# Enantioselective route to key intermediates in the synthesis of carbocyclic phosphoribosyltransferase transition state analogues

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**Abstract**—The enantioselective preparation of key intermediates in the synthesis of transition state analogues of hypoxanthine-guanine phosphoribosyltransferase, (1*S*,2*S*,3*R*,4*R*)-4-acetoxymethyl-1-bromomethyl-2,3-isopropylidenedioxy-1-toluenesulfonamidocyclopentane (**3a**) and the 4-nitrobenzenesulfonamido analogue (**3b**), are described. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Parasitic protozoa cannot carry out the de novo synthesis of purine nucleotides that are required for growth and replication. Rather, they salvage pre-formed purine bases from their hosts. A major purine salvage pathway is controlled by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT), which catalyzes the nucleophilic substitution of the pyrophosphate moiety of $\alpha$-D-5-phosphoribosyl-1-pyrophosphate (PRPP) by the N9 atom of a purine base (Scheme 1). Since HGPRT is apparently dispensable to mammalian metabolism, protozoal HGPRTs have long been viewed as attractive targets for antiprotozoal chemotherapy.[1]

Our work has focused on *Toxoplasma gondii*, a pervasive protozoan that infects as much as half of the population.

Infection by *T. gondii* presents little threat to individuals with a normal immune system.[2] However, in immunosuppressed individuals, such as patients with Acquired Immune Deficiency Syndrome (AIDS), recrudescence of latent *T. gondii* cysts in the brain causes toxoplasmic encephalitis.[3] Disseminated toxoplasmosis is also a serious complication of organ transplantation.

Our approach has been to use the three-dimensional structure of *T. gondii* HGPRT to guide the design of improved HGPRT inhibitors. Structural work carried out by us[4–6] and by others[7–9] has provided many insights into both the overall HGPRT catalytic mechanism as well as the mechanisms by which protozoal HGPRTs are able, unlike the human enzyme, to catalyze the efficient conversion of xanthine to xanthosine 5′-monophosphate.[10] Nonetheless, it has been clear since determination of the human HGPRT crystal
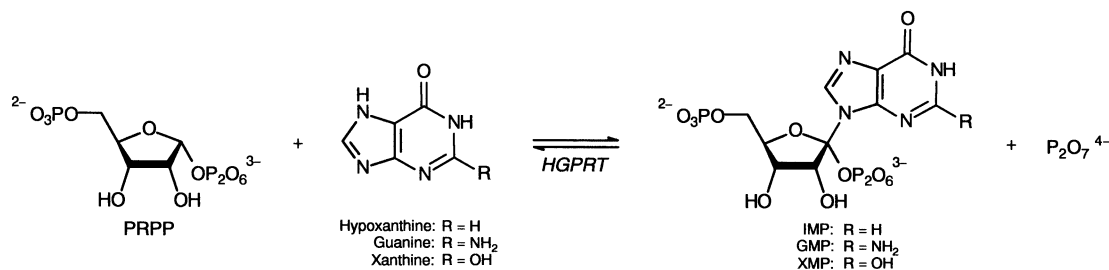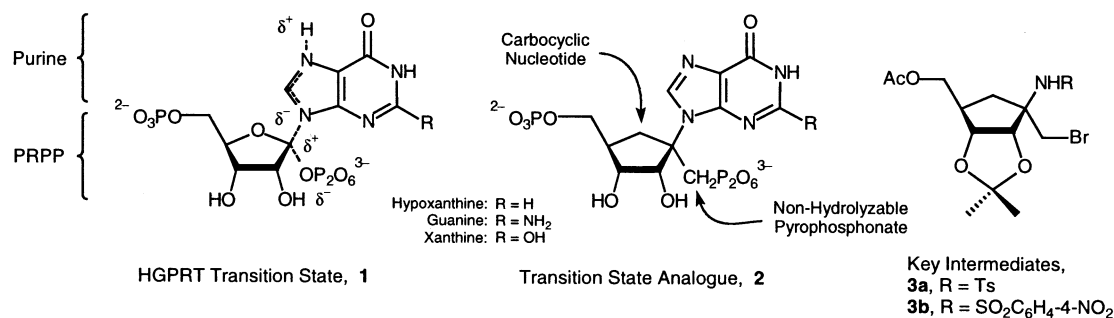


**Scheme 1.**

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**Scheme 2.**

structure that significant motion of a large active site loop (loop II) accompanies catalysis by HGPRT.[11] Despite the findings of recent reports of HGPRT crystal structures[4,7–9] in which loop II is closed over an active site occupied by a substrate and an unreactive substrate analogue (e.g. PRPP and 9-deazaguanine), the true functional role(s) of loop II closure remains unclear, in part because all such HGPRT ternary complexes are bi-substrate (analogue) complexes; they are not images of the enzyme at the transition state. Indeed, the enzyme still functions when loop II is deleted, albeit at a much reduced rate,[12] results consistent with loop II playing a supporting but not critical role in the precise positioning of substrates for catalysis and/or transition-state stabilization.

To capture the essence of the catalytically-competent HGPRT active site, therefore, we felt that it was essential to trap the enzyme closer to the transition state **1** (Scheme 2). Thus, we set out to synthesize HGPRT transition state (TS) analogues, (**2**). The TS analogues **2** mimic the purine and ribose-5′-phosphate aspects of the transition state, whereas the labile PRPP pyrophosphate is replaced by a non-hydrolyzable pyrophosphonate. It is also stabilized against acid-catalyzed decomposition by substitution of the ribose furanyl oxygen by a methylene group, a draw-back of previously-reported analogues based on psico-furanose.[13–15] The target compounds **2** are distinct from the pyrrolidine-based Immucillin nucleoside analogues[16] and the carbocyclic analogue of PRPP,[17,18] neither of which encompass both HGPRT substrates in a single molecule. We report here the enantioselective synthesis of (1*S*,2*S*,3*R*,4*R*)-4-acetoxymethyl-1-bromomethyl-2,3-iso-propylidenedioxy-1-toluenesulfonamidocyclopentane (**3a**) and (1*S*,2*S*,3*R*,4*R*)-4-acetoxymethyl-1-bromomethyl-2,3-isopropylidenedioxy-1-*p*-nitrobenzenesulfonamidocyclo-pentane (**3b**), potential key intermediates toward the synthesis of **2** that embody the correct carbon skeleton, oxidation state, and relative and absolute stereochemistry of the target.
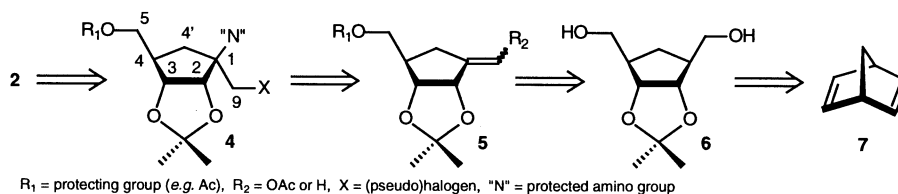
## 2. Results and discussion

### 2.1. Retrosynthetic Analysis

As shown in Scheme 3, functional group simplification leads backwards from **2** to intermediate **4** (O5 phosphorylation, C9 pyrophosphonate construction, and conversion of "N" to a purine ring). Intermediate **4** in turn could be accessed by a variety of routes. We considered spirohydantoin formation at C1. This method was used to prepare carbocyclic analogues of the spironucleoside (+)-hydanto-cidin.[19] Bucherer–Bergs reaction of the cyclopentanone provided the spirohydantoin (**4**, –"N",XCH₂– = –NH(CO)NH(CO)–) with the incorrect stereochemistry (albeit in high yield), however, and under Read reaction conditions the stereochemically-correct aminonitrile was formed in poor yield.[19] Thus, we were interested in explor-ing other synthetic routes (e.g. enolate chemistry, or open-ing of an epoxide or azirdine ring) from the olefin **5** (R₂=OAc, H). Olefin **5** is available as a single enantiomer by lipase-catalyzed[20] monoacetylation of the meso diol **6**,[21] which can be prepared by stereoselective OsO₄-catalyzed *cis*-dihydroxylation of norbornadiene (**7**).

### 2.2. Precursor Synthesis

The precursors for the synthesis of analogue **2** were prepared as shown in Scheme 4. Following the route laid out by Sakai and coworkers,[21] OsO₄-catalyzed *cis*-dihydroxylation of norbornadiene followed by ketalization furnished *exo*-5,6-isopropylidenedioxybicyclo[2.2.1]hept-2-ene (**8**) along with a small amount of the bis-acetonide **9**.[22] Ozonolysis of **8** provided the *meso*-diol **6** in excellent yield. The key desymmetrization of **6**, namely the *Pseudo-monas fluorescens* lipase (PFL)-catalyzed transesterification reaction of **6** and vinyl acetate, afforded the monoacetate (+)-**10a** in >99% enantiomeric excess and 83% yield.[21] The ¹⁹F NMR spectrum of the Mosher ester[23,24] derivative of (+)-**10a, 10c**, exhibited only one signal at −71.93 ppm (referenced to CFCl₃), whereas the Mosher ester of the



R₁ = protecting group (*e.g.* Ac), R₂ = OAc or H, X = (pseudo)halogen, "N" = protected amino group
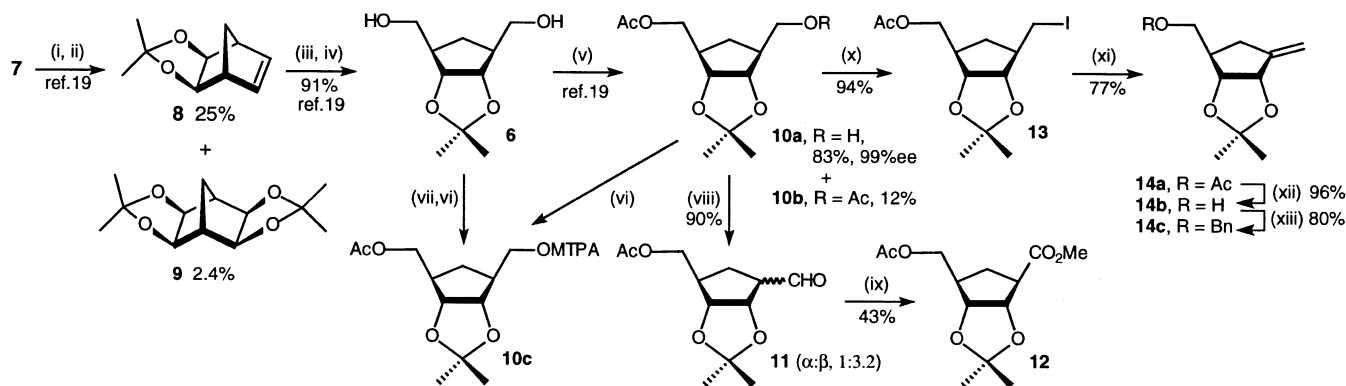
**Scheme 3.**

**Scheme 4.** (i) OsO$_4$, NMNO; (ii) (CH$_3$)CO, TsOH; (iii) O$_3$; (iv) NaBH$_4$; (v) CH$_2$=CHOAc, *P. fluorescens* lipase; (vi) (+)-MTPA-Cl, pyridine; (vii) Ac$_2$O, pyridine; (viii) PCC; (ix) PDC, DMF, CH$_3$OH; (x) PPh$_3$, I$_2$, pyridine; (xi) DBU; (xii) NaOCH$_3$, MeOH; (xiii) Tf$_2$O, BnOH, 2,6-di-*t*-butyl-4-methylpyridine.
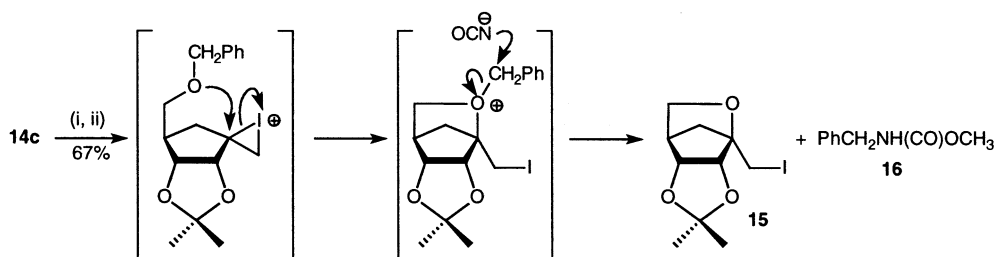


**Scheme 5.** (i) AgNCO, I$_2$; (ii) CH$_3$OH, LiOCH$_3$.

racemate, prepared by partial acetylation (Ac$_2$O, pyridine) of **6**, exhibited two signals at −71.93 and −72.02 ppm. All further work reported here was performed within the highly enantiomerically-enriched series derived from (+)-**10a**.

## 2.3. Enolate Chemistry

Our first approach to functionalization of C1 centred on enolate chemistry of the aldehyde **11**,[25] prepared by oxidation of the monoacetate **10a** (Scheme 4).[26] Attempts to incorporate an azide group at C1, adjacent to the carbonyl group, by reaction of the enolate ion itself or its vinyl trimethylsilyl ether derivative with *p*-toluenesulfonyl azide failed. Since aldol condensation of **11** was likely the source of difficulty, we attempted a similar conversion on the less-reactive methyl ester **12**, prepared by oxidation of **11** with pyridinium dichromate in DMF in the presence of methanol.[27] However, in situ generation of the corresponding enolate by several methods simply resulted in decomposition of ester **12**.

## 2.4. Pseudohalogen Chemistry

Several reports indicate that the addition of iodine isocyanate (INCO) or iodine azide (IN$_3$) to simple alkenes proceeds readily.[28–31] The addition was postulated to proceed through formation of an iodonium ion. We anticipated that reaction of a suitable exocyclic alkene (Scheme 4) with INCO or IN$_3$ should provide an iodonium ion, opening of which would yield a transient tertiary carbenium ion at C1 that could be captured by azide or isocyanate.

Dehydration of alcohol **10a** to an *exo*-olefin (Scheme 4) was

accomplished in two steps by conversion to the iodide **13** followed by elimination of HI to yield **14a**. Addition of alkene **14a** to a solution of INCO in CH$_2$Cl$_2$ at −40°C[28,29] was followed by LiOH-catalyzed methanolysis; the de-acetylated starting material (**14b**) was the only product obtained. We anticipated that exchange of an acetyl protecting group by a benzyl ether would provide the more hydrolysis-resistant analogue (**14c**). Unexpectedly, reaction of **14c** with INCO under identical conditions did not result in the incorporation of INCO, but rather provided the cyclic ether **15** and the co-product benzyl carbamate **16** (Scheme 5). A straightforward mechanism for formation of **15** and **16** is shown in Scheme 5. Intramolecular capture of the intermediate iodonium ion by the benzyl ether oxygen is apparently more facile than intermolecular capture by isocyanate.

In contrast, reaction of alkene **14a** with a solution of IN$_3$ in CH$_3$CN[32] yielded the isomeric iodo azides **17a** and **17b** (Scheme 6). The IR spectra showed bands at 2105 cm$^{-1}$, characteristic of the organic azide functionality. The regiochemistry of the products was determined by examination of their ^{13}C NMR spectra. The chemical shifts observed for the CH$_2$X group (X=I or N$_3$) and the adjacent quaternary
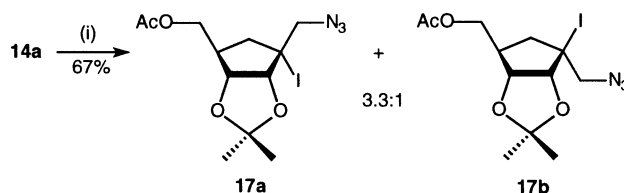


**Scheme 6.** (i) ICl, NaN$_3$, CH$_3$CN.
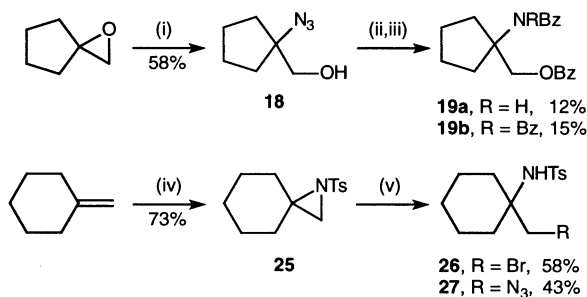
**Scheme 7.** (i) $Et_3Al$, $HN_3$; (ii) $H_2$, 5% Pd/C; (iii) BzCl, pyridine; (iv) PhI=NTs, CuOTf; (v) $Li_2NiBr_4$ or $NaN_3$, $BF_3 \cdot Et_2O$.

carbon of the major stereoisomer **17a**, 62.8 and 56.8 ppm, respectively, were consistent with the presence of a $CH_2N_3$, not a $CH_2I$, moiety. (The calculated $^{13}C$ chemical shift for the $CH_2I$ moiety of the regioisomer is ~10 ppm, in agreement with experimental shifts observed for model compounds.) The minor stereoisomer **17b** exhibited similar chemical shifts (60.6, 52.2 ppm). Thus, nucleophilic attack of the azide ion occurred at the undesired, less hindered end of the iodonium ion rather than at the desired, more hindered tertiary position (C1).

The stereochemistry of the diastereomers **17a** and **17b** was assigned on the basis of homonuclear nOe measurements. Irradiation of the $CH_2N_3$ group in **17a** resulted in a 2–3% nOe enhancement of the C5 $\beta$ proton with no effect on the $\alpha$ proton. The converse was observed for **17b**. Definitive identification of the C5 $\alpha$ and $\beta$ protons in each compound was accomplished by observing the nOe enhancements of these protons upon irradiation of the C3 proton or the acetoxymethyl group protons (both $\beta$).

## 2.5. Epoxidation

A report of Mereyala et al.[33] on the $Et_3Al$-mediated addition of $HN_3$ to epoxides prompted us to examine this route to introduce a nitrogen moiety at C1. This methodology has been applied in a complex natural product synthesis with good results.[33] We first tested the method with 1-oxaspiro[2,4]heptane. Reaction with $Et_3Al/HN_3$ provided the expected azido alcohol, 1-azido-1-hydroxymethylcyclopentane (**18**), in 58% yield (Scheme 7). The regiochemistry

of epoxide opening was confirmed by conversion to its di- and tribenzoyl derivatives **19a** and **19b**. Benzamide **19a** had a distinctive NMR spectrum consistent with a benzamide benzoyl ester, not a benzimide tertiary alcohol.

Encouraged by these results, we turned our attention to the conversion of alkene **14a** to the corresponding epoxide. Reaction with $m$-ClC$_6$H$_4$CO$_3$H ($m$-CPBA)[34] afforded a 4:1 mixture of the diasteromeric epoxides **20a** and **20b** (Scheme 8) which was separated by silica gel chromatography.[35] The stereochemistry of **20b** was assigned by observation of 3% nOe enhancement between the two oxirane ring protons and the $\beta$-disposed protons on C2 and C5 (no nOe enhancements were observed for **20a**). The stereochemistry as assigned is consistent with the major product **20a** resulting from attack of $m$-CPBA from the less-hindered $\beta$-face of the alkene.

Treatment of epoxide **20a** with $Et_3Al/HN_3$ in toluene provided azido alcohol **21** along with its deacetylated analogue **22** in a 2:1 ratio. Diol **22** was easily returned to **21** by acetylation (Ac$_2$O, pyridine). Under these conditions only the 4-hydroxymethyl group was acetylated, indicating that the reaction had produced a tertiary alcohol. In addition, catalytic hydrogenation of **21** followed by acetylation quantitatively provided the acetamide **23**, which still possessed one free (tertiary) hydroxyl group. Thus, in contrast to our results with the model compound 1-oxaspiro[2,4]heptane as well as literature reports, epoxide **20a** reacted with $Et_3Al/$HN$_3$ to afford the undesired primary azide **21**. As previously, nOe enhancement experiments on **21** led to a clear assignment of the stereochemistry ($\beta$-hydroxyl group). Under identical reaction conditions, the diastereomeric epoxide **20b** did not react with $Et_3Al/HN_3$. Reaction in the more polar solvent $CH_3CN$ afforded, however, the azido triol **24** in poor yield, apparently resulting from epoxide opening along with loss of the acetonide group. It is likely that this occurs due to coordination of $Et_3Al$ by the $\alpha$-epoxide oxygen atom (i.e. syn to the acetonide).

This body of results on the addition of $IN_3$ to the terminal alkene **14a** and of $HN_3$ to the epoxides **20a** and **20b** led us to conclude that molecular strain prevents the three-membered ring intermediate in these reactions from opening to form the (desired) tertiary carbenium ion at C1. Rather, formation
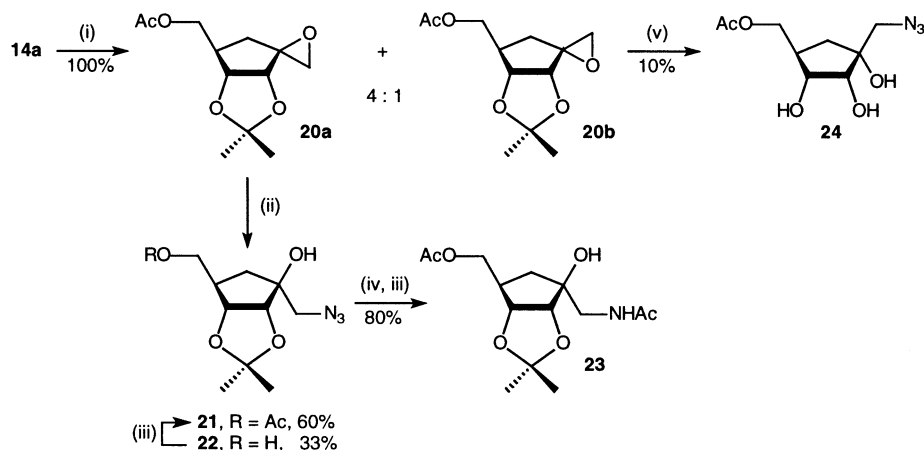


**Scheme 8.** (i) $m$-CPBA; (ii) $Et_3Al$, $HN_3$, toluene; (iii) $Ac_2O$, pyridine; (iv) $H_2$, 5% Pd/C; (v) $Et_3Al$, $HN_3$, $CH_3CN$.
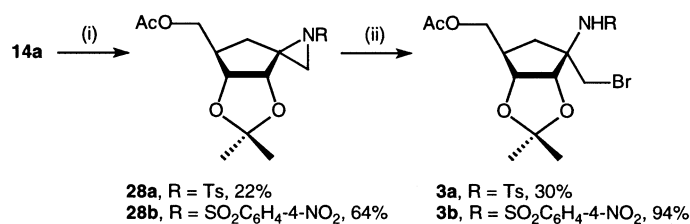
**Scheme 9.** (i) PhI=NTs, CuOTf or PhI=NSO$_2$C$_6$H$_4$-4-NO$_2$, Cu(CH$_3$CN)$_4$$^+$ ClO$_4$$^-$; (ii) Li$_2$NiBr$_4$.

of compounds **17a**, **17b**, **21**, **22**, and **24** results from nucleophilic attack of azide ion on the more accessible exocyclic atom of the three membered ring (iodonium ion intermediate or activated oxirane ring, respectively) in each case. Our observations are in accord with those made by Griengl and co-workers on the opening of epoxides **20a** and **20b** with acetate.[35]

## 2.6. Aziridination

An obvious tactical shift to surmount this barrier was incorporation of the requisite nitrogen atom *prior* to ring opening. Thus, we hypothesized that nucleophilic opening of an aziridine ring would leave the nitrogen at the tertiary carbon C1 and allow for further elaboration of the exocyclic methylene group.

This idea was put to the test with methylene cyclohexane. Reaction with [(4-toluenesulfonyl)imino]-phenyliodinane (PhI=NTs)[36] catalyzed by copper(I) triflate led to formation of the desired *N-p*-toluenesulfonyl-1-azaspiro[2,5]octane (**25**) in 73% yield (Scheme 7). Treatment of this aziridine with Li$_2$NiBr$_4$[37] opened the aziridine ring to give the *primary* bromide **26** in good yield. In addition, BF$_3$·Et$_2$O-mediated reaction of the aziridine with NaN$_3$ in DMF provided the corresponding azido toluenesulfonamide **27**.

Encouraged by these results, we extended the method to our

target molecule (Scheme 9). Reaction of alkene **14a** with PhI=NTs/CuOTf in CH$_3$CN gave *N-p*-toluenesulfonyl-(2*S*,3*R*,4*R*)-6-acetoxymethyl-4,5-isopropylidenedioxy-1-azaspiro[2,4]heptane (**28a**) in 22% yield. Aziridine **28a** reacted with Li$_2$NiBr$_4$ to yield **3a**. NMR and infrared spectroscopic analysis of **3a** suggested that the aziridine ring had been opened to provide the desired regioisomer. The structure of **3a** was unequivocally confirmed by determination of its crystal structure. Slow evaporation of a solution of **3a** in CDCl$_3$ provided crystals suitable for X-ray analysis. The structure was determined with SHELX,[38] and was refined to an *R*-factor of 3.8%. An ORTEP view of the **3a** structure is shown in Fig. 1. The crystal structure confirmed that the regiochemistry of aziridine opening had indeed proceeded in the desired direction, and also validated both the relative and absolute stereochemistry of **3a**. The yields in these last two steps were dramatically improved by carrying out the aziridination of alkene **14a** with [(4-nitrobenzenesulfonyl)-imino]-phenyliodinane,[39] using Cu(CH$_3$CN)$_4$ClO$_4$ as the catalyst,[40] to give **28b** in 68% yield. Like **28a**, aziridine **28b** reacted with Li$_2$NiBr$_4$ to afford the bromide **3b** in 94% yield.

## 3. Summary

We have described the enantiospecific synthesis of the highly-functionalized cyclopentanes **3a** and **3b**. These compounds possess the complete carbon skeleton and functional group oxidation state of the target phosphoribosyltransferase transition state analogue inhibitor **2**. Completion of the synthesis of **2** by purine ring elaboration and incorporation of the phosphate and pyrophosphonate groups will be subject of our next report.

## 4. Experimental

NMR spectra were recorded in CDCl$_3$ on a Nicolet Model NT 300NB spectrometer (300 MHz $^1$H frequency). Chemical shifts are given in ppm relative to residual CHCl$_3$ (unless otherwise stated) at 7.26 ppm (for $^1$H NMR) and 77.0 ppm (for $^{13}$C NMR). Coupling constants are reported in Hz. The symbols s′, d′, t′ and q′ used for $^{13}$C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. $^{13}$C NMR chemical shifts were also calculated using the Bruker SpecEdit program. Fast atom bombardment (FAB) and electron-impact (EI) mass spectra were recorded on a Varian/MAT 311A double-focusing mass spectrometer. For FAB, the matrix was *p*-nitrobenzoic acid (NBA), with or without added LiCl. High resolution mass spectra were obtained on a Bruker Daltonics Bio-TOF
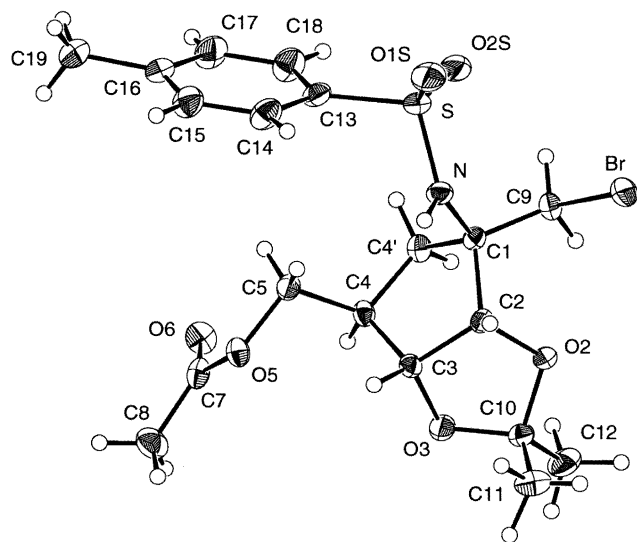


**Figure 1.** Crystal structure of key intermediate **3a**. This thermal-ellipsoid plot shows that the absolute and relative configurations at C2, C3, and C4 correspond to D-ribose, and that the relative configuration at C1 is as desired for an HGPRT transition-state analogue. Figure prepared with ZORTEP.[44]

II ESI mass spectrometer. Optical rotations (one dm path length) were obtained on a Rudolph precision polarimeter, Model 80, and are reported at the $Na_D$ line (578 nm). Thin-layer and column chromatography were performed with silica gel. Unless stated otherwise, reaction mixtures were dried with anhydrous $Na_2SO_4$, solvents were removed in vacuo, and the residue was purified by column chromatography.

### 4.1. (1*S*,2*S*,3*R*,4*R*)-4-Acetoxymethyl-2,3-isopropylidene-dioxycyclopentane-1-methanol (10a), 1,4-diacetoxy-2,3-isopropylidenedioxycyclopentane (10b), and the Mosher ester derivatives (10c)

The asymmetric alcohol (+)-**10a** was prepared according to Tanaka et al.[21] by *P. fluorescens* lipase (PFL)-mediated transesterification of **6** in vinyl acetate. Diol **6** (5.0 g, 25 mmol) dissolved in vinyl acetate (50 ml) was stirred at room temperature with a suspension of PFL (40 mg, 42.5 U/mg, Fluka 62321). The progress of the reaction was monitored by TLC ($CHCl_3/CH_3OH$, 95:5). The reaction was complete after 30 h. Vinyl acetate was evaporated under reduced pressure and the residue was purified by column chromatography ($CHCl_3/CH_3OH$, 95:5) to provide 5.01 g (83%) of (+)-**10a** as a colorless, viscous oil (Lit. mp 42–43°C[21]). Mass $m/z$ 245 $(M+H)^+$, 229 $(M+H-CH_4)^+$ 187 $(M+H-C_3H_6O)^+$; $m/z$ 495 $(2M+Li)^+$, 251 $(M+Li)^+$, 245 $(M+H)^+$. ^{1}H NMR $\delta$ 4.40 (1H, dd, $J=5.0$, 7.0), 4.34 (1H, dd, $J=5.3$, 7.0), 4.11 (2H, d, $J=6.4$), 3.69 (1H, dd, $J=5.9$, 10.5), 3.63 (1H, dd, $J=6.6$, 10.5), 2.4 (1H, m), 2.3 (1H, m), 2.08 (1H, m), 2.07 (3H, s), 1.50 (3H, s), 1.31 (3H, s), 1.27 (1H, m). $[\alpha]_D^{24}$ +8.92° (*c* 1.02, $CHCl_3$) (Lit. $[\alpha]_D^{24}$ +8.55° (*c* 1.07, $CHCl_3$[21])).

The reaction also provided 0.86 g (12%) of the *meso*-diacetate (±)-**10b**. Mass $m/z$ 287 $(M+H)^+$, 271 $(M+H-CH_4)^+$, 229 $(M+H-C_3H_6O)^+$; $m/z$ 293 $(M+Li)^+$, 287 $(M+H)^+$, 271 $(M+H-CH4)^+$, 277 $(M+Li-CH4)^+$, 235 $(M+Li-C_3H_6O)^+$, 229 $(M+H-C_3H_6O)^+$. ^{1}H NMR $\delta$ 4.34 (2H, dd, $J=1.1$, 3.3), 4.12 (2H, dd, $J=6.6$, 11), 4.07 (2H, dd, $J=6.4$, 11), 2.4 (2H, m), 2.10 (1H, dt, $J=7$, 11) 2.07 (6H, s), 1.50 (3H, s), 1.30 (3H, s), 1.25 (1H, m).

The Mosher esters of (+)-**10a** and (±)-**10a** (obtained by partial acetylation of **6** with $Ac_2O$/pyridine) were prepared by esterification in pyridine/$CCl_4$ with excess (*S*)-(+)-$\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetyl chloride[24] and were purified by chromatography ($CH_2Cl_2$/MeOH, 99:1). Mosher ester of (+)-**10a**, (1*S*,2*S*,3*R*,4*R*)-4-acetoxymethyl-2,3-isopropylidenedioxycyclopentane-1-methanol (*S*)-$\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetate (**10c**): Mass $m/z$ 461 $(M+H)^+$, 445 $(M+H-CH_4)^+$, 403 $(M+H-C_3H_6O)^+$, 401 $(M+H-HOAc)^+$. ^{1}H NMR $\delta$ 7.53 (2H, m), 7.41 (3H, m), 4.43 (1H, dd, $J=5.5$, 11.1), 4.32 (1H, dd, $J=6$, 11.1), 4.29 (2H, app t, $J=3.7$), 4.05 (2H, d, $J=6.0$), 3.54 (3H, app d, $J_{H-F}=1.2$), 2.40 (2H, m), 2.05 (3H, s), 2.03 (1H, m), 1.47 (3H, s), 1.27 (3H, s), 1.25 (1H, m). ^{19}F NMR (564.7 MHz, $CDCl_3$, referenced to $CFCl_3$) $\delta$ −71.93 (s). Mosher esters of (±)-**10a**, (1*SR*,2*SR*,3*RS*,4*RS*)-4-acetoxymethyl-2,3-isopropylidenedioxycyclopentane-1-methanol (*S*)-$\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetate: ^{1}H NMR $\delta$ 7.53 (4H, m), 7.41 (6H, m), 4.43 (1H, dd, $J=5.5$, 11.1), 4.37 (1H, d, $J=5.7$), 4.32 (2H, dd, $J=6.0$, 11.1), 4.29 (2H, app t,

$J=3.74$), 4.25 (2H, app t, $J=2.4$), 4.06 (2H, d, $J=5.9$), 4.05 (2H, d, $J=6.0$), 3.55 (6H, app t, $J_{H-F}=1.2$), 2.40 (4H, m), 2.05 (3H, s), 2.04 (3H, s), 2.03 (2H, m), 1.47 (6H, s), 1.269 (3H, s), 1.267 (3H, s), 1.25 (2H, m). ^{19}F NMR $\delta$ −71.93 (s), −72.02 (s). From integration of the ^{19}F NMR signals of **10c**,[23] we estimated the enantiomeric excess of (+)-**10a** to be >99%.

### 4.2. (1*RS*,2*S*,3*R*,4*R*)-4-Acetoxymethyl-2,3-isopropylidenedioxycyclopentane-1-methanal (11)

Monoacetate **10a** (45 mg, 0.184 mmol) was stirred with pyridinium chlorochromate (PCC, 80 mg, 0.37 mmol) in $CH_2Cl_2$ (10 mL) on ice.[26] After 3 h the mixture was warmed to room temperature, and the progress of the reaction was monitored by TLC until no starting material remained. Diethyl ether (25 mL) was added, the mixture was filtered, passed through a plug of Florisil and evaporated under reduced pressure. A colorless oil containing a 3.2:1 mixture of (1*R*,2*S*,3*R*,4*R*)-4-acetoxymethyl-2,3-isopropylidenedioxy-cyclopentane-1-methanal (**11**$\beta$)[25] and the (1*S*,2*S*,3*R*,4*R*)-diastereomer (**11**$\alpha$) (40 mg, 90%) was obtained. Mass $m/z$ 243 $(M+H)^+$, 227 $(M+H-CH_4)^+$, 185 $(M+H-C_3H_6O)^+$. IR (neat) $\nu$ 2987, 2939, 1742, 1455, 1382, 1377, 1235, 1212, 1037 $cm^{-1}$. **11**$\beta$: ^{1}H NMR $\delta$ 9.77 (1H, s), 4.94 (1H, dd, $J=3.3$, 6), 4.44 (1H, dd, $J=2.8$, 6), 4.02 (1H, dd, $J=5.7$, 11.3), 3.93 (1H, dd, $J=6.1$, 11.3), 2.96 (1H, m), 2.48 (1H, m), 2.36 (1H, m), 2.04 (3H, s), 1.86 (1H, dt, $J=5.9$, 13.2), 1.50 (3H, s), 1.33 (3H, s). **11**$\alpha$: ^{1}H NMR $\delta$ 9.77 (1H, s), 5.0 (1H, t, $J=5.7$), 4.52 (1H, d, $J=5.5$), 4.34 (1H, m), 4.1 (1H, m), 3.9 (1H, m), 2.87 (1H, m), 2.29 (1H, m), 2.08 (3H, s), 1.65 (1H, m), 1.42 (3H, s), 1.30 (3H, s). $[\alpha]_D^{20}$ −9.4° (*c* 0.7, MeOH).

### 4.3. (1*S*,2*S*,3*R*,4*R*)-4-Acetoxymethyl-2,3-isopropylidene-dioxycyclopentane-1-carboxylate methyl ester (12)

PDC (13.5 g, 36 mmol) was added to a solution of aldehyde **11** (1.43 g, 6 mmol) and $CH_3OH$ (1.5 mL, 36 mmol) in DMF (20 mL).[27] After stirring 20 h at room temperature hexane (75 mL) and sat. aq. $NaHCO_3$ (30 mL) were added. The mixture was filtered through a Florasil plug, dried and evaporated. The residue was distilled under reduced pressure (bp 105°C, 0.25 torr) to obtain 705 mg (43%) of ester **12**. Mass $m/z$ 279 $(M+Li)^+$, 273 $(M+H)^+$, 257 $(M+H-CH_4)^+$, 215 $(M+H-C_3H_6O)^+$. IR (neat) $\nu$ 2987, 2953, 1741, 1456, 1437, 1381, 1374, 1243, 1211, 1175, 1070, 1037, 865 $cm^{-1}$. ^{1}H NMR $\delta$ 4.85 (1H, dd, $J=4.6$, 6.6), 4.44 (1H, dd, $J=4.2$, 6.8), 4.09 (1H, dd, $J=6.15$, 11.2), 4.04 (1H, dd, $J=6.4$, 11.2), 3.71 (3H, s), 2.94 (1H, ddd, $J=4.6$, 9.0, 16.9), 2.41 (1H, m), 2.32 (1H, dd, $J=7.7$, 13.2), 2.07 (3H, s), 1.80 (1H, dd, $J=9.0$, 13.2), 1.50 (3H, s), 1.32 (3H, s). $[\alpha]_D^{20}$ −25.5° (*c* 1.01, $CHCl_3$). HRMS Calcd for $C_{13}H_{20}O_6$: $m/z$ $(M+H)^+$ 273.1333, $(M+Na)^+$ 295.1152; Found: $m/z$ 273.1335, 295.1159.

### 4.4. (1*S*,2*S*,3*R*,4*R*)-4-Acetoxymethyl-1-iodomethyl-2,3-isopropylidenedioxycyclopentane (13)

A mixture of $Ph_3P$ (8.38 g, 0.032 mol) and $I_2$ (7.62 g, 0.030 mol) in anhydrous $CH_2Cl_2$ (100 mL) was stirred at room temperature for one h.[21] The brownish-red clear solution cooled to −10°C and a solution of alcohol **10a** (4.88 g,

0.020 mol) in $CH_2Cl_2$ (25 mL) and pyridine (2.37 g, 0.030 mol) was added. The mixture stirred for 15 min, and then 6 h at room temperature. The reaction mixture was poured into 5% aq. $Na_2S_2O_3$ (50 mL) and extracted with $Et_2O$ (2 x 100 mL). The combined extracts were washed with $H_2O$, dried and evaporated. The residue was chromatographed (20% EtOAc/hexanes, $R_f$=0.42) to obtain 6.76 g (94%) of iodide **13**. Mass $m/z$ 355 $(M+H)^+$, 339 $(M+H–CH_4)^+$, 297 $(M+H–C_3H_6O)^+$; $m/z$ 361 $(M+Li)^+$, 339 $(M+H–CH_4)^+$. IR (neat) $\nu$ 2986, 2935, 1741, 1380, 1371, 1244, 1212, 1071, 1034 cm$^{-1}$. $^1$H NMR $\delta$ 4.38 (1H, dd, $J$=5.2, 7.0), 4.23 (1H, dd, $J$=5.2, 7.0), 4.13 (1H, dd, $J$=6.4, 11), 4.09 (1H, dd, $J$=6.0, 11), 3.38 (1H, dd, $J$=5.0, 10), 3.24 (1H, dd, $J$=6.8, 10), 3.39 (1H, m), 2.3–2.12 (2H, m), 2.08 (3H, s), 1.5 (3H, s), 1.31 (3H, s), 1.37–1.24 (1H, m). Anal. Calcd for $C_{12}H_{19}IO_4$: C 40.69%, H 5.41%; Found: C 40.79%, H 5.23%. $[\alpha]_D^{20}$ −19.2° ($c$ 0.76, CHCl$_3$).

### 4.5. (2*S*,3*R*,4*R*)-4-Acetoxymethyl-2,3-isopropylidenedioxy-1-methylenecyclopentane (14a)

A mixture of DBU (4.7 g, 30.2 mmol) and iodide **13** (5.38 g, 15.2 mmol) in anhydrous $C_6H_6$ (50 mL) was refluxed for 5 h.[21] The mixture was cooled to room temperature and then partitioned between aq. $NH_4Cl$ and $Et_2O$ (3 × 75 mL). The combined extracts were washed with 5% aq. $Na_2S_2O_3$ (25 mL) and water, and then dried and evaporated. Distillation (bp 85–87°C, 1 mm Hg) yielded 2.70 g (77%) of a colorless oil, alkene **14a**. Mass $m/z$ 227 $(M+H)^+$, 211 $(M+H–CH_4)^+$, 169 $(M+H–C_3H_6O)^+$; $m/z$ 133 $(M+Li)^+$. IR (neat) $\nu$ 2988, 2938, 1744, 1381, 1371, 1242, 1232, 1209, 1161, 1035, 873 cm$^{-1}$. $^1$H NMR $\delta$ 5.23 (1H, d, $J$=1.5), 5.11 (1H, app q, $J$=1), 4.73 (1H, d, $J$=5.6), 3.49 (1H, d, $J$=5.6), 3.90 (1H, d, $J$=1), 2.80 (1H, m), 2.44 (1H, q, $J$=7.5), 2.04 (1H, m), 2.04 (3H, s), 1.48 (3H, s), 1.34 (3H, s). $^{13}$C NMR $\delta$ 171.4 (s′), 148.5 (s′), 113.2 (t′), 110.7 (s′), 82.4 (d′), 81.6 (d′), 64.7 (t′), 42.8 (d′), 32.3 (t′), 26.6 (q′), 24.4 (q′), 20.9 (q′). $[\alpha]_D^{20}$ −124.8° ($c$ 1.2, CHCl$_3$). Anal. Calcd for $C_{12}H_{18}O_4 \cdot (H_2O)_{0.1}$: C 63.19%, H 8.04%; Found: C 62.84%, H 7.80%.

### 4.6. (2*S*,3*R*,4*R*)-4-Methanol-2,3-isopropylidenedioxy-1-methylenecyclopentane (14b) and (2*S*,3*R*,4*R*)-4-benzyloxymethyl-2,3-isopropylidenedioxy-1-methylenecyclopentane (14c)

Alkene **14a** (345 mg, 1.5 mmol) and NaOCH$_3$ (162 mg, 3 mmol) were stirred in anhydrous methanol (10 mL) at room temperature for one h. The solvent was evaporated under reduced pressure and the residue was chromatographed (hexane/EtOAc, 80:20) to provide 270 mg (96%) of alcohol **14b**. Mass $m/z$ 185 $(M+H)^+$, 169 $(M+H–CH_4)^+$, 127 $(M+H–C_3H_6O)^+$. $^1$H NMR $\delta$ 5.22 (1H, d, $J$=1.1), 5.1 (1H, app q, $J$=1.1), 4.74 (1H, d, $J$=5.5), 4.55 (1H, d, $J$=5.7), 3.50 (2H, m), 2.7 (1H, m), 2.30 (1H, m), 2.09 (1H, d, $J$=15.6), 1.48 (3H, s), 1.38 (1H, t, $J$=5.5) 1.34 (3H, s). $[\alpha]_D^{20}$ −79.0° ($c$ 1.0, CHCl$_3$).

Trifluoromethanesulfonic anhydride (Tf$_2$O, 490 mg, 1.74 mmol) was added to anhydrous $CH_2Cl_2$ (5 mL) under N$_2$. A solution of benzyl alcohol (188 mg, 1.74 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (360 mg, 1.74 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise at −70°C and the

mixture stirred for 30 min.[41,42] Alcohol **14b** (160 mg, 0.86 mmol) in $CH_2Cl_2$ (2 mL) was added slowly to the reagent mixture, the reaction was stirred for 30 min, and then warmed to room temperature and stirred for 1 h. Pyridine (300 μL) was added and the mixture was washed with $H_2O$ (3 × 5 mL), dried and evaporated. Chromatography of the residue (hexane/EtOAc, 90:10) gave benzyl ether **14c** (190 mg, 80%). Mass (ESI-MS) $m/z$ 313 $(M+K)^+$, 297 $(M+Na)^+$, 292 $(M+NH_4)^+$, 275 $(M+H)^+$, 217 $(M+H–C_3H_6O)^+$, 91 $(PhCH_2)^+$. $^1$H NMR $\delta$ 7.32 (5H, m), 5.19 (1H, d, $J$=1.3), 5.09 (1H, d, $J$=1.3), 4.69 (1H, d, $J$=6), 4.5 (1H, d, $J$=6), 4.49 (2H, s), 3.27 (2H, d, $J$=7.2), 2.78 (1H, m), 2.45 (1H, m), 2.10 (1H, d, $J$=15), 1.47 (3H, s), 1.32 (3H, s). $[\alpha]_D^{20}$ −5.05° ($c$ 1.5, MeOH). HRMS Calcd for $C_{17}H_{22}O_3$: $m/z$ $(M+Na)^+$ 297.1461; Found: $m/z$ 297.1453.

### 4.7. (1*R*,4*R*,5*R*,6*R*)-1-Iodomethyl-5,6-isopropylidenedioxy-2-oxabicyclo[2.2.1]heptane (15) and *N*-benzyl methyl carbamate (16)

Iodine (61 mg 0.24 mmol) was added to a stirred suspension of AgNCO (36 mg, 0.24 mmol) in anhydrous $CH_2Cl_2$ (5 mL) at −40°C.[29] After 90 min a solution of benzyl ether **14c** (55 mg, 0.20 mmol) in $CH_2Cl_2$ (1 mL) was added and stirred an additional 90 min. The reaction mixture was left at −15°C overnight, then allowed to warm to room temperature. The solvent was evaporated under reduced pressure, the residue was dissolved in anhydrous methanol (2 mL) containing a catalytic amount of LiOCH$_3$, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane/EtOAc, 90:10) to give the cyclic ether **15** (42 mg, 67%) as a colorless oil. Mass (ESI-MS) $m/z$ 311 $(M+H)^+$. IR (neat) $\nu$ 2987, 2935, 1382, 1372, 1265, 1207, 1076, 1048 cm$^{-1}$. $^1$H NMR $\delta$ 4.39 (1H, d, $J$=4.6), 4.00 (1H, dd, $J$=1.7, 5.5), 3.78 (1H, dd, $J$=3.3, 7.9), 3.54 (1H, d, $J$=11.2), 3.50 (1H, d, $J$=11.2), 3.43 (1H, d, $J$=7.9), 2.67 (1H, m), 1.94 (1H, d, $J$=10.5), 1.55 (1H, m), 1.45 (3H, s), 1.31 (3H, s). $[\alpha]_D^{20}$ −45.2° ($c$ 1.0, CHCl$_3$). HRMS Calcd for $C_{10}H_{15}O_3I$: $m/z$ $(M+H)^+$ 311.0139, $(M+Na)^+$ 332.9958; Found: $m/z$ 311.0135, 332.9969. The co-product benzyl carbamate **16** was isolated in 30% yield. Mass (ESI-MS) $m/z$ 166 $(M+H)^+$. IR (neat) $\nu$ 3326 (br), 3062, 3030, 2948, 2925, 1703, 1530, 1455, 1260 cm$^{-1}$. $^1$H NMR $\delta$ 7.29 (5H, m), 5.0 (1H, br s), 4.35 (2H, d, $J$=6), 3.70 (3H, s).

### 4.8. Reaction of (2*S*,3*R*,4*R*)-4-acetoxymethyl-2,3-isopropylidenedioxy-1-methylenecyclopentane (14a) with IN$_3$: (1*R*,2*R*,3*R*,4*R*)-4-Acetoxymethyl-1-azidomethyl-1-iodo-2,3-isopropylidenedioxycyclopentane (17a) and (1*S*,2*R*,3*R*,4*R*)-4-acetoxymethyl-1-azidomethyl-1-iodo-2,3-isopropylidenedioxycyclopentane (17b)

Iodine monochloride (158 mg, 50 μL, 0.98 mmol) was added slowly to a slurry of NaN$_3$ (108 mg, 1.66 mmol) in anhydrous $CH_3CN$ (4 mL) at −30°C.[32] After 15 min a solution of alkene **14a** (75 mg, 0.33 mmol) in $CH_3CN$ (1 mL) was added dropwise. The mixture allowed to warm to room temperature and stirred overnight. The reaction was partitioned between $H_2O$ (10 mL) and $Et_2O$ (3×30 mL). The combined extracts were washed with 5% aq. $Na_2S_2O_3$ until a clear, colorless solution was obtained. The organic layer

was washed with water, dried and concentrated. Chromatography (hexane/EtOAc, 80:20) provided the isomeric iodo azides **17a** and **17b** in 67% yield as a 3.3:1 mixture. **17a**: Mass $m/z$ 396 (M+H)$^+$, 380 (M+H–CH$_4$)$^+$, 338 (M+H–C$_3$H$_6$O)$^+$; $m/z$ 402 (M+Li)$^+$. IR (neat) $\nu$ 2987, 2935, 2104, 1739, 1243, 1208 cm$^{-1}$. $^1$H NMR $\delta$ 4.48 (1H, dd, $J$=5.6, 7.8), 4.22 (1H, dd, $J$=5.9, 11.2), 4.18 (1H, dd, $J$=5.9, 11.2), 3.88 (2H, s), 3.69 (1H, d, $J$=7.7), 2.93 (1H, m), 2.45 (1H, dd, $J$=6.4, 14.5), 2.09 (3H, s), 1.98 (1H, dd, $J$=12, 14.5), 1.72 (3H, s), 1.33 (3H, s). $^{13}$C NMR $\delta$ 170.8 (s$'$), 115.7 (s$'$), 83.4 (d$'$), 82.3 (d$'$), 64.5 (t$'$), 62.8 (t$'$), 56.8 (s$'$), 44.3 (t$'$), 43.3 (d$'$), 26.2 (q$'$), 25.6 (q$'$), 20.8 (q$'$). $[\alpha]_D^{20}$ −34.5° ($c$ 1.0, CHCl$_3$). **17b**: Mass $m/z$ 396 (M+H)$^+$, 338 (M+H–C$_3$H$_6$O)$^+$. IR (neat) $\nu$ 2987, 2935, 2105, 1742, 1232, 1032 cm$^{-1}$. $^1$H NMR $\delta$ 5.09 (1H, d, $J$=5), 4.75 (1H, dd, $J$=2.4, 5.3), 4.51 (1H, dd, $J$=9.2, 11), 4.30 (1H, dd, $J$=6.8, 11), 3.82 (1H, d, $J$=13.4), 3.64 (1H, d, $J$=13.2), 2.71 (1H, dd, $J$=9.9, 15.2), 2.50 (1H, m), 2.29 (1H, dd, $J$=2.85, 15.2), 2.10 (3H, s), 1.45 (3H, s), 1.31 (3H, s). $^{13}$C NMR $\delta$ 170.8 (s$'$), 112.7 (s$'$), 90.4 (d$'$) 84.6 (d$'$), 65.7 (t$'$), 60.6 (t$'$), 52.2 (s$'$), 45.6 (d$'$), 43.1 (t$'$), 27.0 (q$'$), 25.2 (q$'$), 20.9 (q$'$).

### 4.9. Reaction of 1-oxaspiro[2,4]heptane with Et$_3$Al/HN$_3$: 1-azido-1-hydroxymethylcyclopentane (18), 1-benzamido-1-benzoyloxymethylcyclopentane (19a), and *N*-benzoyl-1-benzamido-1-benzoyloxymethylcyclopentane (19b)

A solution of HN$_3$ in C$_6$H$_6$ (1.4 M, 7.15 mL, 10 mmol) was added with stirring to a solution of Et$_3$Al in toluene (5.25 mL of a 1.9 M solution; 10 mmol) under N$_2$ at −20°C. The mixture was then brought to room temperature.[33] The Et$_3$Al/HN$_3$ solution was added slowly to a solution of 1-oxaspiro[2,4]heptane (400 mg, 4.08 mmol) in toluene (2 mL) cooled to −70°C. The mixture was stirred for 1 h and then was warmed to room temperature. The reaction mixture was poured into ice water and Et$_2$O (25 and 60 mL) and mixed thoroughly. The ethereal solution was dried, concentrated, and purified by chromatography (hexane/EtOAc, 80:20) to yield 1-azido-1-hydroxymethylcyclopentane (**18**) (330 mg, 58%) as a colorless oil. Mass (ESI-MS) $m/z$ (molecular ion was not observed) 114 (M+H–N$_2$)$^+$, 113 (M–N$_2$)$^-$ (negative mass detection). IR (neat) $\nu$ 3375, 2961, 2874, 2097, 1455, 1262, 1050 cm$^{-1}$. $^1$H NMR $\delta$ 3.59 (2H, d, $J$=6.2), 2.33 (1H, br m), 1.8–1.6 (10H, m). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 5.21 (1H, t, $J$=5.5), 3.47 (2H, d, $J$=5.5), 1.61 (10H, s). $^{13}$C NMR $\delta$ 73.9 (s$'$), 68.4 (t$'$), 33.9 (t$'$), 24.2 (t$'$). HRMS Calcd for C$_6$H$_{11}$N$_3$O: $m/z$ (M+Na)$^+$ 164.0794; Found: $m/z$ 164.0795.

1-Azido-1-hydroxymethylcyclopentane was reduced and benzoylated as follows: 5% Pd/C (20 mg) was added to a solution of (**18**) (110 mg, 0.78 mmol) in EtOAc (15 mL). The mixture was placed under H$_2$ at ambient pressure overnight. The catalyst was removed by filtration and the solvent was evaporated. The residue was dissolved in anhydrous pyridine (2 mL), benzoyl chloride (545 mg, 450 μL, 3.8 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was partitioned between CH$_2$Cl$_2$ and H$_2$O (50:10 mL), and the organic layer was separated, dried and evaporated. Chromatography (hexane/EtOAc, 80:20) provided 1-benzamido-1-benzoyloxymethylcyclopentane (**19a**) (29.6 mg, 12%) [Mass $m/z$ 362 (M+K)$^+$, 346 (M+Na)$^+$, 324 (M+H)$^+$; $^1$H NMR $\delta$

8.02 (2H, d, $J$=7), 7.74 (2H, dt, $J$=1.5, 6.8), 7.58–7.38 (6H, m), 6.36 (1H, s), 4.64 (2H, s), 2.20 (2H, m), 2.01–1.75 (6H, m); HRMS Calcd for C$_{20}$H$_{21}$O$_3$N: $m/z$ (M+H)$^+$ 324.1594; Found: $m/z$ 324.1601] and *N*-benzoyl-1-benzamido-1-benzoyloxymethylcyclopentane (**19b**) (48.6 mg, 15%) [Mass $m/z$ 466 (M+K)$^+$, 450 (M+Na)$^+$, 445 (M+NH$_4$)$^+$, 428 (M+H)$^+$; $^1$H NMR $\delta$ 7.99 (2H, d, $J$=7), 7.49–7.05 (13H, m), 4.78 (2H, s), 2.6 (2H, m), 2.27 (2H, m), 1.82 (4H, m); HRMS Calcd for C$_{27}$H$_{25}$O$_4$N: $m/z$ (M+H)$^+$ 428.1856; Found: $m/z$ 428.1861].

### 4.10. (3S,4R,5R,6R)-6-Acetoxymethyl-4,5-isopropylidenedioxy-1-oxaspiro[2,4]heptane (20a) and (3R,4R,5R,6R)-6-acetoxymethyl-4,5-isopropylidenedioxy-1-oxaspiro[2,4]heptane (20b)

An aq. solution of NaHCO$_3$ (0.5 M, 3 mL) was mixed with alkene **14a** (226 mg, 1 mmol) in CH$_2$Cl$_2$ (10 mL). Solid *m*-CPBA (275 mg of 75% peracid, i.e. 207 mg, 1.2 mmol) was slowly added in small portions, and the mixture was stirred at room temperature overnight.[34] The consumption of peracid was tested with starch-iodide paper while the consumption of the alkene was followed by TLC. When both reactants were consumed, the two phases were separated and the organic phase was washed with 1 N sodium hydroxide solution (15 mL), water (10 mL) and dried. Chromatography (hexane/EtOAc, 80:20) provided (3S,4R,5R,6R)-6-acetoxymethyl-4,5-isopropylidenedioxy-1-oxaspiro[2,4]heptane (**20a**) (192 mg, 79%) along with the (3R,4R,5R,6R)-isomer **20b** (51 mg, 21%).[35] **20a**: Mass $m/z$ 249 (M+Li)$^+$, 243 (M+H)$^+$, 227 (M+H–CH$_4$)$^+$, 185 (M–C$_3$H$_6$O+H)$^+$. IR (neat) $\nu$ 2989, 2936, 1744, 1382, 1373, 1232, 1210, 1162, 1054, 1036, 878, 868 cm$^{-1}$. $^1$H NMR $\delta$ 4.67 (1H, d, $J$=5.7), 4.22 (1H, dd, $J$=1.3, 5.7), 4.09 (2H, m), 2.99 (1H, d, $J$=4.4), 2.86 (1H, d, $J$=4.4), 2.63–2.50 (2H, m), 2.09 (3H, s), 1.48 (3H, s), 1.32 (1H, d, $J$=15), 1.31 (3H, s). $^{13}$C NMR $\delta$ 170.6 (s$'$), 110.7 (s$'$), 84.6 (d$'$), 82.5 (d$'$), 65.5 (s$'$), 64.7 (t$'$), 47.4 (t$'$), 43.5 (d$'$), 31.6 (t$'$), 26.4 (q$'$), 24.1 (q$'$), 20.9 (q$'$). $[\alpha]_D^{20}$ −58.1° ($c$ 0.9, CHCl$_3$). **20b**: Mass $m/z$ 249 (M+Li)$^+$, 243 (M+H)$^+$, 227 (M+H–CH$_4$)$^+$, 185 (M–C$_3$H$_6$O+H)$^+$. $^1$H NMR $\delta$ 4.54 (1H, d, $J$=5.5), 4.26 (1H, d, $J$=5.7), 4.04 (2H, m), 2.93 (1H, dd, $J$=0.9, 5.3), 2.83 (1H, d, $J$=5.3), 2.59 (1H, m), 2.52 (1H, m), 2.08 (3H, s), 1.55 (3H, s), 1.40 (1H, d, $J$=12.3), 1.32 (3H, s). $^{13}$C NMR $\delta$ 170.7 (s$'$), 111.4 (s$'$), 81.9 (d$'$), 80.2 (d$'$), 65.1 (t$'$), 63.3 (s$'$), 54.4 (t$'$), 41.0 (d$'$), 30.4 (t$'$), 26.3 (q$'$), 24.2 (q$'$), 20.8 (q$'$). $[\alpha]_D^{20}$ −58.7° ($c$ 0.9, CHCl$_3$). HRMS Calcd for C$_{12}$H$_{18}$O$_5$: $m/z$ (M+H)$^+$ 243.1227; Found: $m/z$ 243.1214.

### 4.11. (1S,2R,3R,4R)-4-Acetoxymethyl-1-azidomethyl-1-hydroxy-2,3-isopropylidenedioxycyclopentane (21) and (1S,2R,3R,4R)-4-hydroxymethyl-1-azidomethyl-1-hydroxy-2,3-isopropylidenedioxycyclopentane (22)

A Et$_3$Al/HN$_3$ mixture prepared as above (1.9 mmol) was added dropwise to a solution of epoxide **20a** (196 mg, 0.8 mmol) in anhydrous toluene (4 mL) at −70°C. The mixture stirred for 1 h and then warmed slowly to room temperature. The reaction progress was monitored by TLC. When no starting material remained, the reaction was poured on a mixture of ice water and Et$_2$O (30 and 70 mL), and the organic layer was dried and evaporated. Chromatography (CHCl$_3$/EtOAc, 70:30) of the residue

yielded azido alcohol **21** (140 mg, 60%) and its 4-desacetyl analogue **22** (65 mg, 33%) as colorless oils. **21**: Mass *m/z* 286 (M+H)$^+$, 270 (M+H−CH$_4$)$^+$, 228 (M+H−C$_3$H$_6$O)$^+$. IR (neat) $\nu$ 3450 (br), 2990, 2940, 2105, 1741, 1719, 1383, 1373, 1260, 1240, 1211, 1163, 1072, 1037, 871 cm$^{-1}$. $^1$H NMR $\delta$ 4.61 (1H, d, *J*=5.6), 4.32 (1H, dd, *J*=1.5, 5.6), 4.17 (2H, m), 3.66 (1H, d, *J*=12.1), 3.40 (1H, d, *J*=12.1), 2.61 (1H, d, *J*=0.9), 2.41 (1H, q, *J*=8.4), 2.08 (3H, s), 2.02 (1H, dd, *J*=8.8, 13.8), 1.57 (1H, dd, *J*=1.3, 13.8), 1.44 (3H, s), 1.30 (3H, s). $^{13}$C NMR $\delta$ 171.1 (s′), 111.0 (s′), 86.1 (d′), 83.7 (d′), 82.6 (s′), 66.1 (t′), 56.7 (t′), 44.8 (d′) 35.8 (t′), 26.6 (q′), 24.3 (q′), 20.9 (q′). HRMS Calcd for C$_{14}$H$_{23}$NO$_6$: *m/z* (M+H)$^+$ 286.1397, (M+Na)$^+$ 308.1217; Found: *m/z* 286.1386, 308.1220. **22**: Mass *m/z* 244 (M+H)$^+$, 228 (M+H−CH$_4$)$^+$. Mass *m/z* 250 (M+Li)$^+$, 228 (M+H−CH$_4$)$^+$. IR (neat) $\nu$ 3350 (br), 2990, 2935, 2105, 1447, 1385, 1375, 1212, 1165, 1072, 1045 cm$^{-1}$. $^1$H NMR $\delta$ 4.89 (1H, br s), 4.73 (1H, d, *J*=5.5), 4.32 (1H, dd, *J*=1.3, 5.5), 3.92 (1H, br s), 3.85 (1H, dd, *J*=4, 10.1), 3.68 (1H, dd, *J*=3.3, 10.1), 3.60 (1H, d, *J*=12.3), 3.39 (1H, d, *J*=12.3), 2.33 (1H, m), 2.21 (1H, dd, *J*=9.9, 14.1), 1.65 (1H, d, *J*=14.1), 144 (3H, s), 1.30 (3H, s). $^1$H NMR (300 MHz, DMSO-*d$_6$*) $\delta$ 5.24 (1H, s), 4.81 (1H, s), 4.55 (1H, d, *J*=5.7), 4.21 (1H, dd, *J*=0.9, 5.5), 3.48 (1H, m), 3.38 (1H, m), 3.32 (1H, d, *J*=12.5), 3.21 (1H, d, *J*=12.5), 2.03 (1H, m), 1.85 (1H, dd, *J*=9.0, 13.4), 1.33 (3H, s), 1.20 (3H, s). $^{13}$C NMR $\delta$ 110.7 (s′), 87.1 (d′), 84.2 (d′), 82.3 (s′), 64.5 (t′), 56.1 (t′), 46.7 (d′), 37.7 (t′), 26.7 (q′), 24.2 (q′). $[\alpha]_D^{20}$ −87.5° (*c* 1.0, CHCl$_3$). Diol **22** was converted back to acetate **21** in 98% yield by reaction with Ac$_2$O/pyridine overnight at room temperature.

## 4.12. (*1S,2R,3R,4R*)-4-Acetoxymethyl-1-acetylamido-1-hydroxy-2,3-isopropylidenedioxycyclopentane (23)

5% Pd/C (20 mg) was added to azido alcohol **21** (15 mg, 0.05 mmol) in EtOAc (10 mL) and the mixture was stirred under H$_2$ (1 atm). The progress of the reaction was monitored by TLC. When all the azido alcohol was consumed (~12 h) the mixture was filtered and solvent was removed to provide the crude amine: $^1$H NMR $\delta$ 6.65 (1H, br d, *J*=12), 4.61 (1H, d, *J*=5.7), 4.30 (1H, dd, *J*=1.1, 5.5), 4.18 (2H, m), 3.1 (1H, br d, *J*=12), 2.87 (br s), 2.38 (1H, app q, *J*=7), 2.07 (3H, s), 1.96 (1H, dd, *J*=9, 14), 1.52 (1H, dd, *J*=0.9, 14), 1.43 (3H, s), 1.29 (3H, s). The crude amine was mixed with anhydrous pyridine (1 mL) and Ac$_2$O (100 µL) and stirred at room temperature for 18 h. Excess Ac$_2$O was quenched with EtOH (1 mL) and solvents were evaporated. Chromatography (CHCl$_3$/MeOH, 95:5) yielded 15 mg of **23** (80%). Mass *m/z* 308 (M+Li)$^+$. IR (neat) $\nu$ 3350 (br), 2987, 2985, 1740, 1653, 1550, 1372, 1240, 1211, 1037 cm$^{-1}$. $^1$H NMR $\delta$ 6.1 (1H, br t, *J*=5.3), 4.61 (1H, d, *J*=5.7), 4.32 (1H, dd, *J*=1.3, 5.5), 4.17 (2H, m), 3.72 (1H, dd, *J*=7, 14.3), 3.27 (1H, dd, *J*=5.5, 14.3), 2.4 (1H, app q, *J*=7), 2.07 (3H, s), 2.05 (3H, s), 2.01 (1H, dd, *J*=9, 14), 1.57 (1H, dd, *J*=1.1, 14), 1.47 (3H, s), 1.30 (3H, s). $^1$H NMR (300 MHz, DMSO-*d$_6$*) $\delta$ 7.65 (1H, t, *J*=5.9), 4.99 (1H, s), 4.49 (1H, d, *J*=5.3), 4.21 (1H, d, *J*=4.8), 4.13 (1H, dd, *J*=10, 11), 3.91 (1H, dd, *J*=6.1, 11), 3.41 (1H, dd, *J*=6.6, 13.6), 3.03 (1H, dd, *J*=4.4, 13.6), 2.17 (1H, app q, *J*=7), 2.01 (3H, s), 1.87 (1H, dd, *J*=8.8, 13.6), 1.84 (3H, s), 1.46 (1H, *J*=13.6), 1.35 (3H, s), 1.21 (3H, s). $^{13}$C NMR $\delta$ 172.6 (s′), 171.0 (s′), 110.7 (s′), 86.6 (d′), 83.7 (d′), 83.4 (s′), 66.1

(t′), 46.3 (t′), 44.8 (d′), 36.6 (t′), 26.7 (q′), 24.3 (q′), 23.0 (q′), 21.0 (q′). $[\alpha]_D^{20}$ −87.7° (*c* 0.4, CHCl$_3$). HRMS Calcd for C$_{14}$H$_{23}$NO$_6$: *m/z* (M+Na)$^+$ 324.1417; Found: *m/z* 324.1424.

## 4.13. (*1R,2R,3R,4R*)-4-Acetoxymethyl-1-azidomethyl-1,2,3-trihydroxycyclopentane (24)

A Et$_3$Al/HN$_3$ mixture prepared as above (1.6 mmol) was added dropwise to a solution of epoxide **20b** (50 mg, 0.2 mmol) in anhydrous CH$_3$CN (2 mL) at −40°C. The mixture stirred 30 min, warmed slowly to room temperature, and allowed to proceed overnight. The reaction progress was monitored by TLC. Workup followed by chromatography as before provided ~50% of recovered epoxide **20b**. Additional chromatography (CHCl$_3$/MeOH, 95:5) yielded azido triol **24** (5 mg, 10%) as a colorless oil. Mass *m/z* 252 (M+Li)$^+$. IR (neat) $\nu$ 3400 (br), 2105, 1732, 1252 cm$^{-1}$. $^1$H NMR $\delta$ 4.15 (1H, dd, *J*=5.5, 11.2), 4.06 (1H, dd, *J*=6.1, 11.2), 3.92 (1H, br s), 3.79 (1H, app d, *J*=6.1), 3.38 (2H, s), 3.04 (2H, br s), 2.49 (1H, m), 2.09 (3H, s), 2.05 (1H, dd, *J*=8.5, 14), 1.56 (br s), 1.40 (1H, dd, *J*=8.9, 14). $^1$H NMR (300 MHz, DMSO-*d$_6$*) $\delta$ 4.79 (1H, d, *J*=6.4), 4.66 (1H, d, *J*=6.6), 4.58 (1H, s), 4.08 (1H, dd, *J*=5.3, 11), 3.90 (1H, dd, *J*=7, 11), 3.60 (1H, app q, *J*=6.5), 3.51 (1H, app t, *J*=6), 3.23 (1H, d, *J*=12.5), 3.15 (1H, d, *J*=12.5), 2.23 (1H, m), 2.0 (3H, s), 1.78 (1H, dd, *J*=8.8, 13.8), 1.24 (1H, dd, *J*=9.9, 13.8).

## 4.14. N-4-Toluenesulfonyl-1-azaspiro[2,5]octane (25)

Methylene cyclohexane (144 mg, 1.5 mmol) was added with stirring to CuOTf·0.5C$_6$H$_6$ (3.75 mg, 0.015 mmol) in anhydrous CH$_3$CN (2 mL) under N$_2$. Solid [(4-toluene-sulfonyl)imino]-phenyliodinane (112 mg, 0.3 mmol) was added in one portion.[36] After 1 h, when all of the solid was dissolved, the reaction mixture was filtered through a silica plug, which was then washed with EtOAc (50 mL). Evaporation of the solvent followed by chromatography (hexane/EtOAc, 80:20) gave aziridine **25** (58.5 mg, 73%, based on PhI=NTs) as a colorless oil. Mass *m/z* 266 (M+H)$^+$, 110 (M−Ts)$^+$. IR (neat) $\nu$ 2936, 2858, 1600, 1450, 1318, 1304, 1159, 1091, 943, 842, 817, 735, 722, 567 cm$^{-1}$. $^1$H NMR $\delta$ 7.83 (2H, d, *J*=8.1), 7.31 (2H, d, *J*=8.1), 2.43 (3H, s), 2.40 (2H, s), 2.0−1.7 (6H, m), 1.5 (4H, m). Anal. Calcd for C$_{14}$H$_{19}$NO$_2$S·(H$_2$O)$_{0.4}$: C 61.69%, H 7.32%, N 5.14%; Found: C 61.35%, H 7.06%, N 5.26%.

## 4.15. 1-(4-Toluenesulfonyl)amido-1-bromomethyl-cyclohexane (26)

Li$_2$NiBr$_4$[37] (150 µL of ~0.4 M solution in THF, approx. 0.06 mmol) was added to a solution of aziridine **25** (5.3 mg, 0.02 mmol) in anhydrous THF (0.5 mL) and the mixture was stored at room temperature overnight. The solvent was evaporated and the residue was purified by preparative TLC (hexane/EtOAc, 80:20) to yield the primary bromide **26** (4 mg, 58%). Mass *m/z* 352 and 354 (M+Li)$^+$, 346 and 347 (M+H)$^+$. $^1$H NMR $\delta$ 7.80 (2H, d, *J*=8.1), 7.29 (2H, d, *J*=8.1), 4.53 (1H, br s), 3.56 (3H, s), 2.43 (3H, s), 1.9 and 1.5−1.2 (10H, several m). Anal. Calcd for C$_{14}$H$_{20}$BrNO$_2$S·(H$_2$O)$_{0.3}$: C 47.81%, H 5.90%, N 3.98%; Found: C 47.69%, H 5.57%, N 3.85%.

### 4.16. 1-(4-Toluenesulfonyl)amido-1-azidomethylcyclo-hexane (27)

Sodium azide (0.045 mmol, 3 mg) and $BF_3 \cdot Et_2O$ (6.4 mg, 0.045 mmol, 5.7 μL) were added to a solution of aziridine **25** (6.0 mg, 0.023 mmol) in anhydrous DMF (1 mL). The mixture was stirred at room temperature overnight. The primary azide **27** was purified by preparative TLC (hexane/EtOAc, 80:20) yielding 3.0 mg (43%) of a colorless oil. Mass $m/z$ 309 $(M+H)^+$; $m/z$ 315 $(M+Li)^+$. $^1$H NMR $\delta$ 7.79 (2H, d, $J=8.3$), 7.30 (2H, d, $J=8.3$), 4.4 (1H, br s, $D_2O$ exchangeable), 3.41 (2H, s), 2.43 (3H, s), 1.8 (2H, m), 1.5–1.2 (8H, m). HRMS Calcd for $C_{14}H_{20}N_4O_2S$: $m/z$ $(M+Na)^+$ 331.1199; Found: $m/z$ 331.1211.

### 4.17. (4S,5R,6R)-N-p-Toluenesulfonyl-6-acetoxymethyl-4,5-isopropylidenedioxy-1-azaspiro[2,4]heptane (28a)

Alkene **14a** (113 mg, 0.5 mmol) was added with stirring to $CuOTf \cdot 0.5C_6H_6$ (1.5 mg, 0.0055 mmol) in anhydrous $CH_3CN$ (2 mL) under $N_2$. Solid [(4-toluenesulfonyl)-imino]-phenyliodinane (41 mg, 0.11 mmol) was added in one portion and stirring was continued at room temperature. The progress of the reaction was monitored by TLC. After 1 h additional PhI=NTs (41 mg) and $CuOTf \cdot 0.5C_6H_6$ (3 mg) were added, the mixture was stirred at room temperature for another hour, and then stored at 4°C overnight. The reaction mixture was filtered through a silica plug, which was then washed with EtOAc (50 mL). Evaporation of the solvent followed by chromatography (hexane/EtOAc, 80:20) gave 78 mg of recovered alkene **14a** along with 20 mg of the desired aziridine **28a** (22% based on PhI=NTs; 33% based on **14a**) as an oil. Mass $m/z$ 402 $(M+Li)^+$. IR (neat) $\nu$ 1742, 1600, 1455, 1372, 1323, 1238, 1218, 1213, 1160, 1035, 710, 691 cm$^{-1}$. $^1$H NMR $\delta$ 7.82 (2H, d, $J=8.1$), 7.33 (2H, d, $J=8.1$), 4.87 (1H, d, $J=6$), 4.65 (1H, d, $J=6$), 4.22 (2H, m), 2.81 (1H, s), 2.55 (2H, m), 2.52 (1H, s), 2.44 (3H, s), 2.09 (3H, s), 1.95 (1H, m), 1.47 (3H, s), 1.32 (3H, s). $^{13}$C NMR $\delta$ 170.9 (s′), 144.4 (s′), 137.0 (s′) 129.6 (d′), 127.6 (d′), 111.8 (s′), 82.1 (d′), 82.0 (d′), 64.1 (t′), 56.9 (s′), 43.7 (d′), 36.2 (t′), 32.3 (t′), 26.7 (q′), 24.8 (q′), 21.6 (q′), 20.9 (q′). $[\alpha]_D^{20}$ −65.5° ($c$ 1.3, CHCl$_3$). Anal. Calcd for $C_{19}H_{25}NO_6S$: C 57.71%, H 6.37%, N 3.54%; Found: C 57.46%, H 6.48%, N 3.42%.

### 4.18. (4S,5R,6R)-N-4-Nitrobenzenesulfonyl-6-acetoxy-methyl-4,5-isopropylidenedioxy-1-azaspiro[2,4]heptane (28b)

Alkene **14a** (1.127 g, 5 mmol) and $Cu(CH_3CN)_4 \cdot ClO_4$ (124 mg, 0.34 mmol) were dissolved in anhydrous $CH_3CN$ (15 mL) containing activated 4A molecular sieves. Solid [(4-nitrobenzene sulfonyl)imino]-phenyliodinane (3.043 g, 7.44 mmol)[39] was added portionwise under Ar over a period of 4 h, and the reaction mixture was stirred overnight. Evaporation of the solvent followed by chromatography (cyclohexane/EtOAc, 80:20) gave aziridine **28b** (980 mg, 64%) as a colorless oil. Mass $m/z$ 453 $(M+Li)^+$. $^1$H NMR $\delta$ 8.38 (2H, m), 8.14 (2H, m), 4.84 (1H, d, $J=5.9$), 4.66 (1H, d, $J=6.04$), 4.23 (2H, m), 2.89 (1H, s), 2.57 (3H, m), 2.10 (3H, s), 1.98 (1H, m), 1.47 (3H, s), 1.33 (3H, s). $[\alpha]_D^{20}$ −63.38° ($c$ 1.7, CHCl$_3$). Anal. Calcd for $C_{18}H_{22}N_2O_8S$: C

50.69%, H 5.20%, N 6.56%; Found: C 50.75%, H 4.95%, N 6.54%.

### 4.19. (1S,2S,3R,4R)-4-Acetoxymethyl-2,3-isopropyl-idenedioxy-1-bromomethyl-1-toluenesulfonamido-cyclopentane (3a)

Aziridine **28a** (34 mg, 0.086 mmol) and $Li_2NiBr_4$ (0.5 ml of ~0.4 M THF solution, 0.2 mmol)[37] were mixed in anhydrous THF (0.2 ml) and kept at room temperature for 48 h. The solvent was evaporated and the residue was purified by preparative TLC (hexane/EtOAc, 80:20) to yield the primary bromide **3a** (12 mg, 30%) as a pale yellow oil that eventually crystallized, mp 119–121°C. Mass $m/z$ 482 & 484 $(M+Li)^+$. $^1$H NMR $\delta$ 7.82 (2H, app d, $J=8$), 7.32 (2H, app d, $J=8$), 5.23 (1H, br s, $D_2O$ exchangeable), 4.88 (1H, d, $J=5.7$), 4.38 (1H, dd, $J=2.2$, 5.7), 4.13 (1H, dd, $J=4$, 11.2), 4.02 (1H, dd, $J=8.1$, 11.2), 3.72 (1H, d, $J=11$), 3.52 (1H, d, $J=11$), 2.44 (3H, s), 2.33 (1H, m), 2.14 (1H, dd, $J=8.8$, 14.2), 2.09 (3H, s), 1.89 (1H, dd, $J=4.2$, 14.3), 1.42 (3H, s), 1.27 (3H, s). $[\alpha]_D^{20}$ −4.5° ($c$ 0.3, CHCl$_3$). HRMS Calcd for $C_{19}H_{27}O_6NS^{32}Br^{79}$: $m/z$ 476.07425; Found: $m/z$ 476.07434.

### 4.20. (1S,2S,3R,4R)-4-Acetoxymethyl-2,3-isopropyl-idenedioxy-1-bromomethyl-1-(4-nitrobenzenesulfon-amido)-cyclopentane (3b)

Aziridine **28b** (100 mg, 0.23 mmol) and $Li_2NiBr_4$ (1.5 ml of ~0.4 M THF solution, 0.6 mmol) were mixed in anhydrous THF (0.6 ml) and kept at room temperature for 48 h. The residue was chromatographed (cyclohexane/EtOAc, 85:15) to give **3b** (112 mg, 94%) as a syrup. $^1$H NMR $\delta$ 8.37 (2H, m), 8.14 (2H, m), 5.96 (1H, s), 5.00 (1H, d, $J=5.8$), 4.50 (1H, dd, $J=6.0$, 2.1), 4.33 (1H, dd, $J=8.5$, 11.4), 4.00 (1H, dd, $J=6.8$, 11.4), 3.69 (1H, d, $J=11.5$), 3.53 (1H, d, $J=11.5$), 2.39 (1H, m), 2.16 (1H, dd, $J=8.5$, 14.4), 2.13 (3H, s), 1.84 (1H, dd, $J=4.2$, 14.3), 1.44 (3H, s), 1.30 (3H, s). $[\alpha]_D^{20}$ +4.59° ($c$ 1.02, CHCl$_3$). Anal. Calcd for $C_{18}H_{23}BrN_2O_8S$: C 42.61%, H 4.56%, N 5.52%; Found: C 42.84%, H 4.52%, N 5.56%.

### 4.21. Crystal structure determination of 3a

Bromide **3a** was crystallized by slow evaporation from CDCl$_3$. Diffraction data for a single pale yellow crystal (0.42×0.16×0.14 mm) were collected at 173 K on a Bruker SMART CCD-based area diffractometer (Mo K$\alpha$ radiation, $\lambda=0.71073$ Å). Monoclinic, space group $P2_1$, $a=10.5078$ (7), $b=9.3298$ (6), $c=10.7871$ (7) Å, $\beta=92.3870$ (10)°, $V=1056.60$ (12) Å$^3$, $Z=2$, $F(000)=492$. $\theta$ and $\omega$ scans, $\theta_{min}=1.89°$, $\theta_{max}=27.90°$, 6705 measured reflections, of which 4249 were unique, $3922 > 2\sigma$, 258 parameters, $R_1=0.038$, $wR_2=0.0872$, GOF=1.076 (Bijvoet pairs *not* merged). Max./min. residual electron density 0.581/−0.624 e$^-$/Å$^3$. The positions of the Br and S atoms were determined by visual inspection of the Patterson map; the other non-hydrogen atoms were located in difference Fourier maps (SHELXS-97).[38] The structure was refined against $F^2$ for all observed reflections. Hydrogen atoms, which were located in difference maps, were refined as riding atoms at their calculated positions. The absolute configuration was determined unequivocally by refinement,

against the anomalous scattering data, of either enantiomer of the initial Br/S two-atom model and subsequently the complete molecule. The Flack parameter for the correct enantiomer of the final model was 0.026 (8).[43] Crystallographic data (including structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC-133069).

## Acknowledgements

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