Palladium-Catalyzed Enantioselective Synthesis of Carbanucleosides

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Abstract: A general strategy has been developed for enantioselective synthesis of diverse carbanucleosides. The key step is a Pd(0)-catalyzed enantioselective allylic amination of *cis*-3,5-dibenzoyloxycyclopent-2-ene **10a** with the nucleobase. With guanine-derived nucleobase **13** and chiral ligand **9**, a 93−96% ee was obtained, while 6-chloropurine and chiral ligand **8** gave 94% ee. The reaction was followed by a second Pd(0)-catalyzed allylic alkylation with phenylsulfonyl(nitro)methane **6**. The nitrosulfone, thus obtained, served as a versatile intermediate for divergent synthesis in which the phenylsulfonyl(nitro)methyl group is a surrogate for the hydroxymethyl side chain. With the guanine-derived nucleobase **13**, (−)-carbovir was obtained in only four steps from **10a**. With 6-chloropurine as an adenine equivalent, the obtained nitrosulfone intermediate **26** could be converted into both (−)-aristeromycin and (−)-neplanocin A as well as their 2′,3′-diepi isomers.

Carbanucleosides have been the focus of much recent attention in the development of new antiviral and antitumor therapeutic agents.[1,2] Due to the absence of a glycosidic linkage, carbanucleosides are chemically more stable and not subject to the phosphorylases that cleave the N-glycosidic linkage in conventional nucleosides. Many carbanucleosides that exhibit potent and selective biological activity have now been identified.[1,2] During a large search for new antiviral agents, particularly for the treatment of human immunodeficiency virus (HIV), (−)-carbovir **1** was discovered[3] and subsequently shown to possess significant in vitro activity as an inhibitor of HIV reverse transcriptase.[4] The adenosine analogues (−)-aristeromycin **2** and (−)-neplanocin A **3**, isolated from *Streptomyces citricolor*[5] and *Ampullariella regularis*,[6] respectively, are also strong antiviral agents due to their potent inhibition of the cellular enzyme S-adenosyl homocysteine hydrolase.[7] In addition, (−)-neplanocin A has been shown to possess anticancer activity especially against leukemia.[8] Because of their pharmaceutical importance, these compounds have been the subject of many studies and a number of total and formal syntheses have been reported.[2,9−11] Although none of these three carbanucleosides has been developed into a drug, they have paved the way for the development of analogues that are more effective and less toxic therapeutic agents. One example is the cyclopropylamino derivative of (−)-carbovir, abacavir **4**, which has a higher oral bioavailability than the parent compound and is now in phase III clinical trials for HIV treatment.[12] Another example is the cytosine analogue of neplanocin A, cyclopentenyl cytosine **5**, which is in clinical development for cancer treatment.[13] In any search for analogues, it is important to have an efficient synthetic

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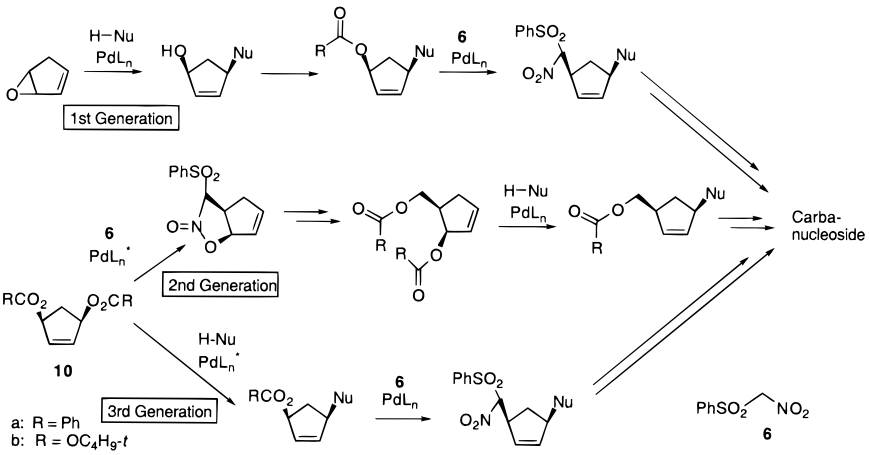
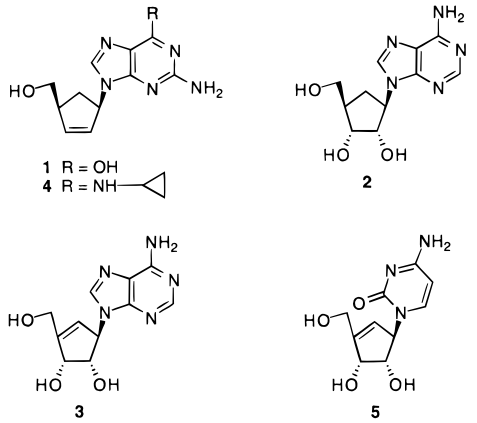
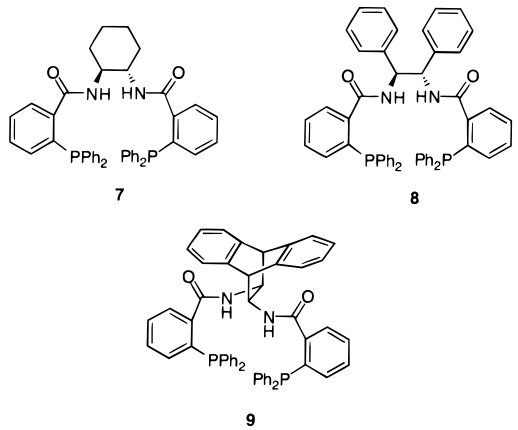
Scheme 1. Stategies to Carbanucleosides Based on Pd-Catalyzed Allylic Alkylation



route that is not only short and enantioselective but also divergent so that modifications can easily be introduced.



Our long time interest in palladium-catalyzed allylic alkylations has led us to develop several strategies for the synthesis of carbanucleosides.[9h,14,15] The key steps are two Pd(0)-catalyzed alkylations on an activated cyclopentene skeleton to introduce the nucleobase and the hydroxymethyl side chain. In our first generation synthesis the nucleobase (Nu) was first reacted with cyclopentadiene monoepoxide (Scheme 1).[14] Then, a second Pd(0)-catalyzed alkylation with the anion of phenylsulfonyl-(nitro)methane (**6**) introduced a one-carbon side chain which can be converted into the hydroxymethyl group. Although rather short, this synthesis gives racemic carbanucleosides.[14] Our development of a series of chiral modular ligands **7**−**9**[16,17]



allowed the development of an asymmetric second-generation synthesis using the cycloaddition of bis-benzoate **10a** with **6** as the enantiodiscriminating step.[9h] However, introduction of the hydroxymethyl side chain and the nucleobase did require a significant number of steps. Since the nucleobase is introduced late in the sequence, this strategy is useful to access a series of analogues in which this unit is varied—as is desired in a medicinal chemistry program. A desire to streamline the route led to the development of a third generation synthesis.[15] In this strategy, the nucleobase is introduced directly in the enantiodiscriminating step followed by a second regio- and diastereoselective Pd(0)-catalyzed alkylation to introduce the phenylsulfonyl(nitro)methyl side chain. Two key questions that needed to be resolved involve the ability to use the nucleobases in the enantiodiscriminating step and to employ the initial alkylation product in a further Pd(0)-catalyzed allylic alkylation without loss of the nucleobase. Here, we report a full account of this third generation carbanucleoside synthesis exemplified by the synthesis of (−)-carbovir, (−)-aristeromycin, and (−)-neplanocin A as well as the 2′,3′-diepi analogues of the latter two.

Results and Discussion

Synthesis of (−)-Carbovir. We have previously examined the asymmetric allylic alkylation (AAA) reaction wherein bis-benzoate **10a**[18] was reacted with a variety of nucleophiles in the presence of Pd(0) and chiral ligand **7**.[17] The asymmetric induction in this case should in principle be independent of the nucleophile. This also seems to be true for simple nucleophiles such as malonates,[16] sulfinates,[19] azide,[20] and amines[16] which all give high yields and ee's in the alkylation reaction. In accordance with our model for this system, the (S,S)-ligand **7** in all cases preferentially ionizes the *pro*-R leaving group. However, nucleobases behave differently and show a remarkable effect on the catalytic turnover and the enantioselectivity, probably as a result of their ability to coordinate with palladium.

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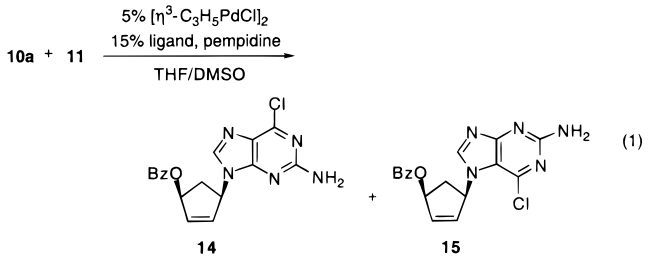
Table 1. AAA Reaction of **10a** with **11**

		yield (%)		$[\alpha]_D$ (CH_2Cl_2) (deg)
entry	ligand	**14**[a]	**15**	of **14**
1	**7**	29 (48)	21	−48
2	**8**	39 (53)	13	−95
3	**9**	28 (31)	32	−132

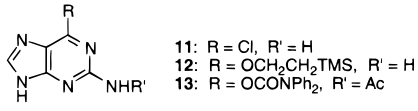
[a] Yields in parantheses are based on recovered **10a**.

For the synthesis of (−)-carbovir, a guanine equivalent was needed for the enantiodiscriminating step. Guanine itself is extremely insoluble in organic solvents, and as a result, 2-amino-6-chloropurine (**11**) is often used as a substitute. We have successfully employed this equivalent in Pd(0)-catalyzed allylic alkylations with achiral ligands without complications. In addition, a base was needed for the enantioselective allylic amination. The choice of base proved to have a significant influence on the conversion using ligand **8** and nucleobase **11** (eq 1). Tertiary amine bases were superior to inorganic bases



(1)

such as sodium hydride and cesium carbonate. In particular, the more sterically hindered amine bases gave better conversion. In the series triethylamine, diisopropylethylamine and 1,2,2,6,6-pentamethylpiperidine (pempidine), the yield of the allylation product more than doubled. As a result, pempidine was selected as the base of choice. An even more profound influence was observed with the choice of ligand. Although no ee has been determined at this point, the measured optical rotations clearly show that ligand **9** is superior to **7** and **8** (Table 1). Bicyclic ligand **9** presumably has a larger P−Pd−P bite angle than **7** and **8**.[16] However, these results are still surprising because ligands **7** and **8** have previously given excellent yields and ee's with the simpler nucleophiles mentioned above.[17] As indicated in Table 1, both products of N-9 and N-7 alkylation were isolated. Especially for ligand **9**, this ratio was not satisfactory. Consequently, other purine nucleophiles were investigated that would give more of the desired N-9 product. The C-6 substituent was changed from chlorine to more sterically demanding groups in an effort to block the N-7 position. Introducing the TMS-ethoxy group as in **12**[21] gave, in fact, only one regioisomer in the alkylation, but only in about 20% yield. A much more gratifying result was obtained with diphenylcarbamate **13**[22] where the electron-donating ability of the 2-amino group has at the same time been reduced by acetylation (eq 2, Table 2).



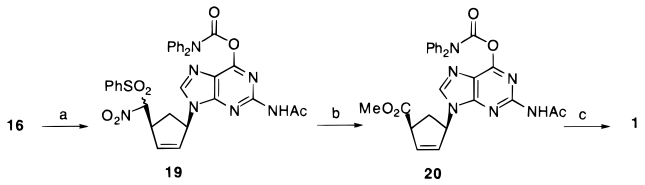
A 57% yield of the desired N-9 alkylation product **16** was obtained in 90% ee. Lowering the reaction temperature from room temperature to 0 °C gave higher catalytic turnover (Table 2, entries 2 and 3), yield (up to 70%), and ee (up to 96%) as well as a better ratio between the N-9 and the N-7 product. One recrystallization from EtOAc enhanced the ee to more than 98%. Surprisingly, the doubly alkylated product **18** was also isolated. The formation of this may, in part, contribute to the higher ee by imposing a partial kinetic resolution of the monoalkylated product after the initial enantiodiscriminating allylic alkylation.

Table 2. AAA Reaction of **10a** with **13**

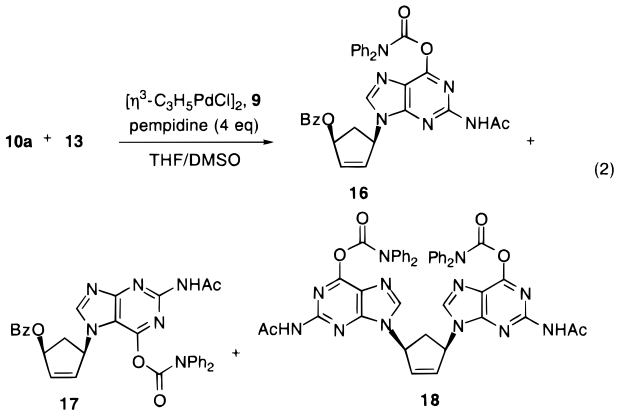
				yield (%)			ee (%)
entry	$[\eta^3$-$C_3H_5PdCl]_2$ (%)	**9** (%)	temp.	**16**[a]	**17**	**18**	of **16**
1	2.5	7.5	rt	49 (57)	13	NI	90
2	2.5	7.5	0 °C	50 (54)	8	21	96
3	1.5	4.5	0 °C	59 (70)	7	16	93

[a] Yields in parentheses are based on recovered **10a**. NI = not isolated.

Scheme 2. Asymmetric Synthesis of (−)-Carbovir[a]



[a] (a) 1% Pd_2dba_3·$CHCl_3$, 8% PPh_3, **6**, Et_3N, THF, rt, 97%. (b) $Me_2NC(NH)NMe_2$, TBA-oxone, Na_2CO_3, MeOH, CH_2Cl_2, rt, 71%. (c) $Ca(BH_4)_2$, THF, then aq. NH_3, rt, 61%.



(2)

Having prepared enantiopure **16** the hydroxymethyl side chain can now be introduced in three steps (Scheme 2). A second Pd(0)-catalyzed alkylation with phenylsulfonyl(nitro)methane (**6**) and triethylamine gives nitrosulfone **19** as a 1:1 diastereomeric mixture almost quantitatively. Previous work relied upon ozonolysis to cleave the nitrosulfone to the ester—an oxidation protocol not compatible with the double bond. Thereby, we developed a new protocol for this transformation.[20] Chemoselective oxidation of the tetramethylguanidine salt with tetrabutylammonium oxone[23] (TBA-oxone) in MeOH/CH_2Cl_2 buffered with sodium carbonate gave methyl ester **20** in 71% yield. The ee's in Table 2 were determined from this methyl ester by NMR spectroscopy using $Eu(hfc)_3$ as the chiral shift reagent. Reduction of the ester with calcium borohydride[24] followed by an aqueous ammonia workup to remove the guanine-protecting groups then generated (−)-carbovir in 61% yield. Employing lithium borohydride in lieu of calcium borohydride gave a slightly lower yield. The spectral data and the optical rotation were in

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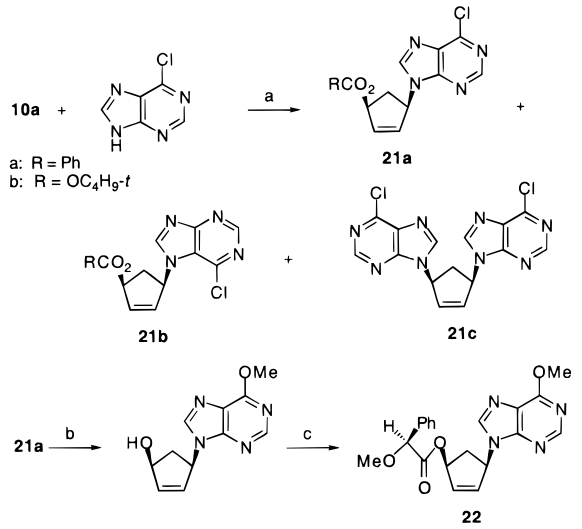
Scheme 3. Asymmetric Alkylation with Adenine Equivalent[a]



[a] (a) For R = Ph, 1% Pd_2dba_3•$CHCl_3$, 3% **8**, Et_3N, THF, rt, **21a**: 53% (76% based on rec. **10**), **21b**: 4%, **21c**: 13%. For R = OC_4H_9-*t*, 2.5 mol % $(dba)_3Pd_2$•$CHCl_3$, 7.5 mol % **8**, DMF, rt, 62% **21a**. (b) NaOH, MeOH, THF, rt, 95%. (c) (*S*)-PhCH(OMe)COOH, DCC, DMAP, CH_2Cl_2, rt, quant.

Table 3. AAA Reaction of **10b** with 6-Chloropurine

entry	solvent	$(C_2H_5)_3N$	yield (%)	ee (%)
1	THF	4 equiv	23	>98
2	CH_2Cl_2	4 equiv	41	>98
3	CH_2Cl_2	none	59	>98
4	DMF	none	62	>98

accordance with literature values.[9] This completes the enantioselective synthesis of (−)-carbovir in only four steps from bis-benzoate **10a** (six steps from cyclopentadiene). Compared to our second-generation synthesis, only half the number of steps were required.

Synthesis of (−)-Aristeromycin and (−)-Neplanocin A and Their 2′,3′-Diepi Isomers. We then turned our attention to the adenine carbanucleosides. Due to the insolubility of adenine in organic solvents, we also turned to the 6-chloro analogue as the nucleophile for the desymmetrization of bis-benzoate **10a** (Scheme 3). Initial experiments with ligand **7** and triethylamine as base in THF gave poor yield and ee of the desired amination product **21a**. However, switching to ligand **8** satisfactorily solved these problems. A 53% yield (76% based on recovered **10a**) of **21a** was isolated. The yield was lower when the reaction was conducted at 0 °C or when pempidine was used as base. The ee was determined by hydrolysis to the corresponding alcohol followed by esterification with (*S*)-*O*-methylmandelic acid to give **22**. Examination of the crude ester **22** by NMR spectroscopy revealed a de of 94%. Recrystallization of **21a** from EtOAc gave material with lower ee. As observed above with the guanine nucleophiles, products of N-7 (e.g., **21b**) and bis-amination (e.g., **21c**) were also obtained here in the desymmetrization reaction, but in lower yields (4% and 13% respectively).

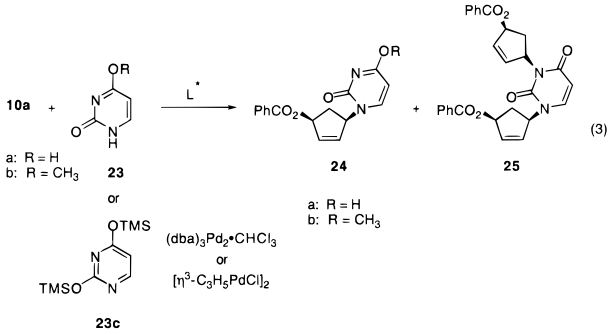
Since the leaving group can affect the enantioselectivity, we also examined use of a better leaving group, a carbonate, which, because ionization could occur at lower temperatures, might lead to enhanced selectivity. As shown in Scheme 3 and Table 3, the reaction does proceed to completion at room temperature. The table reveals several trends. Yields increased in switching from THF to methylene chloride (entries 2 and 3). Best results were obtained in the absence of base (entries 3 and 4). Under these latter conditions, a marginal improvement occurred by going to the more polar DMF as solvent. Satisfyingly, chiral HPLC revealed the presence of a single enantiomer in all cases.

Table 4. AAA Reaction of **10a** with Uracil and Analogues[a]

					yield (%)		ee (%)
entry	nucleophile	solvent	base	ligand	**24**	**25**	**24**
1	**23a**	THF	$(C_2H_5)_3N$	**8**	–	–	–
2	**23a**	THF	$(C_2H_5)_3Al$	**8**	43	–	94
3	**23c**	CH_2Cl_2	NONE	**8**	trace	10	–
4	**23c**	CH_2Cl_2	$(C_2H_5)_3N$	**8**	trace	22	–
5	**23c**	DMF	$(C_2H_5)_3N$	**8**	50	27	98
6	**23c**	DMF	*i*-Pr_2NEt	**8**	27	10	98
7[b]	**23c**	DMF	$(C_2H_5)_3N$	**8**	52	trace	97
8[c]	**23c**	DMF	$(C_2H_5)_3N$	**8**	54	11	97
9	**23c**	DMF	$(C_2H_5)_3N$	**7**	55	–	96
10	**23b**	DMF	$(C_2H_5)_3N$	**8**	36	–	N.D.

[a] All reactions were performed with 3 mol % $(dba)_3Pd_2$•$CHCl_3$ and 7.5 mol % chiral ligand unless noted otherwise. [b] 1 equiv of (n-$C_4H_9)_4NCl$ added. [c] [η^3-$C_3H_5PdCl]_2$ used as Pd source.

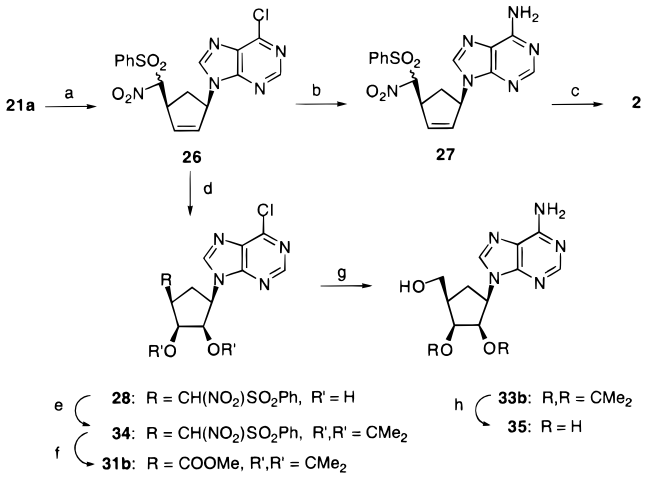
However, the use of the BOC group as the leaving group is not optimal for all cases. For example, use of a pyrimidine base, thymine or uracil, led only to decomposition of the bis-carbonate substrate. On the other hand, the bis-benzoate **10a** does lead to successful alkylation with uracil and its derivatives (see eq 3 and Table 4). The absence of a basic leaving group as in the



case of carbonate necessitated the use of a base. Nevertheless, the reaction did not perceptibly proceed in THF or methylene chloride with tertiary amine bases. On the other hand, triethylaluminum led to the monoalkylation product **24a** with excellent ee (entry 2). Better results were obtained with DMF as solvent, wherein the desired monoalkylation product of 98% ee could be obtained in good yield (entry 5) along with a dialkylation product **25**. The assignment of the second alkylation at N-3 rather than O stems from the ^{13}C NMR spectrum which reveals C-4 at δ 162.8 consistent with the amide function of the pyrimidin-2,4-dione. The addition of tetra-*n*-butylammonium chloride suppresses the formation of the bisalkylation product **25**. The use of [$\eta^3C_3H_5PdCl]_2$ as a palladium source also led to a decreased amount of dialkylation while preserving a good yield of the desired product of good ee (entry 8). Usefully, the standard cyclohexyl ligand **7** gave the best results (entry 9). Thus, both pyrimidine and purine bases can give quite satisfactory results.

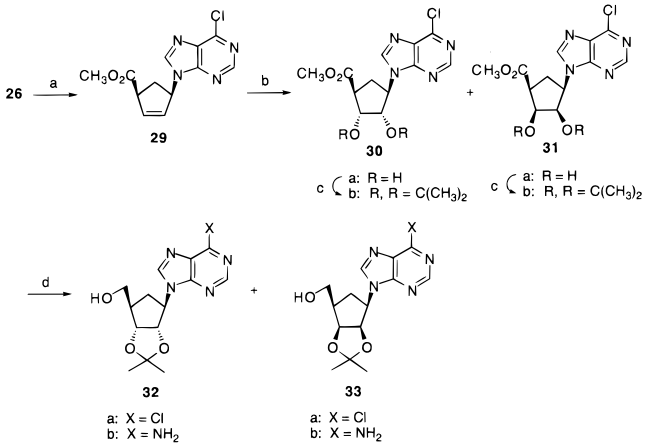
The second Pd(0)-catalyzed alkylation of **21a** with **6** to introduce the one-carbon side chain proceeded straightforwardly to give nitrosulfone **26** in high yield (Scheme 4). This is a pivotal intermediate that can be converted into both aristeromycin and neplanocin A as well as their 2′,3′-diepi isomers. Simple ammonolysis gave adenine derivative **27**, an intermediate in our previous synthesis of aristeromycin where the crucial dihydroxylation requires the use of potassium permanganate under basic conditions[14] to obtain the correct diastereomer.

Scheme 4. Asymmetric Syntheses of Aristeromycin and 2′,3′-Diepi-Aristeromycin[a]



[a] (a) 0.5% Pd_2dba_3·$CHCl_3$, 4% PPh_3, **6**, Et_3N, THF, rt, 95%. (b) aq. NH_3, rt, 75%. (c) 4 steps, ref 14. (d) 5% OsO_4, NMO, H_2O, CH_2Cl_2, rt, 82%. (e) $(MeO)_2CMe_2$, acetone, TsOH, rt, 85%. (f) O_3, DBU, MeOH, THF, −78 °C, 76%. (g) DIBAL-H, THF, CH_2Cl_2, −78 °C, then aq. NH_3, THF, rt, 69%. (h) aq. HCl, ref 14.

Scheme 5. Dihydroxylation Diastereoselectivity of Ester[a]

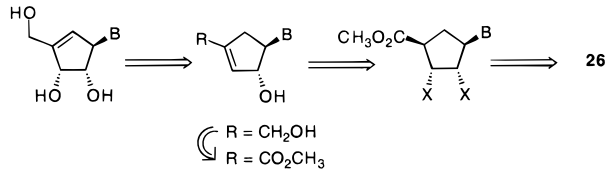


[a] (a) $Me_2NC(NH)NMe_2$, TBA-oxone, Na_2CO_3, CH_3OH, CH_2Cl_2, rt, 72%. (b) 5% OsO_4, NMO, H_2O, CH_2Cl_2, 74%, dr 1:2 *or* 7% $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0 °C, 67%, dr 2:3. (c) $CH_3C(OCH_3)_2CH_3$, CH_3COCH_3, TsOH, rt, quant (d) DIBAL-H, THF, CH_2Cl_2, −78 °C, then aq. NH_3, THF, rt, 62% for **32b**, 69% for **33b**.

On the other hand, as noted in our earlier synthesis of racemic aristeromycin, dihydroxylation of alkene **26** catalyzed by osmium tetroxide gave *syn* diol **28** as the major product (82%) and only a small amount (6%) of the corresponding *anti* epimer was formed. Dihydroxylation catalyzed by ruthenium tetroxide[25] gave more of the *anti* epimer (28%) but the *syn* product was still the major one (53%). In contrast to our earlier work, permangante oxidation of **27** also gave the *syn* isomer as the major product (43%) and the *anti* as the minor one (12%). To ascertain the effect of the nitrosulfone group, it was converted to the ester **29** in a fashion analogous to that employed in our carbovir sequence (Scheme 5) with excellent chemoselectivity. Dihydroxylation with osmium tetroxide still produced the *anti* diol **30a** as the minor epimer but in a larger amount (74%, **30a**:**31a**, 1:2) compared to the nitrosulfone (*anti*:*syn* 1:14). Ruthenium tetroxide gave a slightly more favorable ratio (67%, **30a**:**31a** 2:3) but the *anti* epimer was still the minor one. The

(25) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.

Scheme 6. Retrosynthesis of Neplanocin



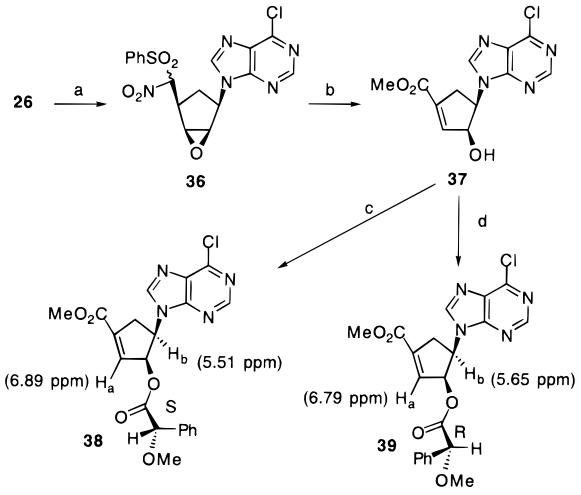
stereochemistry was established by converting the corresponding acetonides **30b** and **31b** initially to the chloropurines **32a** and **33a** which, upon ammonolysis, of the crude alcohols, provided the acetonides of (−)-aristeromycin **32b**, mp 217−218 °C, $[\alpha]_D$ −38.1° (*c* 0.77, MeOH)[10] and (+)-2′,3′-diepi-aristeromycin **33b**, mp 257−259 °C, $[\alpha]_D$ +71.7° (*c* 0.4, MeOH). After our work, dihydroxylation of *cis*-1,4-disubstituted cyclopentenyl systems with osmium tetroxide has been shown in many but not all cases to occur predominantly from the face *syn* to the two allylic substituents.[26] The above also sets the stage for a short diastereoselective synthesis of 2′,3′-diepi-aristeromycin **35** from alkene **26** (Scheme 4). Protection of the diol to give **34** (85%) and ozonolysis of the nitrosulfone in a basic methanolic solution gave methyl ester **31b** in 76% yield. Reduction with DIBAL-H followed by ammonolysis gave **33b** (69%) identical, except for optical rotation, with the compound from our previous synthesis[14] which on hydrolysis with dilute aqueous hydrochloric acid gives 2′,3′-diepi-aristeromycin **35**.

For neplanocin an endocyclic double bond has to be introduced. None of the intermediates for the aristeromycins are functionalized at the 4′ position. The synthesis of neplanocin envisioned a series of addition−eliminations to introduce the correct oxidation pattern as depicted in Scheme 6. As noted above, our early work revealed the diastereoselectivity of the osmylation proceeded preferentially to give the all *cis* product in related systems. Thus, we examined the diastereoselectivity of the epoxidation since the epoxide more readily would participate in the subsequent elimination. Epoxidation of nitrosulfone **26** with MCPBA gave **36** as a 1:1 diastereomeric mixture (Scheme 7). Since the starting alkene **26** is a 1:1 diastereomeric mixture because of the nitrosulfone carbon, it was not possible to ascertain the diastereoselectivity of the epoxidation. However, removal of this stereogenic center in the ozonolysis step gave only one product, **37**. Here the relative stereochemistry of the alcohol can be assigned by making the (*S*)- and (*R*)-*O*-methylmandelates **38** and **39**. In general, the *O*-methylmandelate ester will adopt a conformation in which the methoxy group is eclipsed with the carbonyl group. Hereby the phenyl group will shield one of the adjacent protons H_a or H_b which then, in the ^1H NMR spectrum, will experience an upfield shift when compared with the epimeric *O*-methylmandelate ester.[27] NMR analysis of the two mandelates reveals that H_a shows an upfield shift when changing from the (*S*)-mandelate to the (*R*)-mandelate, while H_b on the other hand shows a downfield shift. This is consistent with the assignment of the two mandelates as **38** and **39**, and, consequently, **37** as the *β*-hydroxyl epimer. Thus, the epoxidation of **26** occurred

(26) For some recent examples, see: Zhang, D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 755; Zhang, D.; Ghosh, A.; Süling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, *37*, 3799; Popescu, A.; Hornfeldt, A.-B.; Gronowitz, S.; Johansson, N. G. *Nucleosides Nucleotides* **1995**, *14*, 1639; and ref 10b. Cieplak effect has been proposed as an explanation for this unusual selectivity, see: Katagiri, N.; Ito, Y.; Kitano, K.; Toyota, A.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 2653; Palmer, C. F.; McCague, R.; Ruecroft, G.; Savage, S.; Taylor, S. J. C.; Ries, C. *Tetrahedron Lett.* **1996**, *37*, 4601.

(27) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

Scheme 7. Diastereoselectivity of Epoxidation[a]

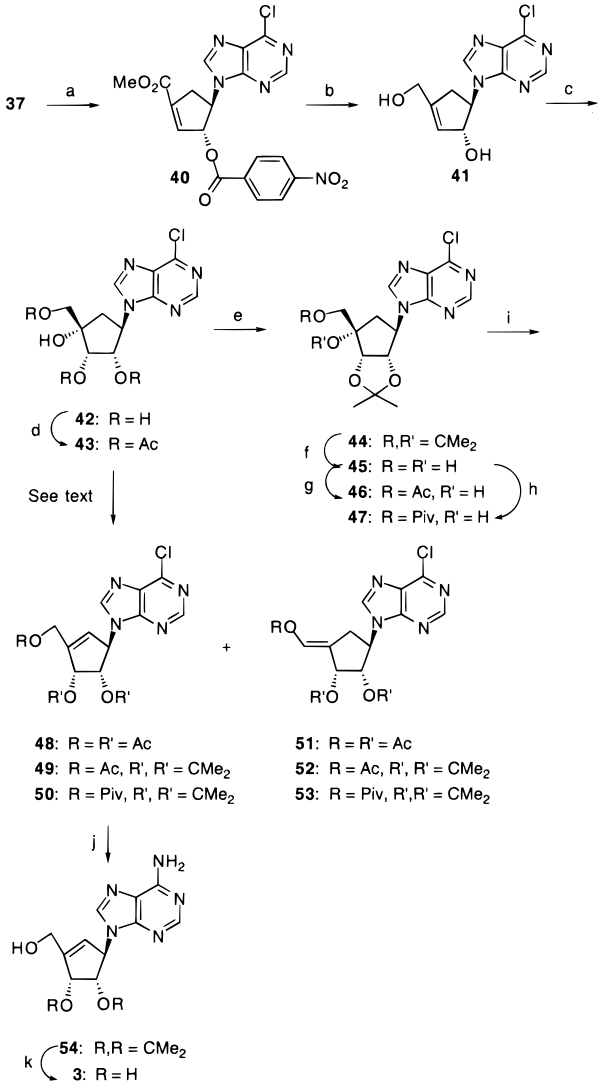


[a] (a) MCPBA, CH_2Cl_2, rt, 73%. (b) O_3, DBU, MeOH, THF, −78 °C′ rt, 67%. (c) (*S*)-PhCH(OMe)COOH, DCC, DMAP, CH_2Cl_2, rt, 95%. (d) (*R*)-PhCH(OMe)COOH, DCC, DMAP, CH_2Cl_2, rt, 95%.

selectively *syn* to the two allylic substituents just like the dihydroxylation with osmium tetroxide.

Nevertheless, the unsaturated ester **37** is a valuable intermediate for the synthesis of the neplanocins. To obtain the α-hydroxy group stereochemistry in neplanocin A, the *β*-hydroxy group in **37** was inverted by esterification using a Mitsunobu reaction[28] to give nitrobenzoate **40** in 62% yield (Scheme 8). Reduction with DIBAL-H converted the methyl ester into the primary alcohol, but left the nitrobenzoate ester unchanged. The latter was subsequently removed in the workup by transesterification to MeOH to give diol **41** in 79% yield. Osmium tetroxide-catalyzed dihydroxylation gave rise to only one tetraol which easily formed a bis-acetonide **44**. Because an acetonide will not form a *trans* fused bicyclo[3.3.0] ring system, the dihydroxylation must have taken place exclusively from the α-face to give the stereochemistry depicted in **42**. Interestingly, this is a complete reversal of the facial selectivity as compared to the dihydroxylation of **26**. Acetylation of tetraol **42** in pyridine gave triacetate **43**. Unfortunately, dehydration of the latter with phosphorus oxychloride or thionyl chloride[29] failed to generate the desired endocyclic double bond in neplanocin A, but instead furnished a mixture of all three possible elimination products: **48**, **51**,[30] and the product containing a 3′,4′-endocyclic double bond. To prevent formation of this latter elimination product, a 2′,3′-*O*-isopropylidene group was introduced. Chemoselective removal of one acetonide from bis-acetonide **44** required use of a bulky Lewis acid such as ferric chloride on silica gel[31] to give diol **45** in 94% yield. Standard acetylation conditions afforded monoaceate **46** in 91% yield.[32] Dehydration of the latter with phosphorus oxychloride and DMAP in CH_2Cl_2 gave a 3:4 mixture of **49**[33] and **52**.[30] To prevent elimination to the exocyclic olefin, the acetate was replaced by the bulkier pivaloyl-protecting group. When the dehydration was repeated on pivalate **47** under the same conditions, only a slight improvement in regioselectivity was obtained, giving a 1:1 mixture of **50** and **53**.[30] However, by switching to thionyl chloride in pyridine as dehydrating agent, this selectivity could be improved to 8:1. In addition, it was discovered that adding 1 equiv of DMF[35] to the mixture led to a significant increase in the rate and the yield for the dehydration. Under these conditions, a 60% yield could be obtained of the desired elimination product **50**. Ammonolysis simultaneously removed the pivalate and converted the chloropurine into the adenine to afford the acetonide **54**. Acid hydrolysis to remove the acetonide completed this asymmetric synthesis of neplanocin A (**3**), mp 214−5 °C, $[\alpha]^{20}_D$ −153.9°

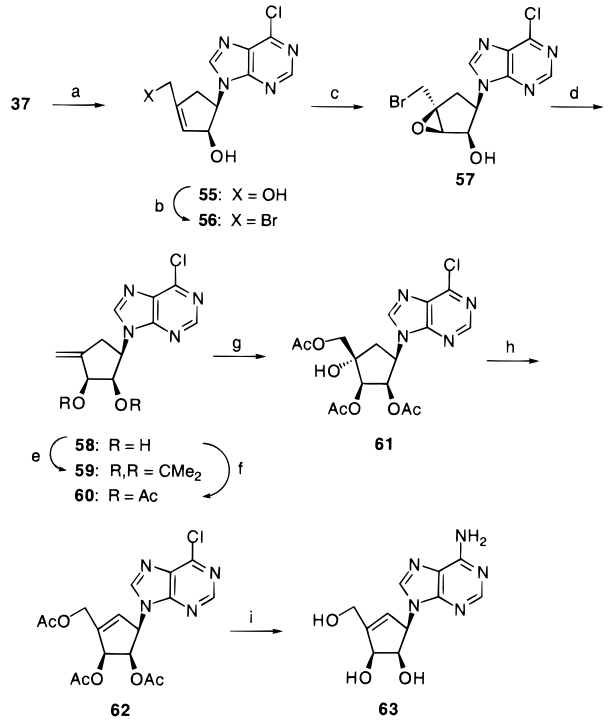
Scheme 8. A Synthesis of (−)-Neplanocin A[a]



[a] (a) *p*-$NO_2C_6H_4COOH$, PPh_3, DEAD, THF, 0 °C, 62%. (b) DIBAL-H, THF, CH_2Cl_2, −78 °C, then Et_3N, MeOH, rt, 79%. (c) 2% OsO_4, NMO, acetone, H_2O, rt, 89%. (d) Ac_2O, pyridine, rt, 71%. (e) $(MeO)_2CMe_2$, TsOH, rt, 71%. (f) $FeCl_3 \cdot H_2O$ on silica gel, CH_2Cl_2, rt, 61% (94% based on rec. **44**). (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 91%. (h) Me_3CCOCl, pyridine, rt, 95%. (i) $SOCl_2$, DMF, pyridine, rt, 60% (+ 8% of **53**). (j) NH_3, MeOH, rt, 73%. (k) aq. HCl, 80 °C, 91%.

(28) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(29) Kirk, D. N.; Shaw, P. M. *J. Chem. Soc. C* **1970**, 182.
(30) The geometry of the exocyclic olefin has not been determined.
(31) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.
(32) This compound has been reported in a previous synthesis of racemic neplanocin A.[33] Unfortunately, the spectral data for **46** are not in accordance with this literature compound, which has been prepared by addition of dimethyloxosulfonium methylide to the corresponding acetonide-protected ketone followed by epoxide ring-opening with potassium acetate. However, later unrelated work has shown that this particular addition to 2,3-*O*-isopropylidene cyclopentanones does actually occur from the same face of the ketone as the acetonide.[34] As a result, we believe the structure of this reported intermediate in the previous neplanocin synthesis is in fact the C-4′ epimer of **46**.
(33) Jung, M.; Offenbächer, G.; Rétey, J. *Helv. Chim. Acta* **1983**, *66*, 1915.
(34) Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron* **1993**, *49*, 5067.
(35) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.

Scheme 9. Synthesis of 2′,3′-Diepi-Neplanocin A[a]



[a] (a) DIBAL-H, THF, CH_2Cl_2, −78 °C, 80% (92% based on rec. **37**). (b) CBr_4, PPh_3, THF, rt, 78% (95% based on rec. **55**). (c) *t*-BuOOH, 10% $VO(acac)_2$, CH_2Cl_2, rt, 95%. (d) Zn(Cu), EtOH, ultrasound, 50 °C, 93%. (e) $(MeO)_2CMe_2$, acetone, TsOH, rt, 90%. (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 98%. (g) 4% OsO_4, NMO, H_2O, CH_2Cl_2, rt, then (f), 65%. (h) $POCl_3$, DMAP, CH_2Cl_2, 0 °C, 98%. (i) NH_3, MeOH, rt, 70%.

(*c* 0.33, H_2O), with spectral and physical data in excellent accord with those reported for the natural substance.[6,11] This strategy effects the enantioselective synthesis of (−)-neplanocin A in 13 steps from bis-benzoate **10a** (15 steps from cyclopentadiene).

Several of the intermediates in the neplanocin synthesis are useful for preparation of analogues of neplanocin. For example, we prepared the 2′,3′-diepi analogue which has not been described previously. Allylic alcohol **37** constitutes an ideal starting point because it already has the required hydroxy group stereochemistry. Reduction of the methyl ester to the alcohol **55** (92%) followed by allylic bromination gave bromide **56** in 95% (Scheme 9). Hydroxyl-directed epoxidation[36] furnished **57** as a single diastereomer (95%) which, on treatment with zinc, underwent reductive elimination[37] to give diol **58** in 93% yield. The *cis* diol stereochemistry was confirmed by preparation of acetonide **59** which formed easily. However, for further use, diol **58** was quantitatively converted into diacetate **60**. Dihydroxylation of the latter also gave a single diastereomer which, in the workup, was acetylated to give triacetate **61**. The dihydroxylation has presumably occurred from the sterically least hindered α-face to give the stereochemistry as depicted in **61**. Contrary to the difficult dehydration described above, dehydration of **61** proceeded smoothly to give the desired endocyclic olefin **62** in near quantitative yield. Ammonolysis then removed the acetates and converted the chloropurine to the adenine to form 2′,3′-diepi-neplanocin A **63**.

(36) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(37) Sarandeses, L. A.; Mouriño, A.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1991**, 818.

Conclusions

A short enantio- and diastereoselective approach for the synthesis of different carbanucleosides has been developed. The key step is a Pd(0)-catalyzed enantioselective allylic amination of bis-benzoate **10a** with the nucleobase. Contrary to a vast number of other nucleophiles including malonates, sulfinates, azide, and amines, the nucleobase shows a remarkable influence on this desymmetrization reaction. This might stem from its ability to serve as a competitive ligand and thereby disrupt the normal coordination of the palladium. Particularly guanine-derived nucleobases were problematic and had to be protected with sterically demanding electron-withdrawing groups in order to function in the desymmetrization reaction. Also the choice of ligand played a major role. While our standard ligand **7** gives excellent results with the simple nucleophiles above, this ligand gave poor results with purines but quite a satisfactory result with a pyrimidine. For purines, high ee's were obtained with ligands **8** and **9**. The desymmetrization reaction is followed by a second Pd(0)-catalyzed reaction with phenylsulfonyl(nitro)-methane (**6**) to introduce the one-carbon side chain. The prospect of performing both Pd(0)-catalyzed reactions in a single pot might further simplify the synthesis.

The strategy has resulted in a six-step synthesis of (−)-carbovir from cyclopentadiene, the shortest synthesis of (−)-carbovir reported to date.[9] By simple exchange of ligand stereochemistry in the desymmetrization reaction, the corresponding L-carbanucleosides could also be prepared by the same route. In addition to the strategy providing either enantiomeric series, analogues can also be easily accessed. The divergence is demonstrated in the synthesis of (−)-aristeromycin and (−)-neplanocin A where the same intermediate **26** is used for preparation of both natural compounds as well as their 2′,3′-diepi isomers. The alkene intermediates also allow for other variation of the substituents on the 2′- and 3′-positions. Thus, the strategy should hold great promise for making diverse carbanucleosides more readily available as potential chemotherapeutic agents.

Experimental Section[38]

(1′*R*,4′*S*)-1′-(2-Acetamido-6-(*N*,*N*-diphenyl)carbamoyloxypurin-9-yl)-4′-benzoyloxy-cyclopent-2′-ene (16). To an ice-cold deoxygenated solution of ligand **9**[16] (60 mg, 0.07 mmol) in THF (3 mL) were added $[\eta^3\text{-}C_3H_5PdCl]_2$ (9 mg, 0.02 mmol) and bis-benzoate **10a**[18] (500 mg, 1.62 mmol) followed by a deoxygenated solution of 2-acetamido-6-(*N*,*N*-diphenyl)carbamoyloxypurine **13**[22] (750 mg, 1.93 mmol) and pempidine (1.1 mL, 6.08 mmol) in DMSO (5 mL). The mixture was stirred vigorously for 8 h at 0 °C. It was then diluted with chloroform (50 mL) and washed with water (50 mL). The aqueous phase was extracted with more chloroform (15 mL), and the combined organic layers were dried and concentrated. The residue was taken up in ethyl acetate, and 137 mg of the bis-N-9 product **18** was filtered off. The filtrate was purified by flash chromatography (2/1 ethyl acetate/hexane → ethyl acetate → acetone) to afford 82 mg (16%) of recovered bis-benzoate **10a** and 546 mg (59%, 70% based on rec. **10a**) of the desired product **16** as a solid, $R_f = 0.48$ (ethyl acetate), ee = 93%. A sample (475 mg) was recrystallized from ethyl acetate (3 mL) to afford 370 mg, ee > 98%, mp 156−158 °C, $[\alpha]^{20}_D$ −108.8° (*c* 0.45, CH_2Cl_2).

IR ($CDCl_3$): 3402, 1737, 1729, 1720, 1621, 1587, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05−7.99 (m, 4H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.47−7.34 (m, 11H), 7.25 (m, 1H), 6.48 (dt, $J = 1.9$, 5.5 Hz, 1H), 6.21 (dd, $J = 2.2$, 5.5 Hz, 1H), 5.99 (m, 1H), 5.69 (m, 1H), 3.21 (dt, $J = 7.7$, 15.2 Hz, 1H), 2.55 (s, 3H), 2.13 (dt, $J = 3.3$, 15.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 165.8, 156.0, 154.5, 152.0, 150.2, 142.1, 135.7, 133.8, 133.2, 129.4, 129.0, 128.4, 127.7−125.3,

(38) For general procedures, see ref 19.

120.7, 77.3, 57.3, 38.3, 25.1. Anal. Calcd for $C_{32}H_{26}N_6O_5$: C, 66.89; H, 4.56; N, 14.63. Found: C, 67.00; H, 4.54; N, 14.69.

In addition, 65 mg (7%) of **17** was obtained as a foam, $R_f = 0.53$ (1/1 ethyl acetate/acetone).

IR ($CDCl_3$): 3402, 1755, 1716, 1689, 1634, 1563, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.06 (s, 1H), 7.95 (d, $J =$ 7.6 Hz, 2H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.45−7.28 (m, 12H), 6.47 (dt, $J = 2.0$, 5.5 Hz, 1H), 6.14 (dd, $J = 1.8$, 5.5 Hz, 1H), 5.89 (m, 1H), 5.34 (m, 1H), 2.74 (dt, $J = 7.7$, 15.2 Hz, 1H), 2.65 (s, 3H), 1.80 (dt, $J = 3.2$, 15.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 173.4, 168.9, 165.3, 164.8, 151.9, 150.8, 149.4, 147.3, 135.4, 133.8, 133.5, 129.5, 129.3, 128.7, 128.2−126.3, 110.8, 77.7, 60.6, 38.5, 24.5. LRMS Calcd for $C_{32}H_{26}N_6O_5$: 574.2. Found: 574.2.

Furthermore, another 85 mg of **18**, raising the total yield of **18** to 222 mg (16%), $R_f = 0.43$ (1/1 ethyl acetate/acetone), mp 228−230 °C (dec) (DMF) was isolated.

IR (KBr): 3349, 1736, 1722, 1622, 1589, 1493, 1444, 1403, 1385, 1320 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 2H), 8.66 (s, 2H), 7.51−7.41 (m, 18H), 7.31 (t, $J = 7.2$ Hz, 2H), 6.40 (s, 2H), 5.76 (t, $J = 7.6$ Hz, 2H), 3.29 (m, 1H), 2.40 (m, 1H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 155.0, 154.6, 151.9, 150.2, 144.9, 141.7, 133.9, 129.4, 127.4−126.7, 120.3, 58.5, 38.7, 24.6. Anal. Calcd for $C_{45}H_{36}N_{12}O_6$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.12; H, 4.45; N, 19.74.

(1′*R*,4′*S*)-1′-(2-Acetamido-6-(*N*,*N*-diphenyl)carbamoyloxypurin-9-yl)-4′-phenylsulfonyl(nitro)methyl-cyclopent-2′-ene (19). To a deoxygenated solution of triphenylphosphine (24 mg, 0.09 mmol) in THF (1 mL) was added $Pd_2dba_3{\cdot}CHCl_3$ (12 mg, 0.01 mmol), and the mixture was stirred for 20 min. It was then added to a deoxygenated solution of monobenzoate **16** (600 mg, 1.04 mmol), phenylsulfonyl-(nitro)methane (**6**)[39] (250 mg, 1.24 mmol), and triethylamine (0.36 mL, 2.58 mmol) in THF (6 mL). After being stirred for 12 h, the reaction mixture was diluted with chloroform (60 mL) and washed with water (60 mL). The aqueous phase was extracted with more chloroform (10 mL), and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (ethyl acetate) to give 660 mg (97%) of **19** as a foam (1:1 mixture of diastereomers), $R_f = 0.48$, which crystallized from methanol, mp 204−205 °C (dec).

IR ($CDCl_3$): 3424, 3399, 1741, 1698, 1620, 1586, 1562, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, $J = 9.8$ Hz, 2H), 8.02 (d, $J = 7.4$ Hz, 2H), 7.94 (m, 4H), 7.76 (t, $J = 7.3$ Hz, 2H), 7.62 (t, $J = 7.5$ Hz, 4H), 7.45−7.25 (m, 20H), 6.57 (dt, $J = 2.1$, 5.6 Hz, 1H), 6.44 (bs, 1H), 6.21 (bs, 1H), 5.98 (m, 3H), 5.66 (m, 1H), 5.60 (m, 1H), 4.01 (m, 1H), 3.93 (m, 1H), 3.11 (dt, $J = 8.8$, 14.8 Hz, 1H), 2.89 (dt, $J = 8.9$, 14.5 Hz, 1H), 2.44 (m, 1H), 2.39 (s, 3H), 2.36 (s, 3H), 2.14 (dt, $J = 6.4$, 14.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.5, 169.3, 155.8, 155.7, 154.3, 154.2, 151.4, 151.3, 150.2, 143.2, 143.0, 141.4, 135.3, 135.2, 134.3, 134.1, 133.3, 132.9, 132.5, 132.0, 131.9, 131.7, 129.7, 129.6, 129.3, 129.2, 128.9, 128.3, 128.2, 127.8−125.4, 121.3, 121.3, 102.4, 102.3, 60.8, 59.9, 43.8, 43.5, 33.1, 32.8, 24.7. Anal. Calcd for $C_{32}H_{27}N_7O_7S$: C, 58.80; H, 4.16; N, 15.00. Found: C, 58.85; H, 4.24; N, 14.80.

(1′*R*,4′*S*)-1′-(2-Acetamido-6-(*N*,*N*-diphenyl)carbamoyloxypurin-9-yl)-4′-methoxycarbonyl-cyclopent-2′-ene (20). To an ice-cold solution of nitrosulfone **19** (1.05 g, 1.61 mmol) in methanol (20 mL) was added tetramethylguanidine (0.24 mL, 1.91 mmol). The mixture was stirred at 0 °C for 15 min followed by addition of TBA-oxone[23] (7.5 g, 36%, 7.59 mmol), sodium carbonate (800 mg, 7.55 mmol), and dichloromethane (25 mL). The solution was stirred at room temperature for 16 h. It was then diluted with chloroform (100 mL) and washed with water (100 mL). The aqueous layer was back-extracted with more chloroform (30 mL), and the combined chloroform layers were dried and concentrated. The residue was purified by flash chromatography (ethyl acetate) to furnish 584.1 mg (71%) of **20** as a solid, $R_f = 0.43$, mp 118−120 °C (EtOAc), $[\alpha]^{20}_D$ −61.0° (*c* 0.5, CH_2Cl_2).

IR ($CDCl_3$): 3398, 1737, 1695, 1620, 1589, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 2H), 7.46−7.24 (m, 10H), 6.25 (dt, $J = 2.2$, 5.5 Hz, 1H), 5.96 (dt, $J = 2.3$, 5.5 Hz, 1H), 5.74 (m, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 2.91 (dt, $J = 9.1$, 14.5 Hz, 1H), 2.54 (s, 3H), 2.29 (dt, $J = 4.9$, 14.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 170.8, 155.9, 154.6, 151.8, 150.3, 142.5, 141.5, 135.2, 132.0, 131.9, 131.8, 131.8, 130.7, 129.0, 128.4, 128.3, 128.0−125.3, 120.7, 59.0, 52.3, 49.5, 34.0, 25.0. Anal. Calcd for $C_{27}H_{24}N_6O_5$: C, 63.27; H, 4.72; N, 16.40. Found: C, 63.09; H, 4.93; N, 16.13.

The ee was determined by ^1H NMR (400 MHz) using 10 mg of **20** and 25−30 mg of $Eu(hfc)_3$ in 0.6 mL of $CDCl_3$. The OMe-singlets for the (1′*S*,4′*R*) and (1′*R*,4′*S*) enantiomers were observed at 4.30 and 4.22 ppm, respectively.

(−)-Carbovir (1). A mixture of calcium chloride (200 mg, 1.80 mmol) and sodium borohydride (300 mg, 7.93 mmol) in THF (10 mL) was stirred for 1 h followed by addition of methyl ester **20** (500 mg, 0.98 mmol). The mixture was stirred for 24 h and then concentrated in vacuo. To the residue was added concentrated aqueous ammonia (10 mL), and the mixture was stirred overnight. Evaporation of the solvent gave a semicrystalline residue which was passed through a short path of silica gel eluting with methanol. The eluate was concentrated and the residue purified by flash chromatography (7/3 chloroform/methanol) to afford 147 mg (61%) of **1** as a white solid, $R_f = 0.43$, mp 255−257 °C (dec) (H_2O), $[\alpha]^{20}_D$ −60.1° (*c* 0.4, MeOH) (Lit.: mp 205−210 °C (dec),[9d] 210−220 °C (dec),[9i] 271−273 °C (dec);[9k] $[\alpha]_D$ −62° (*c* 0.4, MeOH),[9a] $[\alpha]^{24}_D$ −66° (*c* 0.4, MeOH)[9i]).

IR (KBr): 3600−2600, 1736, 1696, 1636, 1570, 1536, 1483, 1417, 1384 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.55 (s, 1H), 7.57 (s, 1H), 6.44 (s, 2H), 6.10 (dt, $J = 2.1$, 5.5 Hz, 1H), 5.85 (dt, $J = 2.1$, 5.5 Hz, 1H), 5.32 (m, 1H), 4.72 (t, $J = 5.3$ Hz, 1H), 3.42 (t, $J = 5.5$ Hz, 1H), 2.84 (m, 1H), 2.57 (dt, $J = 8.7$, 13.7 Hz, 1H), 1.55 (dt, $J = 5.7$, 13.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 156.9, 153.5, 150.8, 138.3, 135.1, 129.7, 116.7, 64.0, 58.5, 47.7, 34.4. IR and ^1H and ^{13}C NMR are in accordance with literature data.[9d]

(1′*R*,4′*S*)-4′-Benzoyloxy-1′-(6-chloropurin-9-yl)-cyclopent-2′-ene (21a). To a deoxygenated solution of ligand **8**[16] (1.5 g, 1.90 mmol) in THF (50 mL) was added $Pd_2dba_3{\cdot}CHCl_3$ (650 mg, 0.63 mmol). After being stirred for 15 min this solution was added to a deoxygenated mixture of bis-benzoate **10a**[18] (17.5 g, 56.8 mmol), 6-chloropurine (11 g, 71.2 mmol), and triethylamine (32 mL, 230 mmol) in THF (170 mL). The reaction was stirred for 5 h at room temperature to give a clear brown solution. The mixture was concentrated and purified by flash chromatography (3/2 ethyl acetate/hexane → ethyl acetate → acetone) to afford 6.02 g of recovered bis-benzoate **10a** together with dibenzylideneacetone. This was crystallized from methanol (5 mL) and gave 5.2 g of recovered **10a**. In addition, 10.3 g (53%, 76% based on rec. **10a**) of the desired product **21a** (R = Ph) was isolated, $R_f = 0.40$ (3/7 hexane/ethyl acetate), ee = 94%, $[\alpha]^{20}_D$ −106.8° (*c* 1.71, CH_2Cl_2), mp 90−92 °C (EtOAc).

IR ($CDCl_3$): 1717, 1590, 1561, 1334 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.28 (s, 1H), 8.02 (m, 2H), 7.60 (dt, $J = 1.3$, 7.4 Hz, 1H), 7.46 (m, 2H), 6.57 (dt, $J = 2.0$, 5.6 Hz, 1H), 6.30 (dd, $J = 2.4$, 5.6 Hz, 1H), 6.04 (dt, $J = 2.5$, 7.4 Hz, 1H), 5.87 (m, 1H), 3.25 (ddd, $J = 7.7$, 8.0, 15.3 Hz, 1H), 2.16 (dt, $J = 3.0$, 15.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 151.8, 151.2, 150.9, 143.3, 136.4, 133.6, 133.3, 131.6, 129.4, 129.3, 128.5, 77.3, 57.4, 38.5. Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44. Found: C, 60.16; H, 4.00; N, 16.67.

In addition, 0.74 g (4%) of **21b** (R = Ph), $R_f = 0.41$ (ethyl acetate), mp 120−121 °C (EtOAc) was obtained.

IR (KBr): 3071, 1718, 1597, 1538, 1475, 1450, 1384 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.39 (s, 1H), 7.95 (d, $J = 7.9$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 2H), 6.62 (m, 1H), 6.37 (dd, $J = 2.3$, 5.5 Hz, 1H), 6.11 (m, 1H), 6.02 (m, 1H), 3.28 (p, $J = 7.7$ Hz, 1H), 2.13 (dt, $J = 2.7$, 15.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 162.0, 152.3, 146.5, 142.7, 137.4, 133.3, 132.6, 129.4, 129.1, 128.4, 121.9, 77.1, 60.3, 39.9. Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44. Found: C, 59.72; H, 4.00; N, 16.26.

In addition, 2.9 g of recovered 6-chloropurine, $R_f = 0.37$ (2/1 ethyl acetate/acetone) was obtained.

^1H NMR (300 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.67 (s, 1H).

In addition, 2.7 g (13%) of **21c**, $R_f = 0.36$ (1/1 ethyl acetate/acetone), mp 250−251 °C (dec) (DMF) was isolated.

(39) Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S. *J. Org. Chem.* **1981**, *46*, 765.

IR (KBr): 1590, 1561, 1495, 1435, 1402, 1382, 1335 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 2H), 8.80 (s, 2H), 6.45 (s, 2H), 5.92 (dd, J = 6.4, 8.5 Hz, 2H), 3.41 (dt, J = 8.6, 14.1 Hz, 1H), 2.41 (dt, J = 6.1, 14.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.6, 149.0, 145.8, 134.1, 134.0, 131.2, 58.9, 38.3. Anal. Calcd for $C_{15}H_{10}Cl_2N_8$: C, 48.28; H, 2.70; N, 30.02. Found: C, 48.36; H, 2.54; N, 29.79.

(1′*R*,4′*S*)-1′-(6-Chloropurin-9-yl)-4′-phenylsulfonyl(nitro)methyl-cyclopent-2′-ene (26). To a deoxygenated solution of triphenylphosphine (400 mg, 1.52 mmol) in tetrahydrofuran (10 mL) was added Pd_2dba_3·$CHCl_3$ (200 mg, 0.19 mmol), and the mixture was stirred for 15 min. It was then added to a deoxygenated solution of monobenzoate **21a** (13.5 g, 39.6 mmol), phenylsulfonyl(nitro)methane (**6**)[39] (9.3 g, 46.2 mmol), and triethylamine (13 mL, 93.3 mmol) in THF (200 mL). After the mixture stirred for 12 h and was concentrated, the semicrystalline residue was taken up in chloroform (350 mL) and washed with 0.2 M hydrochloric acid (300 mL). The aqueous phase was extracted with more chloroform (50 mL), and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (ethyl acetate → 3/1 ethyl acetate/acetone) to give 15.8 g (95%) of **26** as a foam (1:1 mixture of diastereomers), R_f = 0.40 (ethyl acetate).

IR ($CDCl_3$): 1591, 1558, 1336 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.72 (s, 2H), 8.14 (s, 1H), 8.13 (s, 1H), 8.00−6.90 (m, 10H), 6.59 (dt, J = 2.1, 5.7 Hz, 1H), 6.08 (m, 5H), 4.79 (m, 2H), 3.98 (m, 2H), 3.20 (dt, J = 8.8, 14.9 Hz, 1H), 3.04 (dt, J = 8.8, 14.6 Hz, 1H), 2.45 (dt, J = 5.7, 14.9 Hz, 1H), 2.14 (dt, J = 5.8, 14.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 151.5, 151.2, 151.2, 151.1, 151.0, 143.7, 143.6, 135.6, 135.6, 134.4, 134.3, 134.2, 134.0, 132.2, 132.2, 132.1, 132.0, 129.6, 129.6, 102.9, 102.8, 61.0, 59.8, 44.2, 43.9, 33.8, 33.6.

(1′*S*,2′*S*,3′*R*,4′*R*)-4′-(6-Chloropurin-9-yl)-1′-phenylsulfonyl(nitro)-methyl-cyclopentane-2′,3′-diol (28). To a solution of olefin **26** (100 mg, 0.24 mmol) and NMO (50 mg, 0.43 mmol) in dichloromethane (2 mL) was added osmium tetroxide (4% aqueous solution, 80 μL, 0.01 mmol). After the mixture stirred for 5 h and after addition of ethyl acetate (1 mL), water (1 mL), and sodium bisulfite (30 mg, 0.29 mmol) and stirring for an additional 30 min, the phases were separated, and the aqueous phase was extracted with ethyl acetate (3 mL). The combined organic phases were dried, concentrated, and purified by flash chromatography (ethyl acetate) to give 88.2 mg (82%) of **28** as a foam, R_f = 0.40, mp 227−229 °C (dec) (MeOH).

IR (KBr): 3800−3000, 1594, 1561, 1450, 1329, 1210, 1157, 1085 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (10:1 mixture of diastereomers, only data for major diastereomer shown): δ 8.79 (s, 1H), 8.77 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.88 (t, J = 7.5 Hz, 1H), 7.73 (t, J = 7.8 Hz, 2H), 6.62 (d, J = 10.8 Hz, 1H), 5.69 (d, J = 4.0 Hz, 1H), 5.36 (d, J = 5.5 Hz, 1H), 5.26 (q, J = 8.0 Hz, 1H), 4.28 (bs, 1H), 3.92 (d, J = 3.7 Hz, 1H), 3.04 (m, 1H), 2.76 (dt, J = 7.7, 14.9 Hz, 1H), 2.44 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 152.6, 151.3, 148.6, 148.3, 135.8, 134.1, 130.4, 129.8, 129.6, 102.2, 73.1, 70.8, 54.4, 37.9, 32.7. Anal. Calcd for $C_{17}H_{16}ClN_5O_6S$: C, 44.99; H, 3.55; N, 15.43. Found: C, 44.79; H, 3.61; N, 15.30.

(1′*S*,2′*S*,3′*R*,4′*R*)-4′-(6-Chloropurin-9-yl)-2′,3′-*O*-isopropylidene-1′-methoxycarbonyl-cyclopentane-2′,3′-diol (31b). To a solution of nitrosulfone **34** (87 mg, 0.18 mmol) in methanol (3 mL) and THF (2 mL) was added DBU (50 μL, 0.33 mmol). The solution was cooled to −78 °C, and ozone was bubbled through over 30 min. After the mixture was quenched with acetic acid (2 drops) and concentrated to half the volume, the residue was taken up in chloroform (10 mL) and washed with water (10 mL). The aqueous phase was extracted with more chloroform (2 mL), and the combined organic phases were dried, concentrated, and chromatographed (4/1 ethyl acetate/hexane) to give 47.1 mg (76%) of **31b** as a solid, R_f = 0.40, mp 238−240 °C (EtOAc), $[\alpha]^{20}_D$ +66.5° (*c* 0.9, $CHCl_3$).

IR (KBr): 2988, 2949, 1749, 1592, 1562, 1344, 1254, 1205, 1169, 1100, 1068, 948 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.37 (s, 1H), 4.99 (t, J = 5.5 Hz, 1H), 4.93 (dt, J = 5.4, 12.8 Hz, 1H), 4.77 (t, J = 5.0 Hz, 1H), 3.78 (s, 3H), 2.97 (dt, J = 5.9, 11.9 Hz, 1H), 2.78 (q, J = 12.5 Hz, 1H), 2.32 (dt, J = 5.9, 11.9 Hz, 1H), 1.50 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.7, 151.8, 151.7, 150.9, 144.8, 131.3, 111.7, 79.3, 77.5, 54.5, 52.0, 45.7, 28.1, 25.2, 23.7. Anal. Calcd for $C_{15}H_{17}ClN_4O_4$: C, 51.07; H, 4.86; N, 15.88. Found: C, 51.15; H, 5.02; N, 16.07.

(1′*R*,2′*R*,3′*S*,4′*S*)-1′-(6-Chloropurin-9-yl)-2′,3′-epoxy-4′-phenylsulfonyl(nitro)methyl-cyclopentane (36). MCPBA (85%, 500 mg, 2.46 mmol) was added to a solution of the olefin **26** (684 mg, 1.63 mmol) in dichloromethane (10 mL), and the mixture was stirred for 44 h. Precipitated *m*-chlorobenzoic acid was filtered off. The filtrate was concentrated and the residue purified by flash chromatography (1/1 hexane/ethyl acetate) to afford 518 mg (73%) of the epoxide **36** as a solid, R_f = 0.49 (ethyl acetate), mp 205−206 °C (acetone, cocrystallized with 1 equiv of acetone).

IR (KBr): 2950, 1593, 1560, 1449, 1404, 1338 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)(4:3 mixture of diastereomers): Major diastereomer: δ 8.78 (s, 1H), 8.43 (s, 1H), 7.92 (m, 2H), 7.82 (m, 1H), 7.67 (m, 2H), 5.70 (d, J = 10.5 Hz, 1H), 5.38 (t, J = 8.8 Hz, 1H), 3.95 (dd, J = 1.2, 2.7 Hz, 1H), 3.63 (bd, J = 1.9 Hz, 1H), 3.41 (bq, J = 8.0 Hz, 1H), 2.90 (dt, J = 8.0, 13.5 Hz, 1H), 1.79 (dt, J = 9.5, 13.5 Hz, 1H). Minor diastereomer: δ 8.74 (s, 1H), 8.41 (s, 1H), 7.97 (m, 2H), 7.83 (m, 1H), 7.67 (m, 2H), 5.75 (d, J = 10.8 Hz, 1H), 5.33 (t, J = 8.8 Hz, 1H), 4.31 (dd, J = 1.1, 2.7 Hz, 1H), 4.03 (dd, J = 1.2, 2.7 Hz, 1H), 3.49 (bq, J = 8.0 Hz, 1H), 2.53 (dt, J = 8.0, 12.9 Hz, 1H), 1.70 (dt, J = 9.5, 12.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) (both diastereomers): δ 152.0, 152.0, 151.5, 151.1, 143.0, 142.9, 135.9, 133.7, 133.5, 131.2, 129.7, 129.7, 129.6, 129.5, 101.8, 101.8, 58.0, 56.4, 55.5, 55.3, 54.3, 53.4, 38.3, 38.1, 29.5, 28.8. Anal. Calcd for $C_{17}H_{14}ClN_5O_5S$· acetone: C, 48.63; H, 4.08; N, 14.18. Found: C, 48.46; H, 4.19; N, 13.96.

(3′*S*,4′*R*)-4′-(6-Chloropurin-9-yl)-3′-hydroxy-1′-methoxycarbonyl-cyclopent-1′-ene (37). A solution of epoxide **36** (1.5 g, 3.44 mmol) and DBU (2.5 mL, 16.5 mmol) in THF (130 mL) was stirred at room temperature for 10 min. Methanol (60 mL) was then added and the mixture cooled to −78 °C. Ozone was bubbled through over 40 min until the starting material had disappeared by TLC. The solution was allowed to warm to room temperature over 3 h and then concentrated. The residue was dissolved in chloroform (100 mL) and washed with water (80 mL). The aqueous layer was extracted with more chloroform (20 mL), and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (ethyl acetate) to furnish 675 mg (67%) of **37** as a solid, R_f = 0.37, mp 205−206 °C (EtOAc), $[\alpha]^{20}_D$ +147.4° (*c* 1.04, MeOH).

IR (KBr): 3300−3200, 1723, 1592, 1571, 1439, 1407, 1340 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.24 (s, 1H), 6.92 (q, J = 2.0 Hz, 1H), 5.40 (q, J = 7.2 Hz, 1H), 5.18 (dt, J = 2.0, 6.4 Hz, 1H), 3.84 (s, 3H), 3.64 (d, J = 6.5 Hz, 1H), 3.23−3.19 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD): δ 166.1, 153.8, 152.9, 151.0, 148.1, 142.2, 138.2, 132.0, 75.1, 57.4, 52.5, 36.0. Anal. Calcd for $C_{12}H_{11}ClN_4O_3$: C, 48.91; H, 3.76; N, 19.01. Found: C, 48.86; H, 4.00; N, 18.90.

(3′*R*,4′*R*)-4′-(6-Chloropurin-9-yl)-1′-methoxycarbonyl-3′-(*p*-nitrobenzoyl)oxy-cyclopent-1′-ene (40). To an ice-cooled solution of alcohol **37** (100 mg, 0.34 mmol), *p*-nitrobenzoic acid (100 mg, 0.60 mmol), and triphenylphosphine (150 mg, 0.57 mmol) in THF (3 mL) was added DEAD (90 μL, 0.57 mmol). The reaction was stirred at 0 °C for 6 h. The mixture was diluted with chloroform (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with more chloroform (2 mL), and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (3/2 ethyl acetate/hexane) to give 94 mg (62%) of **40** as a foam, R_f = 0.32, $[\alpha]^{20}_D$ −178.3° (*c* 1, $CHCl_3$).

IR ($CDCl_3$): 1729, 1592, 1564, 1532, 1443, 1410, 1341 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.30 (d, J = 8.9 Hz, 2H), 8.18 (s, 1H), 8.17 (d, J = 8.9 Hz, 2H), 6.91 (q, J = 1.9 Hz, 1H), 6.56 (dq, J = 2.0, 5.6 Hz, 1H), 5.35 (ddd, J = 5.6, 6.9, 8.9 Hz, 1H), 3.86 (s, 3H), 3.47 (ddt, J = 1.9, 8.9, 17.1 Hz, 1H), 3.38 (ddt, J = 2.0, 6.9, 17.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7, 163.4, 151.7, 151.4, 151.3, 150.7, 144.1, 138.3, 136.3, 133.9, 132.1, 130.8, 123.5, 83.6, 60.9, 52.2, 36.0. HRMS Calcd for $C_{19}H_{14}{}^{35}ClN_5O_6$: 443.0633. Found: 443.0616.

(3′*R*,4′*R*)-4′-(6-Chloropurin-9-yl)-3′-hydroxy-1′-hydroxymethyl-cyclopent-1′-ene (41). To a solution of ester **40** (1.95 g, 4.39 mmol) in THF (25 mL) and dichloromethane (25 mL) at −78 °C was added DIBAL-H (1 M hexane solution, 20 mL, 20 mmol). The reaction was stirred at −78 °C for 1 h and then quenched with ethyl acetate (5 mL). The mixture was warmed to room temperature and saturated aqueous

Rochelle salt (30 mL) and ethyl acetate (60 mL) were added. After the mixture stirred for 3 h, the phases were separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The extracts were dried and concentrated to give 1.9 g of a foam which was taken up in methanol (50 mL) and triethylamine (1 mL, 7.17 mmol). The mixture was stirred for 2 h and then concentrated to give a solid residue which was purified by flash chromatography (1/1 ethyl acetate/acetone) to afford 920 mg (79%) of **41** as a white solid, $R_f = 0.37$, mp 190−191 °C (dec) (MeOH), $[\alpha]^{20}_D$ −62.7° (*c* 0.3, MeOH).

IR (KBr): 3600−3000, 3112, 2860, 1592, 1561, 1495, 1436, 1402, 1338, 1206, 1038, 944 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 8.77 (s, 1H), 5.62 (bd, $J = 1.7$ Hz, 1H), 5.44 (d, $J = 5.8$ Hz, 1H), 5.15 (m, 1H), 4.96 (t, $J = 5.4$ Hz, 1H), 4.90 (dt, $J = 6.0$, 8.1 Hz, 1H), 4.01 (m, 2H), 2.87−2.77 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.9, 151.2, 149.1, 146.9, 144.6, 131.4, 125.8, 79.3, 64.4, 59.7, 36.1. Anal. Calcd for $C_{11}H_{11}ClN_4O_2$: C, 49.54; H, 4.16; N, 21.01. Found: C, 49.30; H, 4.26; N, 20.88.

(−)-Neplanocin A (3). A mixture of acetonide **54** (61.5 mg, 0.20 mmol) in 1 M aqueous hydrochloric acid (15 mL) was stirred at 80 °C for 6 h and then concentrated in vacuo. The residue was dissolved in methanol and poured onto a column of Amberlite IRA-400 (OH) ion-exchange resin (5 mL). The column was eluted with methanol, and the eluate concentrated to give 48.5 mg (91%) of a white solid, $R_f =$ 0.30 (3/2 ethyl acetate/methanol), mp 214−215 °C (H_2O), $[\alpha]^{20}_D$ −153.9° (*c* 0.33, H_2O) (Lit.: mp 220−222 °C,[6] 211−213 °C,[10f] 220−222 °C,[10g] 212−213 °C;[11g] $[\alpha]^{20}_D$ −157° (*c* 0.5, H_2O),[6] $[\alpha]^{20}_D$ −153.3° (*c* 0.3, H_2O),[10f] $[\alpha]^{20}_D$ −152° (*c* 0.3, H_2O),[10g] $[\alpha]^{20}_D$ −153.8° (*c* 0.3, H_2O)[11g]).

IR (KBr): 3600−2600, 2930, 1668, 1648, 1612, 1583, 1486, 1420, 1333, 1306, 1256, 1116, 1035 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.11 (s, 1H), 8.05 (s, 1H), 7.20 (bs, 2H), 5.69 (s, 1H), 5.33 (bd, $J =$ 2.5 Hz, 1H), 5.16−4.92 (bs, 3H), 4.42 (d, $J = 5.4$ Hz, 1H), 4.30 (t, J = 5.4 Hz, 1H), 4.11 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 156.0, 152.3, 150.1, 149.7, 139.5, 123.4, 119.2, 76.6, 72.2, 64.2, 58.6. IR and ^1H and ^{13}C NMR data are in accordance with literature values.[6,11]

2′,3′-Diepi-Neplanocin A (63). The triacetate **62** (110 mg, 0.27 mmol) was dissolved in a saturated solution of ammonia in methanol (4 mL). The flask was sealed and the mixture stirred at room temperature for 4 days. Concentration in vacuo and chromatography (3/2 ethyl acetate/methanol) gave a syrupy residue which was dissolved in methanol and poured on a column of Amberlite IRA-400 (OH) ion-exchange resin (6 mL). The column was eluted with methanol, and the eluate concentrated to afford 49.5 mg (70%) of **63** as a white solid, $R_f = 0.30$, mp 228−230 °C (H_2O/MeOH), $[\alpha]^{20}_D$ +16.0° (*c* 0.33, H_2O).

IR (KBr): 3600−2600, 1669, 1648, 1610, 1574, 1480, 1417, 1335, 1306 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.11 (s, 1H), 7.90 (s, 1H), 7.18 (s, 2H), 5.71 (s, 1H), 5.41 (bs, 1H), 5.39 (bd, $J = 4.5$ Hz, 1H), 4.93 (bs, 2H), 4.38 (d, $J = 5.6$ Hz, 1H), 4.33 (t, $J = 5.8$ Hz, 1H), 4.23 (d, $J = 15.8$ Hz, 1H), 4.12 (d, $J = 15.8$ Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.9, 152.0, 151.9, 149.6, 141.2, 121.5, 118.7, 72.8, 70.8, 58.4, 58.3. HRMS Calcd for $C_{11}H_{13}N_5O_3$: 263.1018. Found: 263.1013.

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Supporting Information Available: Experimental procedures and characterization data for **14**, **15**, **21b**, **22**, **24a**, **27**, **29**, **30a**−**34**, **38**, **39**, **42**−**47**, **49**, **50**, and **54**−**62** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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