**, "reagent-controlled" Charette asymmetric cyclopropanation was employed as a key step, resulting in desired glycosyl donor ***5α*** as a single stereoisomer, which was attacked from the more sterically hindered side, whereas (*N*)-conformers **4a** and **4b** were synthesized via "substrate-controlled" Simmons–Smith cyclopropanation as a key step, giving desired glycosyl donor **7** as a single stereoisomer.

EXPERIMENTAL SECTION

General Information. All reactions involving air- or moisture-sensitive condition were routinely carried out under an inert atmosphere of dry nitrogen. All solvents were purified and dried by standard techniques just before use. All reagents were obtained from commercial suppliers and were used without purification. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under UV light, and by colorizing with charring after dipping in a *p*-anisaldehyde solution (Anis) or phosphomolybdic acid solution (PMA). The crude compounds were purified by column chromatography on silica gel (Kieselgel 60, 230–400 mesh, Merck). Microwave-assisted reactions were carried out in sealed vessels using a Biotage Initiator+ US/JPN (part no. 356007) microwave reactor, and the reaction temperatures were monitored by an external surface IR sensor. Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained on a Jeol JNM-ECZ 400s (400/100 MHz), Bruker AV 500 (500/125 MHz), Jeol JNM-ECA600 (600/150 MHz), or Bruker AV 800 (800/200 MHz) spectrometer. Chemical shifts are reported in ppm (δ) with residual solvents as the internal standard. Optical rotations were determined on a Jasco P-2000 in an appropriate solvent. UV spectra were recorded on a PerkinElmer Lambda25 in methanol. Melting points were determined on a Barnstead Electrothermal 9100 instrument. High-resolution mass spectra (HRMS) were recorded on a fast atom bombardment (FAB), electrospray ionization (ESI), or chemical ionization (CI).

*(3aR,4R,6aS)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-ol (**12**).* To a stirred solution of **11** (2.1 g, 13.6 mmol, 1.0 equiv) in MeOH (40 mL) was added cerium(III) chloride heptahydrate ($CeCl_3{\cdot}7H_2O$, 6.2 g, 16.3 mmol, 1.2 equiv) at 23 °C. After 5 min, sodium borohydride ($NaBH_4$, 618.3 mg, 16.3 mmol, 1.2 equiv) was added portionwise to the reaction mixture at 0 °C. After 15 min, acetic acid (0.2 mL) and water were added, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 9:1) to afford **12** (2.02 g, 95%) as a colorless oil, whose spectroscopic and physical data were identical to those of a known compound.[20]

*(3aS,4S,6aS)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]-dioxol-4-yl 2-((4-Methoxybenzyl)oxy)acetate (**10**).* To a stirred solution of **12** (1.53 g, 9.79 mmol, 1.0 equiv), triphenylphosphine (PPh_3, 3.93 g, 15 mmol, 1.5 equiv), and 2-((4-methoxybenzyl)oxy)-acetic acid (2.95 g, 15 mmol, 1.5 equiv) in THF (60 mL) was added diisopropyl azodicarboxylate (DIAD, 3.0 mL, 15 mmol, 1.5 equiv) dropwise at 0 °C. After 20 min, the reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 24:1) to

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828–9837

afford **10** (2.38 g, 73%) as a colorless oil. TLC: (hexanes:EtOAc, 2:1), R_f = 0.66 (Anis); $[\alpha]^{25}_D$: +110.8 (*c* 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27−7.23 (m, 2H), 6.87−6.83 (m, 2H), 6.12- 6.08 (m, 1H), 5.90−5.86 (m, 1H), 5.66−5.62 (m, 1H), 5.24−5.20 (m, 1H), 4.56 (d, *J* = 6.0 Hz, 1H), 4.53 (s, 2H), 4.03 (s, 2H), 3.76 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.0, 159.6, 138.1, 131.1, 129.9, 129.1, 113.9, 112.4, 84.0, 83.6, 83.1, 73.1, 66.8, 55.4, 27.4, 25.8; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{18}H_{22}O_6Na$ 357.1309; Found 357.1312.

*(S)-2-((3aS,4R,6aR)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta-[d][1,3]dioxol-4-yl)-2-((4-methoxybenzyl)oxy)acetic acid (**13**).* To a stirred solution of **10** (3.18 g, 9.51 mmol, 1.0 equiv) in THF (300 mL) were added chlorotrimethylsilane (TMSCl, 5.4 mL, 42.75 mmol, 4.5 equiv), and triethylamine (Et_3N, 4.6 mL, 33.2 mmol, 3.5 equiv) at −78 °C. After 5 min, lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF, 33 mL, 33.2 mmol, 3.5 equiv) was added dropwise to the reaction mixture. After 30 min, the reaction mixture was warmed to 23 °C, and stirred for 2 h. The reaction mixture was cooled to 0 °C, saturated NH_4Cl aqueous solution and acetic acid to acidify were added, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 4:1 with 0.18% acetic acid) to afford **13** (2.8 g, 88%, 1.2:1 d.r.) as a colorless oil. TLC: (hexanes:EtOAc, 2:3), R_f = 0.15 (Anis); *Note*: ^{1}H NMR and ^{13}C NMR of **13** were taken with a sample containing a 1.2:1 mixture of inseparable diastereomers; $[\alpha]^{25}_D$: −14.0 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (brs, 1.9H), 7.26−7.18 (m, 4.4H), 6.91−6.83 (m, 4.4H), 5.97−5.85 (m, 2.2H), 5.72 (dd, *J* = 6.0, 2.8 Hz, 1.2H), 5.68 (dd, *J* = 5.6, 2.8 Hz, 1H), 5.15−5.09 (m, 2.2H), 4.77−4.62 (m, 3.2H), 4.45 (d, *J* = 5.7 Hz, 1.2H), 4.41−4.30 (m, 2.2H), 4.10 (d, *J* = 4.5 Hz, 1.2H), 3.98 (d, *J* = 4.0 Hz, 1H), 3.79 (s, 3.6H), 3.78 (s, 3H), 3.31−3.24 (m, 2.2H), 1.39 (s, 3H), 1.37 (s, 3.6H), 1.33 (s, 3H), 1.30 (s, 3.6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 175.8, 175.6, 159.6, 159.5, 134.2, 133.8, 131.8, 130.6, 129.8, 129.6, 128.7, 128.6, 113.9, 113.8, 110.28, 110.22, 85.2, 85.0, 80.9, 79.3, 77.0, 72.44, 72.40, 67.8, 55.2, 54.8, 54.5, 27.34, 27.30, 25.69, 25.62; HRMS (FAB) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{23}O_6$ 335.1495; Found 335.1492.

*(3aS,4S,6aR)-4-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimeth-yl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole (**9**).* To a stirred solution of **13** (547.5 mg, 1.64 mmol, 1.0 equiv) in toluene (8 mL) wrapped in aluminum foil to protect from the light were added 4-dimethylaminopyridine (DMAP, 42.2 mg, 0.35 mmol, 0.21 equiv), *N*-hydroxypyridine-2-thione (315.6 mg, 2.48 mmol, 1.5 equiv), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 503.1 mg, 2.44 mmol, 1.5 equiv) at 23 °C. After 2 h, the reaction mixture was added to a stirred solution of *tert*-butyl mercaptan (*t*-BuSH, 1.3 mL, 11.5 mmol, 7.0 equiv) in toluene (50 mL) wrapped in aluminum foil at 110 °C. After 1 h, the reaction mixture was cooled to 23 °C, and concentrated under reduced pressure. To the resulting mixture was added water, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 49:1) to afford **9** (335 mg, 70%) as a colorless oil. TLC: (hexanes:EtOAc, 2:1), R_f = 0.77 (Anis); $[\alpha]^{25}_D$: −66.2 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.15 (m, 2H), 6.87−6.78 (m, 2H), 5.81 (dt, *J* = 6.0, 2.0 Hz, 1H), 5.72 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.08 (d, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.39 (s, 2H), 3.73 (s, 3H), 3.41 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.28 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.05−2.94 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 134.2, 132.3, 130.4, 129.3, 113.9, 110.1, 85.2, 81.6, 72.9, 70.9, 55.4, 52.7, 27.5, 25.7; HRMS (CI) *m*/*z*: $[M - H]^+$ Calcd for $C_{17}H_{21}O_4$ 289.1440; Found 289.1442.

*((3aS,4S,6aR)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d]-[1,3]dioxol-4-yl)methanol (**14**).* To a stirred solution of **9** (492 mg, 1.69 mmol, 1.0 equiv) in CH_2Cl_2/H_2O (9.9 mL, 10:1, *v*/*v*) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 468.3 mg, 2.06 mmol, 1.2 equiv) at 23 °C. After 3 h, saturated $NaHCO_3$ aqueous solution was added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 6:1) to afford **14** (253 mg, 88%) as a colorless oil. TLC: (hexanes:EtOAc, 2:1), R_f = 0.24 (Anis); $[\alpha]^{25}_D$: −82.0 (*c* 0.46, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 5.9, 1.9 Hz, 1H), 5.74−5.70 (m, 1H), 5.13−5.09 (m, 1H), 4.56 (d, *J* = 5.5 Hz, 1H), 3.71 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.53 (dd, *J* = 10.5, 5.5 Hz, 1H), 2.98−2.93 (m, 1H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 133.3, 133.0, 109.8, 84.9, 81.2, 63.5, 54.6, 27.2, 25.4; HRMS (CI) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{15}O_3$ 171.1021; Found 171.1023.

*(3aR,6aS)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]-dioxole-6-carbaldehyde (**15**).* To a stirred solution of oxalyl chloride ($(COCl)_2$, 2.0 M in CH_2Cl_2, 1.5 mL, 3.0 mmol, 2.0 equiv) in CH_2Cl_2 (9 mL) was carefully added dimethyl sulfoxide (DMSO, 0.43 mL, 6.0 mmol, 4.0 equiv) dropwise at −78 °C. After 30 min, a solution of **14** (253 mg, 1.49 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added to the stirred reaction mixture dropwise. After 1 h, the reaction mixture was warmed to 0 °C, and triethylamine (Et_3N, 2.1 mL, 15 mmol, 10.0 equiv) was added. After stirring at 23 °C for 2 h, saturated NH_4Cl aqueous solution was added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 6:1) to afford **15** (180 mg, 72%) as a colorless oil. TLC: (hexanes:EtOAc, 2:1), R_f = 0.35 (Anis); $[\alpha]^{25}_D$: −6.5 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.84 (t, *J* = 2.4 Hz, 1H), 5.30 (d, *J* = 6.0 Hz, 1H), 4.85 (td, *J* = 6.0, 2.0 Hz, 1H), 2.88−2.68 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.0, 151.4, 145.7, 111.0, 81.6, 78.0, 39.3, 27.2, 25.1; HRMS (FAB) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{13}O_3$ 169.0865; Found 169.0874.

*((3aR,6aS)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]-dioxol-6-yl)methanol (**6**).* To a stirred solution of **15** (86.7 mg, 0.52 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) were added sodium borohydride ($NaBH_4$, 15 mg, 0.4 mmol, 0.8 equiv) and MeOH (3 mL) at −78 °C. After 1 h, the reaction mixture was warmed to 23 °C. After 30 min, saturated NH_4Cl aqueous solution was added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 4:1) to afford **6** (81 mg, 92%) as a colorless oil. TLC: (hexanes:EtOAc, 2:1), R_f = 0.26 (Anis); $[\alpha]^{25}_D$: +4.8 (*c* 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.61 (s, 1H), 5.02 (d, *J* = 5.9 Hz, 1H), 4.74 (t, *J* = 5.9 Hz, 1H), 4.27 (dd, *J* = 13.7, 1.4 Hz, 1H), 4.22 (dd, *J* = 13.8, 1.3 Hz, 1H), 2.60−2.50 (m, 1H), 2.49−2.39 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.7, 126.8, 110.4, 85.2, 78.6, 60.3, 37.8, 27.5, 25.8; HRMS (FAB) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{15}O_3$ 171.1021; Found 171.1019.

*tert-Butyl(((3aR,6aS)-2,2-dimethyl-3a,6a-dihydro-4H-cyclo-penta[d][1,3]dioxol-6-yl)methoxy)diphenylsilane (**16**).* To a stirred solution of **6** (212 mg, 1.25 mmol, 1.0 equiv) in DMF (6 mL) were added *tert*-butyldiphenylchlorosilane (TBDPSCl, 0.49 mL, 1.88 mmol, 1.5 equiv) and imidazole (170.2 mg, 2.5 mmol, 2.0 equiv) at 23 °C. After 19 h, water was added, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 99:1) to afford **16** (457 mg, 90%) as a colorless oil. TLC: (hexanes: EtOAc, 4:1), R_f = 0.64 (Anis); $[\alpha]^{23}_D$: +16.2 (*c* 0.26, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.65 (m, 4H), 7.45−7.34 (m, 6H), 5.71 (s, 1H), 4.97 (d, *J* = 5.5 Hz, 1H), 4.77 (t, *J* = 5.3 Hz, 1H), 4.36 (dd, *J* = 14.6, 2.3 Hz, 1H), 4.34−4.28 (m, 1H),

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837

2.62−2.55 (m, 1H), 2.53−2.46 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.08 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 135.5, 135.4, 133.5, 129.6, 127.6, 124.8, 110.0, 84.5, 78.5, 61.3, 37.7, 27.4, 26.7, 25.9, 19.2; HRMS (FAB) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O_3Si$ 409.2199; Found 409.2190.

*(1R,2S)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)cyclopent-3-ene-1,2-diol (**17**).* To a stirred solution of **16** (450 mg, 1.10 mmol, 1.0 equiv) in THF (4 mL) was added 80% aqueous acetic acid (4 mL) at 23 °C. After stirring at 60 °C for 23 h, the reaction mixture was cooled to 0 °C, solid $NaHCO_3$ was added for neutralization, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 33:1) to afford **17** (330 mg, 81%) as a colorless oil. TLC: (hexanes:EtOAc, 1:1), R_f = 0.38 (Anis); $[\alpha]^{23}_D$: −376.9 (*c* 0.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.45−7.34 (m, 6H), 5.68 (s, 1H), 4.57 (d, *J* = 5.6 Hz, 1H), 4.37−4.28 (m, 3H), 2.61−2.49 (m, 1H), 2.34 (d, *J* = 16.8 Hz, 1H), 1.05 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.6, 135.57, 135.54, 132.9, 132.8, 129.8, 127.7, 127.4, 76.5, 71.2, 62.3, 38.9, 26.7, 19.1; HRMS (FAB) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}O_3Si$ 369.1886; Found 369.1892.

*((3aS,3bS,4aS,5aR)-2,2-Dimethyltetrahydrocyclopropa[3,4]-cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (**5α**).* To a stirred solution of diethylzinc (Et_2Zn, 1.0 M in hexanes, 24.7 mL, 24.7 mmol, 2.0 equiv) and 1,2-dimethoxyethane (DME, 2.6 mL, 24.7 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) at −15 °C was added diiodomethane (CH_2I_2, 4.0 mL, 49.48 mmol, 4.0 equiv) dropwise. After 15 min, a solution of the butylboronic acid *N,N,N′,N′*-tetramethyl-D-tartaric acid diamide ester (3.7 mL, 14.8 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) was added immediately followed by a solution of **6** (2.11 g, 12.37 mmol, 1.0 equiv) in CH_2Cl_2 (18 mL), and the mixture was slowly warmed to 23 °C. After 24 h, the mixture was re-cooled to −15 °C, and another 2.0 equiv of the $Zn(CH_2I)_2$·DME in CH_2Cl_2 was added (preparation of $Zn(CH_2I)_2$·DME in CH_2Cl_2 as described above). After stirring at 23 °C for 14 h, the reaction mixture was cooled to 0 °C, saturated NH_4Cl aqueous solution and brine were added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 3:1) to afford **5α** (2.00 g, 88%) as a colorless oil. TLC: (hexanes:EtOAc, 2:3), R_f = 0.21 (Anis); $[\alpha]^{25}_D$: −29.5 (*c* 0.32, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 4.94 (d, *J* = 6.6 Hz, 1H), 4.68 (t, *J* = 7.2 Hz, 1H), 3.65 (d, *J* = 10.8 Hz, 1H), 3.58 (d, *J* = 10.8 Hz, 1H), 2.18−2.13 (m, 1H), 1.93 (d, *J* = 15.0 Hz, 1H), 1.84 (brs, 1H), 1.46 (s, 3H), 1.41−1.35 (m, 1H), 1.23 (s, 3H), 0.97 (t, *J* = 4.8 Hz, 1H), 0.68−0.62 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 111.2, 84.1, 82.7, 66.7, 37.5, 32.6, 26.5, 26.0, 24.4, 15.7; HRMS (CI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{17}O_3$ 185.1178; Found 185.1177.

*((3aS,3bR,4aR,5aR)-2,2-Dimethyltetrahydrocyclopropa[3,4]-cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (**5β**).* To a stirred solution of diethylzinc (Et_2Zn, 1.0 M in hexanes, 2.6 mL, 2.6 mmol, 2.0 equiv) and 1,2-dimethoxyethane (DME, 0.27 mL, 2.6 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL) at −15 °C was added diiodomethane (CH_2I_2, 0.85 mL, 10.6 mmol, 4.0 equiv) dropwise. After 15 min, a solution of the butylboronic acid *N,N,N′,N′*-tetramethyl-L-tartaric acid diamide ester (0.39 mL, 1.6 mmol, 1.2 equiv) in CH_2Cl_2 (2 mL) was added immediately followed by a solution of **6** (225 mg, 1.32 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL), and the mixture was slowly warmed to 23 °C. After 24 h, the mixture was re-cooled to −15 °C, and another 2.0 equiv of the $Zn(CH_2I)_2$·DME in CH_2Cl_2 was added (preparation of $Zn(CH_2I)_2$·DME in CH_2Cl_2 as described above). After stirring at 23 °C for 24 h, one other addition of 2.0 equiv of the $Zn(CH_2I)_2$·DME in CH_2Cl_2 was done. After stirring at 23 °C for 22 h, the reaction mixture was cooled to 0 °C, saturated NH_4Cl aqueous solution and brine were added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 3:1) to afford **5β** (158 mg, 65%) as a colorless oil. TLC: (hexanes:EtOAc, 2:3), R_f = 0.46 (Anis); $[\alpha]^{23}_D$: −20.7 (*c* 0.13, MeOH); ^1H NMR (600 MHz, $CDCl_3$) δ 4.60 (d, *J* = 4.8 Hz, 1H), 4.41−4.34 (m, 1H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.53 (d, *J* = 11.4 Hz, 1H), 2.06 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.97−1.90 (m, 1H), 1.53−1.48 (m, 1H), 1.47 (s, 3H), 1.27 (s, 3H), 0.61−0.56 (m, 1H), −0.01 to −0.06 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 112.2, 84.6, 81.4, 65.1, 35.7, 33.1, 27.6, 25.0, 22.4, 15.2; HRMS (CI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{17}O_3$ 185.1178; Found 185.1177.

*((3aS,3bS,4aS,5aR)-2,2-Dimethyltetrahydrocyclopropa[3,4]-cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (**5α**) and ((3aS,3bR,4aR,5aR)-2,2-Dimethyltetrahydrocyclopropa[3,4]-cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (**5β**).* (Table 1, entry 1). To a stirred solution of diethylzinc (Et_2Zn, 1.0 M in hexanes, 2.6 mL, 2.6 mmol, 2.0 equiv) in CH_2Cl_2 (4 mL) was added diiodomethane (CH_2I_2, 0.4 mL, 5.29 mmol, 4.0 equiv) carefully at 0 °C. After 15 min, a solution of **6** (225 mg, 1.32 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added to the reaction mixture dropwise, and the mixture was warmed to 23 °C. After 24 h, the mixture was re-cooled to 0 °C, and another 2.0 equiv of the $Zn(CH_2I)_2$ in CH_2Cl_2 was added (preparation of $Zn(CH_2I)_2$ in CH_2Cl_2 as described above) to the reaction mixture. After stirring at 23 °C for 22 h, reaction mixture was cooled to 0 °C, saturated NH_4Cl aqueous solution and brine were added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 3:1) to afford **5α** (84.9 mg, 35%) and **5β** (41.7 mg, 17%) as a colorless oil.

*6-Chloro-9-(((3aS,3bS,4aS,5aR)-2,2-dimethyltetrahydrocyclo-propa[3,4]cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methyl)-9H-purine (**20a**) and 2,6-Dichloro-9-(((3aS,3bS,4aS,5aR)-2,2-dimethyl-tetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methyl)-9H-purine (**20b**).* To a stirred solution of **5α** (215 mg for **20a** or 278 mg for **20b**, 1.0 equiv) in THF (15 mL) were added triphenylphosphine (PPh_3, 611 mg for **20a** or 796 mg for **20b**, 2.0 equiv), and 6-chloropurine (360 mg, 2.0 equiv for **20a**) or 2,6-dichloropurine (569 mg, 2.0 equiv for **20b**) at 23 °C. The reaction mixture was cooled to 0 °C, and diisopropyl azodicarboxylate (DIAD, 0.46 mL for **20a** or 0.59 mL for **20b**, 2.0 equiv) was added dropwise. After stirring at 23 °C until **5α** was consumed, the reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexane:EtOAc, 3:1) to afford **20a** (247 mg, 66%) as a colorless oil or **20b** (256 mg, 48%) as a pale-yellow solid. **20a**: TLC: (hexanes:EtOAc, 2:3), R_f = 0.31 (Anis); $[\alpha]^{25}_D$: +22.4 (*c* 0.13, $CHCl_3$); UV (MeOH) λ_{max}: 265.8 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.49 (s, 1H), 4.78 (d, *J* = 6.4 Hz, 1H), 4.69 (t, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 14.4 Hz, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 2.19 (dt, *J* = 14.8, 5.6 Hz, 1H), 2.01 (d, *J* = 15.2 Hz, 1H), 1.74 (dt, *J* = 8.4, 5.2 Hz, 1H), 1.46 (s, 3H), 1.26−1.21 (m, 1H), 1.20 (s, 3H), 0.90−0.81 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 152.0, 151.0, 146.0, 131.6, 111.8, 84.7, 82.7, 49.6, 34.0, 31.9, 29.0, 26.5, 24.4, 17.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}ClN_4O_2$ 321.1113; Found 321.1113. **20b**: TLC: (hexanes:EtOAc, 2:3), R_f = 0.32 (Anis); mp 103−105 °C; $[\alpha]^{25}_D$: −36.5 (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max}: 275.0 nm; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.70 (t, *J* = 6.6 Hz, 1H), 4.52 (d, *J* = 13.8 Hz, 1H), 4.06 (d, *J* = 14.4 Hz, 1H), 2.24−2.17 (m, 1H), 2.01 (d, *J* = 15.0 Hz, 1H), 1.72 (dt, *J* = 8.4, 5.4 Hz, 1H), 1.43 (s, 3H), 1.23−1.20 (m, 1H), 1.19 (s, 3H), 0.83−0.79 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.5, 152.9, 151.7, 146.7, 130.8, 111.9, 84.9, 82.9, 50.0, 33.7, 31.9, 29.2, 26.5, 24.4, 17.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}Cl_2N_4O_2$ 355.0723; Found 355.0726.

*(1S,2S,3R,5S)-1-((6-Chloro-9H-purin-9-yl)methyl)bicyclo[3.1.0]-hexane-2,3-diol (**21a**) and (1S,2S,3R,5S)-1-((2,6-Dichloro-9H-purin-9-yl)methyl)bicyclo[3.1.0]hexane-2,3-diol (**21b**).* To a stirred solution of **20a** (206 mg, 0.64 mmol) or **20b** (168 mg, 0.47 mmol) in

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837

THF (3.5 mL) was added 50% aqueous formic acid (50% aq. HCOOH, 7.0 mL) dropwise at 23 °C. After stirring until **20a** or **20b** was consumed, the reaction mixture was concentrated under reduced pressure, and azeotroped with toluene. The resulting crude residue was purified by flash column chromatography (CH_2Cl_2 → CH_2Cl_2:MeOH, 39:1) to afford **21a** (126 mg, 70%) or **21b** (128 mg, 86%) as a white solid. **21a**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.47 (Anis, PMA); mp 178−179 °C; $[\alpha]^{25}_D$: −88.7 (*c* 0.21, MeOH); UV (MeOH) λ_{max}: 265.7 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.71 (s, 1H), 8.64 (s, 1H), 4.52 (d, *J* = 14.6 Hz, 1H), 4.44 (d, *J* = 14.7 Hz, 1H), 4.22 (dd, *J* = 6.0, 1.1 Hz, 1H), 3.90 (t, *J* = 6.0 Hz, 1H), 2.07 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.76 (d, *J* = 14.4 Hz, 1H), 1.53 (dt, *J* = 7.8, 4.2 Hz, 1H), 1.34 (t, *J* = 4.2 Hz, 1H), 0.78−0.72 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.8, 153.0, 151.1, 148.9, 132.2, 77.3, 72.1, 50.1, 35.0, 33.7, 23.1, 15.0; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{14}ClN_4O_2$ 281.0800; Found 281.0802. **21b**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.5 (Anis, PMA); mp 246−248 °C; $[\alpha]^{25}_D$: −86.3 (*c* 0.25, MeOH); UV (MeOH) λ_{max}: 275.3 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (s, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 4.32 (d, *J* = 14.8 Hz, 1H), 4.21 (dd, *J* = 6.4, 1.2 Hz, 1H), 3.90 (t, *J* = 6.4 Hz, 1H), 2.14−2.04 (m, 1H), 1.75 (d, *J* = 14.0 Hz, 1H), 1.51 (dt, *J* = 8.4, 4.4 Hz, 1H), 1.34 (t, *J* = 4.4 Hz, 1H), 0.77−0.72 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$) δ 153.8, 150.8, 149.3, 148.8, 130.3, 75.0, 69.9, 48.5, 33.8, 32.2, 21.0, 13.9; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{13}Cl_2N_4O_2$ 315.0410; Found 315.0404.

*(1S,2S,3R,5S)-1-((6-((3-Iodobenzyl)amino)-9H-purin-9-yl)-methyl)bicyclo[3.1.0]hexane-2,3-diol (**3a**) and (1S,2S,3R,5S)-1-((2-Chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)bicyclo-[3.1.0]hexane-2,3-diol (**3b**).* To a stirred suspension of **21a** (19.8 mg, 0.07 mmol, 1.0 equiv) or **21b** (31.6 mg, 0.1 mmol, 1.0 equiv) in EtOH (2 mL) were added 3-iodobenzylamine hydrochloride (3-I-Bn-NH_2-HCl, 47.3 mg for **3a** or 67.9 mg for **3b**, 2.5 equiv) and triethylamine (Et_3N, 0.05 mL for **3a** or 0.07 mL for **3b**, 5.0 equiv) at 23 °C. The reaction mixture in a sealed tube was placed under microwave irradiation at 100 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (CH_2Cl_2 → CH_2Cl_2:MeOH, 39:1) to afford **3a** (26.1 mg, 78%) or **3b** (47.6 mg, 93%) as a white solid. **3a**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.50 (Anis, PMA); mp 74−75 °C; $[\alpha]^{25}_D$: +49.9 (*c* 0.09, MeOH); UV (MeOH) λ_{max}: 271.7 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.24 (s, 1H), 8.14 (s, 1H), 7.73 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 4.75 (brs, 2H), 4.42 (d, *J* = 14.7 Hz, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 4.18 (d, *J* = 5.5 Hz, 1H), 3.90 (t, *J* = 6.2 Hz, 1H), 2.04 (dt, *J* = 14.2, 5.5 Hz, 1H), 1.73 (d, *J* = 14.2 Hz, 1H), 1.47 (dt, *J* = 8.2, 4.6 Hz, 1H), 1.31 (t, *J* = 4.5 Hz, 1H), 0.65−0.61 (m, 1H); ^{13}C{^{1}H} NMR (200 MHz, CD_3OD) δ 156.6, 154.5, 151.1, 143.9, 143.6, 138.3, 138.1, 132.1, 128.6, 120.9, 95.7, 77.6, 72.8, 49.5, 45.0, 35.6, 34.7, 23.6, 15.3; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{21}IN_5O_2$ 478.0734; Found 478.0728. **3b**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.54 (Anis, PMA); mp 175−176 °C; $[\alpha]^{25}_D$: +135.1 (*c* 0.09, MeOH); UV (MeOH) λ_{max}: 273.8 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.11 (s, 1H), 7.77 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 4.69 (brs, 2H), 4.35 (d, *J* = 14.4 Hz, 1H), 4.23 (d, *J* = 14.4 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 3.91 (t, *J* = 6.0 Hz, 1H), 2.10−2.02 (m, 1H), 1.74 (d, *J* = 14.4 Hz, 1H), 1.48 (dt, *J* = 8.4, 4.3 Hz, 1H), 1.31 (t, *J* = 4.2 Hz, 1H), 0.67−0.63 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $(CD_3)_2SO$) δ 154.6, 152.8, 150.2, 142.0, 141.8, 136.0, 135.5, 130.4, 126.8, 117.8, 94.6, 74.5, 70.0, 47.1, 42.4, 33.9, 32.5, 20.8, 13.6; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{20}ClIN_5O_2$ 512.0345; Found 512.0350.

*(1S,2R,5S)-5-(((4-Methoxybenzyl)oxy)methyl)cyclopent-3-ene-1,2-diol (**8**).* To a stirred solution of **9** (783.1 mg, 2.7 mmol, 1.0 equiv) in MeOH (27 mL) was added 1 N HCl aqueous solution (3 mL) dropwise at 0 °C. After stirring at 50 °C for 2 h, the reaction mixture was cooled to 0 °C, solid $NaHCO_3$ was added for neutralization, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc, 3:2) to afford **8** (454 mg, 67%) as a white solid. TLC: (hexanes:EtOAc, 2:3), R_f = 0.19 (Anis); mp 60−63 °C; $[\alpha]^{25}_D$: −75.5 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.20 (m, 2H), 6.89−6.84 (m, 2H), 5.90−5.84 (m, 2H), 4.59−4.54 (m, 1H), 4.45 (s, 2H), 4.04−3.98 (m, 1H), 3.79 (s, 3H), 3.50 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.44 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.92−2.84 (m, 1H), 2.30 (brs, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 135.8, 132.4, 130.3, 129.4, 114.0, 75.2, 74.6, 73.1, 70.9, 55.4, 52.2; HRMS (ESI) *m*/*z*: [M + Na]$^+$ Calcd for $C_{14}H_{18}O_4Na$ 273.1097; Found 273.1104.

*(1R,2R,3S,4S,5S)-4-(((4-Methoxybenzyl)oxy)methyl)bicyclo-[3.1.0]hexane-2,3-diol (**22**).* To a stirred solution of diethylzinc (Et_2Zn, 1.0 M in hexanes, 2.6 mL, 2.6 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL) was added diiodomethane (CH_2I_2, 0.42 mL, 5.2 mmol, 4.0 equiv) dropwise at 0 °C. After 5 min, a solution of **8** (326 mg, 1.23 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added to the reaction mixture, and warmed to 23 °C. After 24 h, the mixture was re-cooled to 0 °C, and another 2.0 equiv of the $Zn(CH_2I)_2$ in CH_2Cl_2 was added (preparation of $Zn(CH_2I)_2$ in CH_2Cl_2 as described above). After stirring at 23 °C for 24 h, the reaction mixture was cooled to 0 °C, saturated NH_4Cl aqueous solution and brine were added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 3:2) to afford **22** (136 mg, 40%, 53% brsm) as a white solid and recovered **8** (83 mg, 25%). TLC: (hexanes:EtOAc, 3:2), R_f = 0.17 (Anis); mp 57−58 °C; $[\alpha]^{25}_D$: +10.0 (*c* 0.23, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2H), 6.88−6.84 (m, 2H), 4.51−4.45 (m, 1H), 4.43 (s, 2H), 3.87−3.83 (m, 1H), 3.78 (s, 3H), 3.42 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.34 (dd, *J* = 9.0, 6.6 Hz, 1H), 2.28−2.24 (m, 1H), 2.19 (brs, 2H), 1.58−1.53 (m, 1H), 1.19−1.15 (m, 1H), 0.92−0.88 (m, 1H), 0.49 (td, *J* = 7.8, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.1, 130.3, 129.1, 113.7, 74.8, 73.4, 72.8, 72.1, 55.2, 48.4, 22.5, 18.0, 7.9; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{15}H_{21}O_4$ 265.1434; Found 265.1434.

*(1R,2R,3S,4S,5S)-4-(((4-Methoxybenzyl)oxy)methyl)bicyclo-[3.1.0]hexane-2,3-diyl Diacetate (**23**).* To a stirred solution of **22** (188 mg, 0.71 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) were added triethylamine (Et_3N, 0.6 mL, 4.3 mmol, 6.0 equiv) and 4-dimethylaminopyridine (DMAP, 8.6 mg, 0.071 mmol, 0.1 equiv) at 23 °C. The reaction mixture was cooled to 0 °C, and acetic anhydride (Ac_2O, 0.2 mL, 2.13 mmol, 3.0 equiv) was added dropwise. After stirring at 23 °C for 2 h, the reaction mixture was cooled to 0 °C, saturated $NaHCO_3$ aqueous solution was added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:EtOAc, 9:1) to afford **23** (188 mg, 76%) as a colorless oil. TLC: (hexanes:EtOAc, 3:2), R_f = 0.68 (Anis); $[\alpha]^{25}_D$: −9.6 (*c* 0.14, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2H), 6.88−6.84 (m, 2H), 5.44 (t, *J* = 5.9 Hz, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 4.47−4.41 (m, 2H), 3.78 (s, 3H), 3.46−3.38 (m, 2H), 2.29 (t, *J* = 4.6 Hz, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.68−1.62 (m, 1H), 1.32−1.27 (m, 1H), 0.90−0.86 (m, 1H), 0.59 (tdd, *J* = 7.8, 5.4, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.4, 169.7, 159.1, 130.2, 129.1, 113.8, 74.9, 73.7, 72.9, 71.3, 55.2, 47.0, 20.87, 20.82, 19.8, 17.9, 7.9; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{25}O_6$ 349.1646; Found 349.1654.

*(1R,2R,3S,4S,5S)-4-(Hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diyl Diacetate (**7**).* To a stirred solution of **23** (142 mg, 0.41 mmol, 1.0 equiv) in CH_2Cl_2/H_2O (4.4 mL, 10:1, *v*/*v*) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 110.7 mg, 0.49 mmol, 1.2 equiv) at 23 °C. After 2 h, saturated $NaHCO_3$ aqueous solution was added, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude residue was purified by flash column

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837

chromatography (hexanes:EtOAc, 3:1) to afford **7** (74 mg, 80%) as a colorless oil. TLC: (hexanes:EtOAc, 3:2), R_f = 0.26 (Anis); $[\alpha]^{25}_D$: −26.7 (*c* 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.43 (t, *J* = 6.0 Hz, 1H), 5.10 (d, *J* = 6.6 Hz, 1H), 3.68 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.61 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.24−2.19 (m, 1H), 2.08 (brs, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.70−1.65 (m, 1H), 1.27−1.23 (m, 1H), 0.88−0.85 (m, 1H), 0.64 (tdd, *J* = 8.4, 4.8, 0.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 170.4, 75.1, 73.8, 64.5, 49.6, 21.1, 21.0, 20.1, 17.3, 8.2; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{16}O_5Na$ 251.0890; Found 251.0881.

*(1R,2R,3S,4S,5S)-4-((6-Chloro-9H-purin-9-yl)methyl)bicyclo-[3.1.0]hexane-2,3-diyl Diacetate (**24a**) and (1R,2R,3S,4S,5S)-4-((2,6-Dichloro-9H-purin-9-yl)methyl)bicyclo[3.1.0]hexane-2,3-diyl Diacetate (**24b**).* To a stirred solution of **7** (203 mg for **24a** or 191 mg for **24b**, 1.0 equiv) in THF (6 mL) were added triphenylphosphine (PPh_3, 458 mg for **24a** or 432 mg for **24b**, 2.0 equiv), and 6-chloropurine (273 mg, 2.0 equiv for **24a**) or 2,6-dichloropurine (316 mg, 2.0 equiv for **24b**) at 23 °C. The reaction mixture was cooled to 0 °C, and diisopropyl azodicarboxylate (DIAD, 0.35 mL for **24a** or 0.32 mL for **24b**, 2.0 equiv) was added dropwise. After stirring at 23 °C until **7** was consumed, the reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:acetone, 5.7:1) to afford **24a** (contaminated with triphenylphosphine oxide (TPPO) at a 1:1 ratio based on ^{1}H NMR, 203.5 mg of **24a**, 63%) or **24b** (296.4 mg, 89%) as a white solid. **24a** (contaminated with TPPO): TLC: (hexanes:EtOAc, 2:3), R_f = 0.23 (Anis); mp 127−128 °C; $[\alpha]^{25}_D$: +2.8 (*c* 0.39, $CHCl_3$); UV (MeOH) λ_{max}: 265.7 nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.16 (s, 1H), 7.67−7.61 (m, 6H, TPPO), 7.54−7.49 (m, 3H, TPPO), 7.46−7.41 (m, 6H, TPPO), 5.38 (t, *J* = 6.0 Hz, 1H), 5.03 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.40−4.31 (m, 2H), 2.65 (td, *J* = 7.8, 2.4 Hz, 1H), 2.01 (s, 3H), 1.92 (s, 3H), 1.77−1.71 (m, 1H), 1.25−1.20 (m, 1H), 0.92 (dt, *J* = 5.4, 4.2 Hz, 1H), 0.68 (tdd, *J* = 7.8, 5.4, 0.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4, 169.7, 152.3, 152.2, 151.4, 145.2, 133.2, 132.3, 132.2, 132.14, 132.11, 131.6, 128.7, 128.6, 73.8, 47.3, 46.9, 20.88, 20.84, 20.2, 17.8, 9.0; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{18}ClN_4O_4$ 365.1011; Found 365.1025. **24b**: TLC: (hexanes:EtOAc, 2:3), R_f = 0.25 (Anis); mp 115−116 °C; $[\alpha]^{25}_D$: +28.6 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max}: 274.9 nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 5.41 (t, *J* = 6.0 Hz, 1H), 4.99 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.37−4.28 (m, 2H), 2.64 (td, *J* = 7.8, 2.4 Hz, 1H), 2.02 (s, 3H), 1.93 (s, 3H), 1.79−1.74 (m, 1H), 1.25−1.20 (m, 1H), 0.94 (dt, *J* = 6.0, 3.6 Hz, 1H), 0.73 (tdd, *J* = 8.4, 5.4, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 169.8, 153.5, 153.3, 152.1, 145.9, 130.8, 73.7, 47.1, 47.0, 20.88, 20.85, 20.2, 17.7, 9.1; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{17}Cl_2N_4O_4$ 399.0621; Found 399.0610.

*(1R,2R,3S,4S,5S)-4-((6-((3-Iodobenzyl)amino)-9H-purin-9-yl)-methyl)bicyclo[3.1.0]hexane-2,3-diol (**4a**) and (1R,2R,3S,4S,5S)-4-((2-Chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)bicyclo-[3.1.0]hexane-2,3-diol (**4b**).* To a stirred solution of **24a** and TPPO mixture (35.2 mg of **24a**, 0.1 mmol, 1.0 equiv of **24a**) or **24b** (27.9 mg, 0.07 mmol, 1.0 equiv) in EtOH (2 mL) were added 3-iodobenzylamine hydrochloride (3-I-Bn-NH_2-HCl, 53.9 mg for **4a** or 37.8 mg for **4b**, 2.0 equiv) and triethylamine (Et_3N, 0.06 mL for **4a** or 0.04 mL for **4b**, 4.0 equiv) at 23 °C. The reaction mixture in a sealed tube was placed under microwave irradiation at 100 °C for 4 h. After it was removed from the microwave, a saturated ethanolic ammonia solution (NH_3/EtOH, 2 mL) was added to the reaction mixture at 23 °C, and stirred for 4 d. The reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (hexanes → hexanes:acetone, 2:3) to afford **4a** (26.8 mg, 58%) or **4b** (18.9 mg, 53%) as a white solid. **4a**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.44 (Anis, PMA); mp 78−80 °C; $[\alpha]^{25}_D$: −3.6 (*c* 0.09, MeOH); UV (MeOH) λ_{max}: 270.7 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.25 (s, 1H), 8.12 (s, 1H), 7.74 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 4.75 (brs, 2H), 4.29 (t, *J* = 6.0 Hz, 1H), 4.26 (dd, *J* = 13.8, 7.2 Hz, 1H), 4.17 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.75 (d, *J* = 6.0 Hz, 1H), 2.55−2.51 (m, 1H), 1.56−1.50 (m, 1H), 1.24−1.18 (m, 1H), 1.02−0.98 (m, 1H), 0.48 (tdd, *J* = 7.8, 4.8, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 156.0, 153.9, 150.4, 143.2, 142.7, 137.6, 137.4, 131.5, 128.0, 120.4, 95.1, 74.9, 73.9, 50.1, 47.7, 44.4, 23.1, 19.0, 8.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{21}IN_5O_2$ 478.0734; Found 478.0745. **4b**: TLC: (CH_2Cl_2:MeOH, 9:1), R_f = 0.46 (Anis, PMA); mp 115−116 °C; $[\alpha]^{25}_D$: +68.3 (*c* 0.09, MeOH); UV (MeOH) λ_{max}: 273.9 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.09 (s, 1H), 7.77 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 4.69 (brs, 2H), 4.27 (t, *J* = 5.3 Hz, 1H), 4.22 (dd, *J* = 14.2, 6.8 Hz, 1H), 4.13 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.73 (d, *J* = 6.4 Hz, 1H), 2.53−2.48 (m, 1H), 1.56−1.50 (m, 1H), 1.23−1.18 (m, 1H), 1.02−0.97 (m, 1H), 0.49 (tdd, *J* = 8.4, 5.4, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 156.4, 155.7, 151.8, 143.0, 142.8, 138.0, 137.5, 131.5, 128.3, 119.3, 95.0, 75.0, 73.9, 50.0, 47.8, 44.5, 23.1, 18.9, 8.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{20}ClIN_5O_2$ 512.0345; Found 512.0335.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00705.

X-ray crystal structure analysis of compound **21a** and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 2068270 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Lak Shin Jeong − *Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 08826, Korea;* orcid.org/0000-0002-3441-707X; Email: lakjeong@snu.ac.kr

Authors

Young Eum Hyun − *Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 08826, Korea*

Hong-Rae Kim − *Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 08826, Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00705

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the Mid-career Research Program (2021R1A2B5B02001544) of the National Research Foundation, Korea.

■ REFERENCES

(1) (a) Fang, Z.; Song, Y.; Zhan, P.; Zhang, Q.; Liu, X. Conformational Restriction: an Effective Tactic in 'Follow-On'-Based Drug Discovery. *Future Med. Chem.* **2014**, *6*, 885−901. (b) de Sena M. Pinheiro, P.; Rodrigues, D. A.; do Couto Maia, R.; Thota, S.; Fraga, C. A.M. The Use of Conformational Restriction in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2019**, *19*, 1712−1733.

(2) Altona, C.; Sundaralingam, M. Conformational Analysis of the Sugar Ring in Nucleosides and Nucleotides. A New Description Using the Concept of Pseudorotation. *J. Am. Chem. Soc.* **1972**, *94*, 8205−8212.
(3) (a) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr HIV-1 Reverse Transcriptase Can Discriminate between Two Conformationally Locked Carbocyclic AZT Triphosphate Analogues. *J. Am. Chem. Soc.* **1998**, *120*, 2780−2789. (b) Roey, V. P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. Correlation between Preferred Sugar Ring Conformation and Activity of Nucleoside Analogues against Human Immunodeficiency Virus. *Proc. Natl. Acad. Sci. U. S. A.* **1989**, *86*, 3929−3933. (c) Roey, V. P.; Taylor, E. W.; Chu, C. K.; Schinazi, R. F. Correlation of Molecular Conformation and Activity of Reverse Transcriptase Inhibitors. *Ann. N. Y. Acad. Sci.* **1990**, *616*, 29−40. (d) Marquez, V. E.; Ben-Kasus, T.; Barchi, J. J., Jr; Green, K. M.; Nicklaus, M. C.; Agbaria, R. Experimental and Structural Evidence that Herpes 1 Kinase and Cellular DNA Polymerase(s) Discriminate on the Basis of Sugar Pucker. *J. Am. Chem. Soc.* **2004**, *126*, 543−549. (e) Marquez, V. E.; Choi, Y.; Comin, M. J.; Russ, P.; George, C.; Huleihel, M.; Ben-Kasus, T.; Agbaria, R. Understanding How the Herpes Thymidine Kinase Orchestrates Optimal Sugar and Nucleobase Conformations to Accommodate Its Substrate at the Active Site: A Chemical Approach. *J. Am. Chem. Soc.* **2005**, *127*, 15145−15150. (f) Toti, K. S.; Osborne, D.; Ciancetta, A.; Boison, D.; Jacobson, K. A. South (S)- and North (N)-Methanocarba-7-Deazaadenosine Analogues as Inhibitors of Human Adenosine Kinase. *J. Med. Chem.* **2016**, *59*, 6860−6877. (g) Jacobson, K. A.; Ji, X.-d.; Li, A.-H.; Melman, N.; Siddiqui, M. A.; Shin, K.-J.; Marquez, V. E.; Ravi, R. G. Methanocarba Analogues of Purine Nucleosides as Potent and Selective Adenosine Receptor Agonists. *J. Med. Chem.* **2000**, *43*, 2196−2203.
(4) An, S.; Kim, D.; Kim, H. J.; Ahn, S.; Kim, H. Y.; Ko, H.; Hyun, Y. E.; Nguyen, M.; Jeong, J.; Liu, Z.; Han, J.; Choi, H.; Yu, J.; Kim, J. W.; Lee, H. W.; Jacobson, K. A.; Cho, W. J.; Kim, Y.-M.; Kang, K. W.; Noh, M.; Jeong, L. S. Discovery and Structure-Activity Relationships of Novel Template, Truncated 1′-Homologated Adenosine Derivatives as Pure Dual PPARγ/δ Modulators. *J. Med. Chem.* **2020**, *63*, 16012−16027.
(5) (a) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Barchi, J., Jr Synthesis of Cyclopropane-Fused Dideoxycarbocyclic Nucleosides Structurally Related to Neplanocin C. *Tetrahedron Lett.* **1993**, *34*, 6233−6236. (b) Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. 4′,6′-Methano Carbocyclic Thymidine: A Conformationally Constrained Building Block for Oligonucleotides. *Tetrahedron Lett.* **1994**, *35*, 2331−2334. (c) Lee, J. A.; Kim, H. O.; Tosh, D. K.; Moon, H. R.; Kim, S.; Jeong, L. S. Stereoselective Synthesis of 2′-C-Methylcyclopropyl-Fused Carbanucleosides as Potential Anti-HCV Agents. *Org. Lett.* **2006**, *8*, 5081−5083. (d) Joshi, B. V.; Moon, H. R.; Fettinger, J. C.; Marquez, V. E.; Jacobson, K. A. A New Synthetic Route to (North)-Methanocarba Nucleosides Designed as A_3 Adenosine Receptor Agonists. *J. Org. Chem.* **2005**, *70*, 439−447.
(6) (a) Shin, K. J.; Moon, H. R.; George, C.; Marquez, V. E. Construction of the Bicyclo[3.1.0]hexane Template of a Conformationally Locked Carbocyclic Adenosine via an Olefin Keto-Carbene Cycloaddition. *J. Org. Chem.* **2000**, *65*, 2172−2178. (b) Melman, A.; Zhong, M.; Marquez, V. E.; Jacobson, K. A. Synthesis of Enantiomerically Pure (*S*)-Methanocarbaribo Uracil Nucleoside Derivatives for Use as Antiviral Agents and P2Y Receptor Ligands. *J. Org. Chem.* **2008**, *73*, 8085−8088.
(7) (a) Charette, A. B.; Juteau, H. Design of Amphoteric Bifunctional Ligands: Application to the Enantioselective Simmons-Smith Cyclopropanation of Allylic Alcohols. *J. Am. Chem. Soc.* **1994**, *116*, 2651−2652. (b) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. Enantioselective Cyclopropanation of Allylic Alcohols with Dioxaborolane Ligands: Scope and Synthetic Applications. *J. Am. Chem. Soc.* **1998**, *120*, 11943−11952.
(8) (a) Simmons, H. E.; Smith, R. D. A New Synthesis of Cyclopropanes from Olefins. *J. Am. Chem. Soc.* **1958**, *80*, 5323−5324. (b) Simmons, H. E.; Smith, R. D. A New Synthesis of Cyclopropanes. *J. Am. Chem. Soc.* **1959**, *81*, 4256−4264. (c) Furukawa, J.; Kawabata, N.; Nishimura, J. A Novel Route to Cyclopropanes from Olefins. *Tetrahedron Lett.* **1966**, *7*, 3353−3354. (d) Furukawa, J.; Kawabata, N.; Nishimura, J. Synthesis of Cyclopropanes by the Reaction of Olefins with Dialkylzinc and Methylene Iodide. *Tetrahedron* **1968**, *24*, 53−58.
(9) (a) Choi, W. J.; Park, J. G.; Yoo, J. S.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S. Syntheses of D- and L-Cyclopentenone Derivatives Using Ring-Closing Metathesis: Versatile Intermediates for the Synthesis of D- and L-Carbocyclic Nucleosides. *J. Org. Chem.* **2001**, *66*, 6490−6494. (b) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. Improved and Alternative Synthesis of D- and L-Cyclopentenone Derivatives, the Versatile Intermediates for the Synthesis of Carbocyclic Nucleosides. *Tetrahedron: Asymmetry* **2002**, *13*, 1189−1193.
(10) Comin, M. J.; Agbaria, R.; Ben-Kasus, T.; Huleihel, M.; Liao, C.; Sun, G.; Nicklaus, M. C.; Deschamps, J. R.; Parrish, D. A.; Marquez, V. E. Sculpting the Bicyclo[3.1.0]hexane Template of Carbocyclic Nucleosides to Improve Recognition by Herpes Thymidine Kinase. *J. Am. Chem. Soc.* **2007**, *129*, 6216−6222.
(11) (a) Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. Approaches to the Assembly of the Antifungal Agent FR-900848: Studies on Double Asymmetric Cyclopropanation and an X-Ray Crystallographic Study of (1*R*2*R*)-1,2-Bis-[(1*S*2*S*)-2-methylcyclopropyl]-l,2-ethanediyl 3,5-Dinitrobenzoate. *J. Chem. Soc., Chem. Commun.* **1994**, 1781−1782. (b) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J. Stereochemical Elucidation of the Pentacyclopropane Antifungal Agent FR-900848. *J. Org. Chem.* **1996**, *61*, 3280−3288. (c) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. Synthesis of Optically Active *cis*- and *trans*- 1,2-Disubstituted Cyclopropane Derivatives by the Simmons-Smith Reaction of Allyl Alcohol Derivatives Derived from (*R*)-2,3-*O*-Isopropylideneglyceraldehyde. *J. Org. Chem.* **1994**, *59*, 97−103. (d) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, G.; Chu, C. K. Asymmetric Synthesis of (l′*S*2′*R*)-Cyclopropyl Carbocyclic Nucleosides. *J. Org. Chem.* **1995**, *60*, 5236−5242.
(12) (a) Charette, A. B.; Lebel, H. Enantioselective Total Synthesis of (+)-U-106305. *J. Am. Chem. Soc.* **1996**, *118*, 10327−10328. (b) Barrett, A. G. M.; Kasdorf, K. Total Synthesis of the Pentacyclopropane Antifungal Agent FR-900848. *J. Am. Chem. Soc.* **1996**, *118*, 11030−11037. (c) Kuzniewski, C. N.; Gertsch, J.; Wartmann, M.; Altmann, K.-H. Total Synthesis of Hypermodified Epothilone Analogs with Potent in Vitro Antitumor Activity. *Org. Lett.* **2008**, *10*, 1183−1186. (d) Tanino, K.; Takahashi, M.; Tomata, Y.; Tokura, H.; Uehara, T.; Narabu, T.; Miyashita, M. Total synthesis of solanoeclepin A. *Nat. Chem.* **2011**, *3*, 484−488. (e) Gritsch, P. J.; Stempel, E.; Gaich, T. Enantioselective Synthesis of Cyclohepta[*b*]-indoles: Gram-Scale Synthesis of (*S*)-SIRT1-Inhibitor IV. *Org. Lett.* **2013**, *15*, 5472−5475.
(13) Charette, A. B.; Juteau, H.; Lebel, H.; Deschenes, D. The Chemo- and Enantioselective Cyclopropanation of Polyenes: Chiral Auxiliary vs Chiral Reagent-Based Approach. *Tetrahedron Lett.* **1996**, *37*, 7925−7928.
(14) Fukuyama, Y.; Hirono, M.; Kodama, M. Total Synthesis of (+)-Bicyclohumulenone. *Chem. Lett.* **1992**, *21*, 167−170.
(15) (a) Charette, A. B.; Juteau, H. Application of the Chemo- and Enantioselective Cyclopropanation of Polyenes to the Total Synthesis of (+)-Bicyclohumulenone. *Tetrahedron* **1997**, *53*, 16277−16286. (b) Charette, A. B.; Cote, B.; Marcoux, J.-F. Carbohydrates as Chiral Auxiliaries: Asymmetric Cyclopropanation Reaction of Acyclic Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 8166−8167.
(16) (a) Yang, Z.; Lorenz, J. C.; Shi, Y. Exploring New Reactive Species for Cyclopropanation. *Tetrahedron Lett.* **1998**, *39*, 8621−8624. (b) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. A Novel Class of Tunable Zinc Reagents ($RXZnCH_2Y$) for Efficient Cyclopropanation of Olefins. *J. Org. Chem.* **2004**, *69*, 327−334.
(17) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. New Family of Cyclopropanating Reagents: Synthesis, Reactivity, and Stability

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837

Studies of Iodomethylzinc Phenoxides. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539−4542.
(18) Denmark, S. E.; Edwards, J. P. A Comparison of (Chloromethyl)- and (Iodomethyl)zinc Cyclopropanation Reagents. *J. Org. Chem.* **1991**, *56*, 6974−6981.
(19) (a) Chan, J. H.-H.; Rickborn, B. Relative Rates and Stereochemistry of the Iodozincmethyl Iodide Methylenation of Some Hydroxy- and Methoxy-Substituted Cyclic Olefins. *J. Am. Chem. Soc.* **1968**, *90*, 6406−6411. (b) Cheng, D.; Kreethadumrongdat, T.; Cohen, T. Allylic Lithium Oxyanionic Directed and Facilitated Simmons-Smith Cyclopropanation: Stereoselective Synthesis of (±)-*cis*-Sabinene Hydrate and a Novel Ring Expansion. *Org. Lett.* **2001**, *3*, 2121−2123.
(20) Klepper, F.; Jahn, E.-M.; Hickmann, V.; Carell, T. Synthesis of the Transfer-RNA Nucleoside Queuosine by Using a Chiral Allyl Azide Intermediate. *Angew. Chem., Int. Ed.* **2007**, *46*, 2325−2327.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on June 29, 2021. The preliminary biological data results were removed from the paper. The modified version was reposted on July 16, 2021.

https://doi.org/10.1021/acs.joc.1c00705
J. Org. Chem. 2021, 86, 9828−9837