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Bisubstrate Inhibitors of Catechol *O*-Methyltransferase (COMT): the Crucial Role of the Ribose Structural Unit for Inhibitor Binding Affinity

Ralph Paulini,[a] Christian Trindler,[a] Christian Lerner,[a] Lukas Brändli,[a] W. Bernd Schweizer,[a] Roland Jakob-Roetne,[b] Gerhard Zürcher,[b] Edilio Borroni,[b] and François Diederich*[a]

Inhibition of the enzyme catechol O-methyltransferase offers a therapeutic handle to regulate the catabolism of catecholamine neurotransmitters, providing valuable assistance in the treatment of CNS disorders such as Parkinson's disease. A series of ribose-modified bisubstrate inhibitors of COMT featuring 2′-deoxy-, 3′-deoxy-, 2′-aminodeoxy-3′-deoxy-, and 2′-deoxy-3′-aminodeoxyribose-derived central moieties and analogues containing the carbocyclic skeleton of the natural product aristeromycin were synthesized and evaluated to investigate the molecular recognition properties of the ribose binding site in the enzyme. Key synthetic intermediates in the ribose-derived series were obtained by deoxygenative [1,2]-hydride shift rearrangement of adenosine derivatives; highlights in the synthesis of carbocyclic aristeromycin analogues include a diastereoselective cyclopropanation step and nucleobase introduction with a modified Mitsunobu protocol. In vitro biological evaluation and kinetic studies revealed dramatic effects of the ribose modification on binding affinity: 3′-deoxygenation of the ribose gave potent inhibitors (IC_{50} values in the nanomolar range), which stands in sharp contrast to the remarkable decrease in potency observed for 2′-deoxy derivatives (IC_{50} values in the micromolar range). Aminodeoxy analogues were only weakly active, whereas the change of the tetrahydrofuran skeleton to a carbocycle unexpectedly led to a complete loss of biological activity. These results confirm that the ribose structural unit of the bisubstrate inhibitors of COMT is a key element of molecular recognition and that modifications thereof are delicate and may lead to surprises.

Introduction

Regulation of the catabolism of catechol-based neurotransmitters and their biosynthetic precursors is an important therapeutic approach to the treatment of central nervous system (CNS) disorders such as Parkinson's disease[1] and possibly schizophrenia[2] and depression.[1d,3] Catechol *O*-methyltransferase (COMT) is an important enzyme involved in catecholamine catabolism, which in the presence of Mg^{2+} ions catalyzes the transfer of a methyl group from the cofactor *S*-adenosylmethionine (SAM) to one of the phenolic hydroxy groups of biologically active catechols such as dopamine or its precursor L-Dopa.[4] Striatal dopamine deficiency stands at the origin of the symptoms of Parkinson's disease, yet the compensating oral administration of L-Dopa suffers from inefficacy, among other things, as a result of COMT-catalyzed inactivation. Thus, COMT inhibitors were shown to substantially decrease peripheral metabolic degradation of L-Dopa and were successfully developed as therapeutic adjuncts to the L-Dopa-based treatment of Parkinson's disease, significantly prolonging the beneficial effects of L-Dopa.[5]

Nitro-substituted catechols are potent COMT inhibitors; the two derivatives in current therapeutic use (tolcapone (Tasmar)[5a,d] and entacapone (Comtan)[5b,c]) share this structural feature and bind to the substrate binding site of COMT. By using X-ray structure-based design, we developed a new class of highly active bisubstrate inhibitors that block both the SAM and catechol binding sites (Figure 1).[6] We showed that in addition to providing high potency, the bisubstrate inhibition approach eliminates, for the first time, the need for nitro-substitution of the catechol structural unit in this class of COMT inhibitors.[7]

In contrast to the substitution of the catechol substructure, for which a variety of lipophilic groups are tolerated, we found

[a] *R. Paulini, C. Trindler, Dr. C. Lerner, L. Brändli, Dr. W. B. Schweizer, Prof. Dr. F. Diederich*
Laboratorium für Organische Chemie
ETH-Hönggerberg, HCI
8093 Zürich (Switzerland)
Fax: (+41) 1-632-1109
E-mail: diederich@org.chem.ethz.ch

[b] *Dr. R. Jakob-Roetne, G. Zürcher, Dr. E. Borroni*
Pharma Division, Präklinische Forschung
F. Hoffmann–La Roche AG
4070 Basel (Switzerland)

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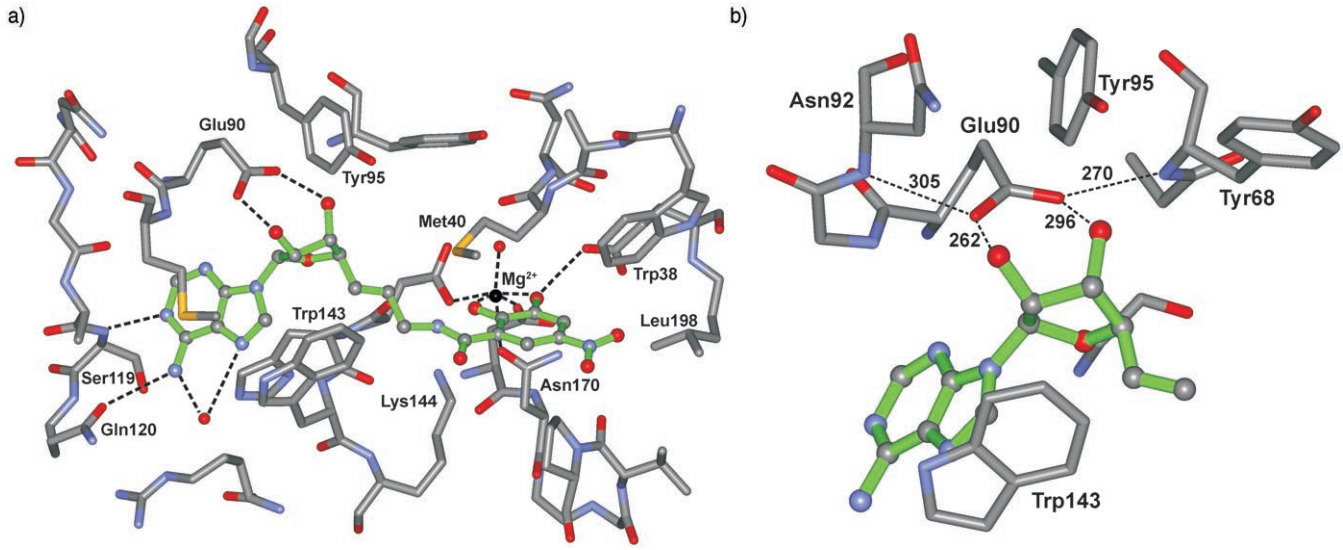
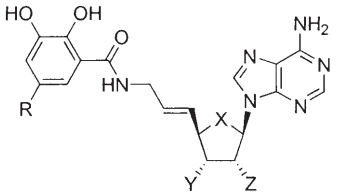


Figure 1. a) Crystal structure of bisubstrate inhibitor (−)-**1** in the complex with COMT and a Mg^{2+} ion.[6b,c] b) Detailed view of the ribose binding site showing the conformation of the side chain of Glu 90 rigorously locked by two hydrogen bonds to two NH residues of the peptide backbone. Distances are given in pm. Color code: inhibitor skeleton, green; C atoms, gray; O atoms, red; N atoms, blue; S atoms, yellow; Mg atom, black.

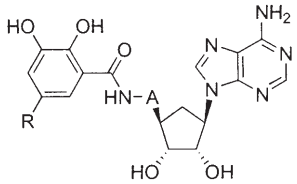
in earlier studies[6c,7,8] with bisubstrate inhibitors (−)-**1** (IC_{50} = 9 nM), (−)-**2** (40 nM), (−)-**3** (28 μM), (−)-**4** (3 μM), and (+)-**5** (1 μM) that the ribose moiety seems to be very sensitive to even minor structural modifications. This observation led to the comprehensive investigation of the effects of ribose modification on ligand affinity and binding mode reported herein. Specifically, we describe the synthesis and biological evaluation of the enantiomerically pure deoxy and aminodeoxy derivatives (−)-**3** to (−)-**12** (Table 1) and ligands (−)-**13** to (+)-**17**, containing the carbocyclic skeleton of the natural product aristeromycin (Table 2).[9] We demonstrate a dramatic difference in activity between inhibitors with a 2′- or a 3′-deoxyribose moiety, which might be a more general phenomenon in nucleoside-based ligand binding.

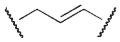
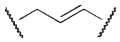
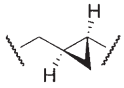
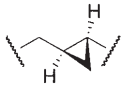
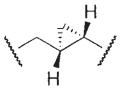
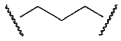
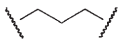
Table 1. Structures of inhibitors **1**–**12**.



Compd	R	X	Y	Z
(−)-**1**	NO_2	O	OH	OH
(−)-**2**	4-methylphenyl	O	OH	OH
(−)-**3**	NO_2	O	OH	H
(−)-**4**	NO_2	O	H	H
(+)-**5**	NO_2	CH_2	H	H
(−)-**6**	NO_2	O	H	OH
(−)-**7**	4-methylphenyl	O	H	OH
(−)-**8**	NO_2	O	NH_3^+ HCO_2^-	H
(+)-**9**	4-methylphenyl	O	NH_3^+ HCO_2^-	H
(+)-**10**	NO_2	O	N_3	H
(−)-**11**	NO_2	O	H	NH_3^+ $CF_3CO_2^-$
(−)-**12**	4-methylphenyl	O	H	NH_3^+ $CF_3CO_2^-$

Table 2. Structures of inhibitors **13**–**20**.



Compd	A	R
(−)-**13**		NO_2
(−)-**14**		4-methylphenyl
(+)-**15**		NO_2
(+)-**16**		4-methylphenyl
(+)-**17**		NO_2
(−)-**18**		NO_2
(−)-**19**		4-methylphenyl
(+)-**20**		NO_2

Results and Discussion

Synthesis

The synthesis of 3′-deoxy derivatives (−)-**6** and (−)-**7** (Scheme 1) followed the protocol developed for ligands (−)-**1** to (−)-**3**.[6c,7] Thus, regioselective one-pot oxidation of the primary OH group of 3′-deoxyadenosine (cordycepin, (−)-**21**)[10]

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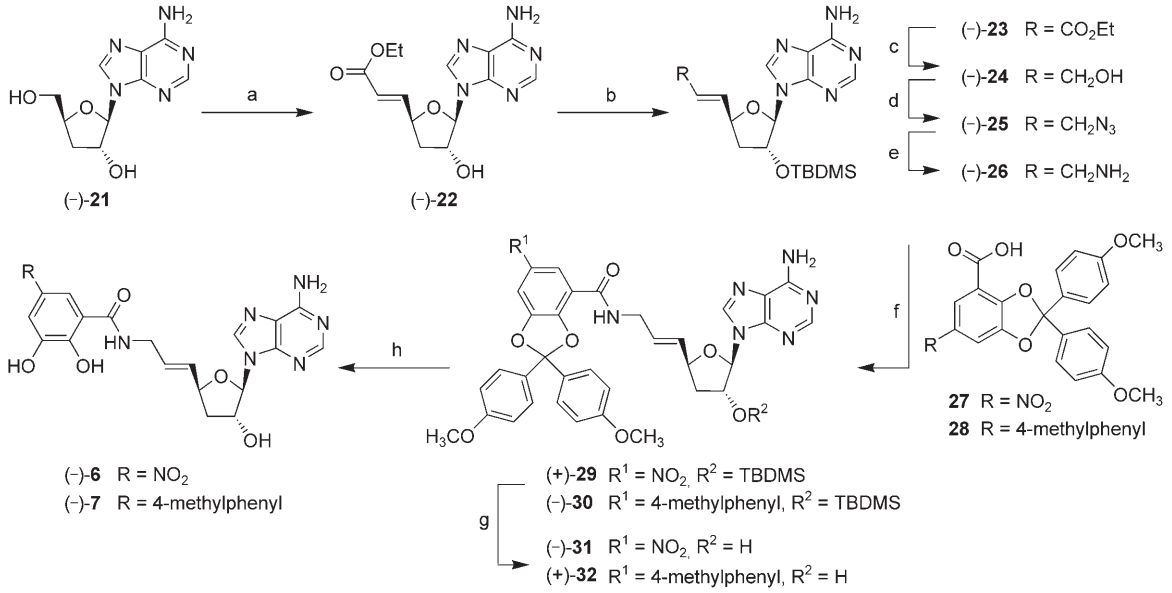
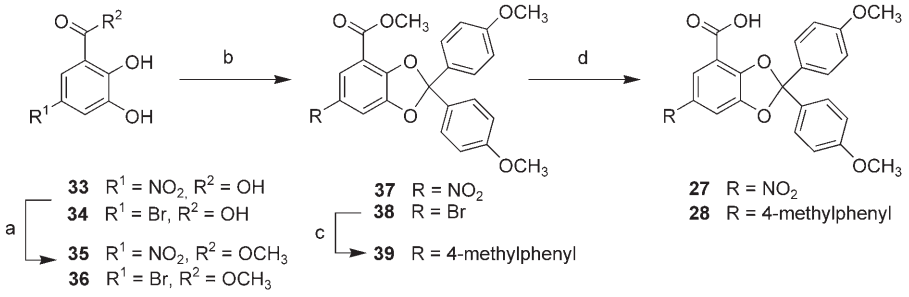


Scheme 1. Synthesis of inhibitors (−)-**6** and (−)-**7**: a) $Ph_3P{=}CHCO_2Et$, IBX, Me_2SO, 16 h, 20 °C, 57%; b) TBDMS-Cl, pyridine, 16 h, 20 °C, 58%; c) DIBAL-H, CH_2Cl_2, 3 h, −78 °C, 62%; d) PPh_3, DIAD, $(PhO)_2PON_3$, THF, 16 h, 20 °C, 84%; e) PPh_3, dioxane, 16 h, 20 °C, then H_2O, 20 °C, 3 h, 69%; f) 1. **27** or **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (−)-**26**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 68–69%; g) nBu_4NF, THF, 2 h, 20 °C, 72–86%; h) TFA/H_2O (1:1), 60 min, 0 °C, 59–99%. IBX = *o*-iodoxybenzoic acid; TBDMS = *tert*-butyl(dimethyl)silyl; DIBAL-H: diisobutylaluminum hydride; DIAD = diisopropyl azodicarboxylate; EDC = 1-(dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

with IBX, followed by olefination of the resulting aldehyde with $Ph_3P{=}CHCO_2Et$[11] provided the unsaturated ester (−)-**22** in 57% overall yield. Silyl-protection of the 2′-OH group (→(−)-**23**) and reduction with DIBAL-H yielded the allylic alcohol (−)-**24** (36% for the two steps), which was transformed into the corresponding azide (−)-**25** in a Mitsunobu reaction employing diphenylphosphoryl azide ($(PhO)_2PON_3$) as a soluble source of nucleophilic azide anion (84%). Staudinger reduction gave the primary amine (−)-**26** (69%), which was coupled to di(4-methoxyphenyl)methyl ketal protected catechol carboxylic acids **27** and **28**, activated as *N*-hydroxysuccinimide esters, to provide (+)-**29** (69%) and (−)-**30** (68%), respectively. Sequential removal of silyl (→(−)-**31** and (+)-**32**) and ketal protecting groups, using fluoride anion (nBu_4NF), followed by acid (TFA/H_2O), provided cordycepin derivatives (−)-**6** and (−)-**7** in 71% and 51% yield, respectively, for the two deprotection steps.



Scheme 2. Synthesis of catechol building blocks **27** and **28**: a) $SOCl_2$, MeOH, 14 h, reflux, 71–91%; b) 1. 4,4′-dimethoxybenzophenone, $(COCl)_2$, 60 °C, 30 min; 2. **35** or **36**, 160 °C, 40 min, 88–89%; c) 4-methylphenylboronic acid, $[Pd(PPh_3)_4]$, K_2CO_3, toluene/EtOH/H_2O, 16 h, reflux, 79%; d) LiOH, THF/H_2O (1:1), 3 h, reflux, 93–100%.

The protected catechol carboxylic acids **27** and **28** employed as coupling partners in the key amide-forming reaction (Scheme 1) were prepared starting from 5-nitro-**33**[6a] or 5-bromo-2,3-dihydroxybenzoic acid (**34**)[12] by acid-catalyzed esterification to give methyl esters **35** and **36** (Scheme 2). Subsequent protection with dichloro(4,4′-dimethoxydiphenyl)methane, generated in situ from 4,4′-dimethoxybenzophenone and oxalyl chloride,[13] provided **37** and **38** in good yields (64% and 80%, starting from **33** and **34**, respectively). Substitution of the phenyl rings in the ketal moiety by electron-donating methoxy groups was introduced to facilitate the acid-catalyzed catechol deprotection in the last step of the ligand synthesis. Suzuki cross-coupling of **38** with 4-methylphenylboronic acid afforded **39** in 79% yield. Finally, ester hydrolysis under standard basic conditions (LiOH, THF/H_2O) provided the desired catechol building blocks **27** and **28** in near quantitative yields.

The synthesis of 2′-aminodeoxy-3′-deoxy derivatives (−)-**11** and (−)-**12** started from 3′-deoxy-β-D-*threo*-pentofuranosyladenine (−)-**40**, prepared by deoxygenative [1,2]-hydride shift rearrangement of the corresponding *N*,*O*-pivaloyl-protected 3′-*O*-mesyl nucleoside using $NaBH_4$ as a hydride source (Scheme 3).[14] Protection of the 2′-OH group was carried out by regioselective silylation (TBDPS-Cl) of the 5′-OH group (→(+)-**41**), followed by protection of the 2′-OH functionality (TIPS-OTf) and subsequent careful removal of the more base-labile TBDPS protecting group with hydroxide anion (→(−)-**42**). TIPS protection of the secondary OH group could only be

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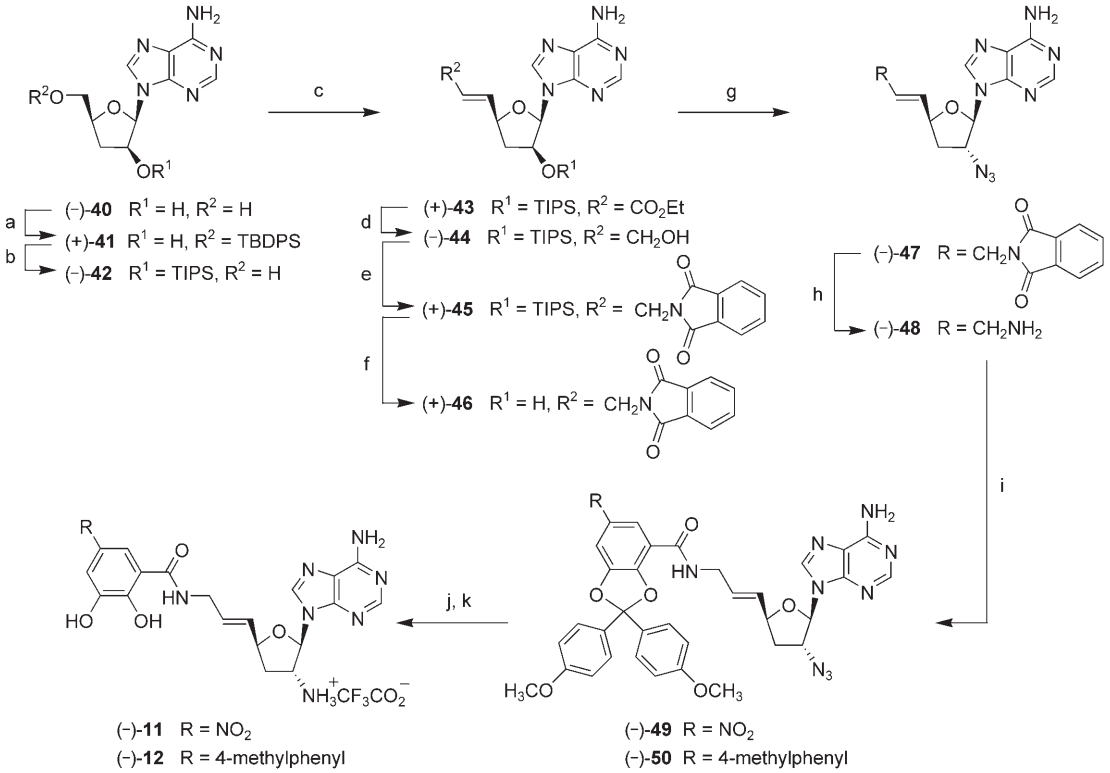

Scheme 3. Synthesis of inhibitors (−)-**11** and (−)-**12**: a) TBDPS-Cl, pyridine, 16 h, 20 °C, 70%; b) 1. TIPS-OTf, imidazole, DMF, 16 h, 20 °C; 2. NaOH, MeOH, 8 h, 20 °C, 73%; c) $Ph_3P{=}CHCO_2Et$, IBX, DMSO, 16 h, 20 °C, 89%; d) DIBAL-H, CH_2Cl_2, 3 h, −78 °C, 86%; e) PPh_3, DIAD, phthalimide, THF, 16 h, 20 °C, 77%; f) nBu_4NF, THF, 5 min, 0 °C, 90%; g) PPh_3, DIAD, $(PhO)_2PON_3$, THF, 16 h, 20 °C, 72%; h) $MeNH_2$, EtOH, 16 h, 20 °C, 72%; i) 1. **27** or **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (−)-**48**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 42–62%; j) 1,3-propanedithiol, Et_3N, MeOH, 16 h, 20 °C; k) TFA/H_2O (1:1), 60 min, 0 °C, 69–80%. TBDPS = *tert*-butyldiphenylsilyl; TIPS = triisopropylsilyl; OTf = trifluoromethanesulfonate; DMF = *N*,*N*-dimethylformamide.

achieved by using the more reactive TIPS-OTf reagent; the corresponding chloride proved unsuitable in this case. For the installation of the linker, a similar reaction sequence as described for the synthesis of (−)-**6** and (−)-**7** was employed, featuring IBX oxidation of the 5′-OH group, Wittig olefination (→(+)-**43**), and DIBAL-H reduction to give allylic alcohol (−)-**44** (77% over three steps). Transformation of allylic alcohol (−)-**44** into *N*-alkylated phthalimide (+)-**45** under Mitsunobu conditions (77%), silyl deprotection of the 2′-OH group with Bu_4NF (→(+)-**46**; 90%), conversion into azide (−)-**47** (72%) by Mitsunobu inversion, and subsequent cleavage of the phthalimide group with methylamine provided allylic amine (−)-**48** (72%). Short reaction times proved crucial to prevent premature hydrolytic ring-opening of the phthalimide functionality during the silyl deprotection of (+)-**45**.

To complete the synthesis, amine (−)-**48** was coupled with the *N*-hydroxysuccinimide esters of **27** and **28** to give amides (−)-**49** and (−)-**50**, respectively. The azido group was selectively reduced under mild conditions using propane-1,3-dithiol as reducing agent,[15] and acid-catalyzed ketal deprotection provided the targeted inhibitors (−)-**11** and (−)-**12** in good yields (80% and 69%, respectively).

In analogy to the synthesis of (−)-**11** and (−)-**12**, the preparation of 3′-aminodeoxy-2′-deoxy derivatives (−)-**8** and (+)-**9** started with the $LiEt_3BH$-promoted deoxygenative [1,2]-hydride shift rearrangement of 5′-*O*-silyl-protected 2′-*O*-tosyl-adenosine,[16] prepared by regioselective 2′-tosylation[17] and subsequent 5′-*O*-silylation (TBDPS-Cl) of adenosine. The resulting 5′-silyl-protected 2′-deoxy-β-D-*threo*-pentofuranosyladenine ((−)-**51**) was converted into allylamine (+)-**52** in a seven-step reaction sequence, analogously to the transformation of (−)-**40** into (−)-**48**, with a high overall yield of 36% (Scheme 4; the complete reaction sequence is shown in Scheme 1S, Supporting Information).

Amide coupling of (+)-**52** with the succinimide ester of **28**, reduction of the azido moiety to the corresponding amino group, and acidic deprotection of the diarylmethylketal (dichloroacetic acid/H_2O) followed by HPLC purification afforded (+)-**9**. Similarly, coupling of (+)-**52** with unprotected, activated nitrocatechol **53**[6a] gave access to (+)-**10** (88%), which was converted into (−)-**8** using the dithiol reduction procedure (57%).

To impart greater stability to the inhibitors against acid- and enzyme-catalyzed degradation,[18] we prepared derivatives containing the carbonucleosidic skeleton of the natural product aristeromycin. Furthermore, we hoped that the change to the carbocyclic analogues could provide the additional benefit of enhanced affinity and bioavailability resulting from an increase in lipophilicity. Numerous approaches to the synthesis of aristeromycin have been reported,[19] and the different strategies employed for the preparation of carbocyclic nucleosides have been extensively reviewed.[20] Our synthesis of the aristeromy-

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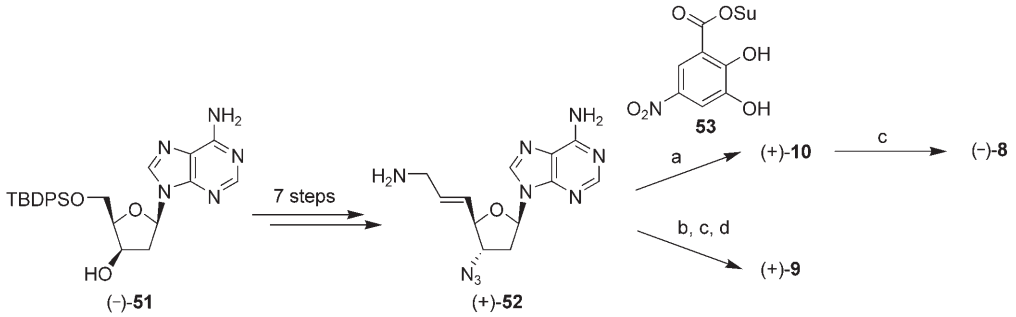
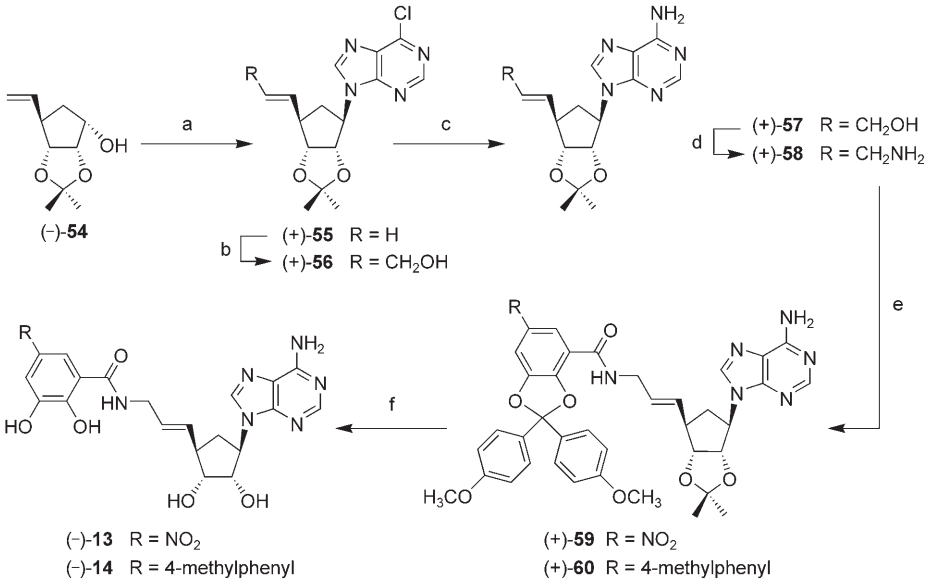


Scheme 4. Synthesis of inhibitors (−)-**8**, (+)-**9**, and (+)-**10**: a) **53**, Et_3N, DMF, 16 h, 20 °C, 88%; b) 1. **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (+)-**52**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 51%; c) 1,3-propanedithiol, Et_3N, MeOH, 16 h, 20 °C, 57%; d) TFA/H_2O (1:1), 60 min, 0 °C, 50%. Su = succinimide.

cin analogues (−)-**13**–(+)-**20** followed the elegant route reported by Yang et al.[19a] for the synthesis of enantiopure vinyl-functionalized precursor (−)-**54** (Scheme 5), starting from (−)-D-ribose.

The preparation of carbonucleosidic ligands (−)-**13** and (−)-**14** continued with the introduction of the purine nucleobase to give (+)-**55**, which was achieved in 76% yield by Mitsunobu inversion of the secondary OH group of (−)-**54** with 6-chloropurine, following the procedure of Yang et al. (Scheme 5).[19a] One-pot OsO_4-catalyzed dihydroxylation and subsequent diol cleavage, followed by Wittig olefination with $Ph_3P{=}CHCHO$ and Luche reduction ($NaBH_4/CeCl_3$) of the resulting unsaturated aldehyde provided allylic alcohol (+)-**56** (41%). This sequence was superior to the route calling for conversion of (+)-**55** into the analogous unsaturated ester, as the following DIBAL-H reduction led to the undesired formation of a 7,8-dihydropurine derivative, which partly decomposed upon reoxidation to (+)-**56**.[21] Installation of the amino group at C6 of the purine moiety gave the adenine derivative (+)-**57** (79%), and Mitsunobu substitution (phthalimide, then $MeNH_2$) afforded allylic amine (+)-**58** (63%). Coupling of (+)-**58** with succinimide esters **27** (→(+)-**59**) and **28** (→(+)-**60**) and acid-catalyzed removal of the ketal protecting groups yielded ligands (−)-**13** and (−)-**14**.

By cyclopropanation of the olefinic linker, we hoped to further increase the lipophilicity and metabolic stability of our ligands. For the synthesis of cyclopropanated derivatives (+)-**15**, (+)-**16**, and (+)-**17** (Schemes 6 and 7), intermediate (−)-**54** was converted into the corresponding benzyl ether (−)-**61** (93%) prior to the installation of the olefinic linker in a four-step reaction sequence via unsaturated ester (−)-**62** (52% overall). The allylic alcohol (−)-**63** subsequently served as point of attachment for the chiral dioxaborolane auxiliary (−)-**64** in an asymmetric Charette cyclopropanation reaction[22] to yield cyclopropane (−)-**65** in quantitative yield and high diastereomeric excess (*R*,*R*-configured cyclopropane 97:3 d.r.; Scheme 6). The minor diastereomer was readily removed by chromatographic separation, and the diastereomeric purity subsequently verified by analytical HPLC. Similarly, allyl alcohol (−)-**63** was allowed to react with (+)-**64** to give diastereomer (−)-**66** with the *S*,*S*-configured cyclopropane ring in 97% yield and 92:8 d.r. (Scheme 7).



Scheme 5. Synthesis of inhibitors (−)-**13** and (−)-**14**: a) PPh_3, DIAD, 6-chloropurine, THF, 16 h, 20 °C, then 24 h, 60 °C, 76%; b) 1. $NaIO_4$, OsO_4, MeOH/H_2O (2:1), 1 h, 0 °C, then 3 h, 20 °C; 2. $Ph_3P{=}CHCHO$, toluene, 16 h, 4 °C; 3. $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 15 min, 0 °C, then 20 min, 20 °C, 41%; c) NH_3, MeOH, 100 °C, 24 h, 79%; d) 1. PPh_3, DIAD, phthalimide, THF, 16 h, 20 °C; 2. $MeNH_2$, EtOH, 16 h, 20 °C, 63%; e) 1. **27** or **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (+)-**58**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 44-51%; f) TFA/H_2O (1:1), 60 min, 0 °C, 76-98%.

Both diastereomeric cyclopropane derivatives were individually carried on in the synthetic sequence; however, substantial differences in reactivity were observed. Thus, whereas (−)-**65**, with the *R*,*R*-configured cyclopropane ring, was smoothly converted via fully protected (−)-**67** (83%) into the secondary alcohol (−)-**68** (quantitative), acetylation followed by hydrogenolytic removal of the benzyl protecting group furnished the

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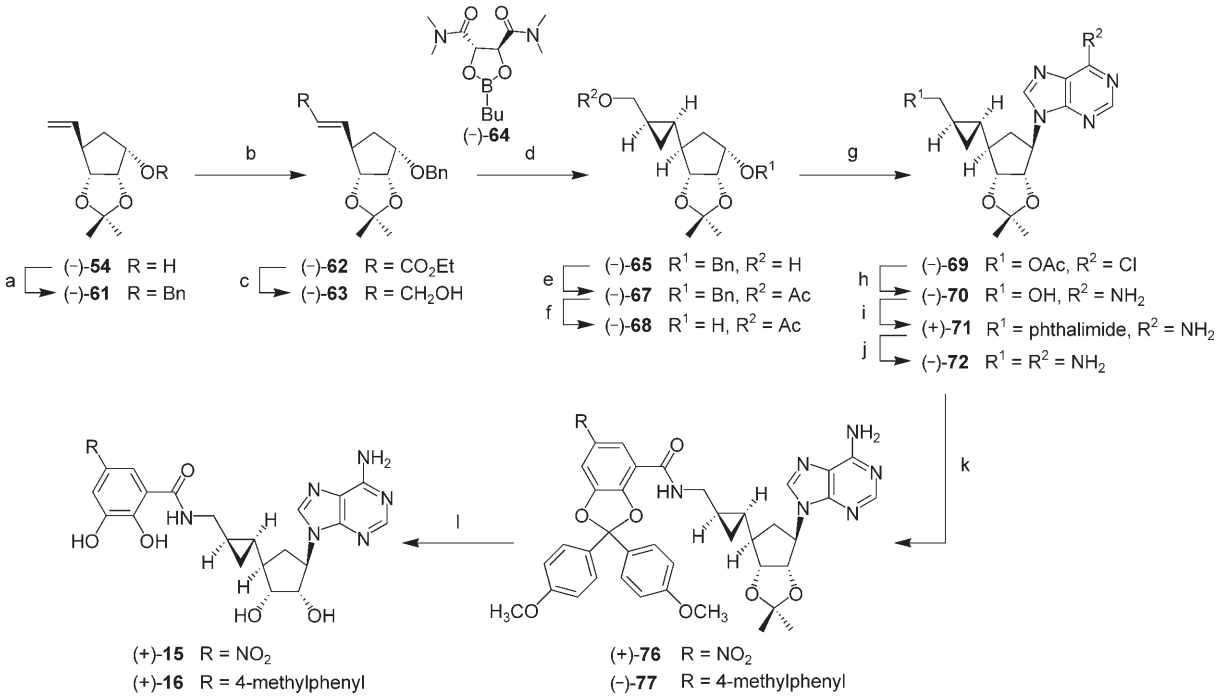
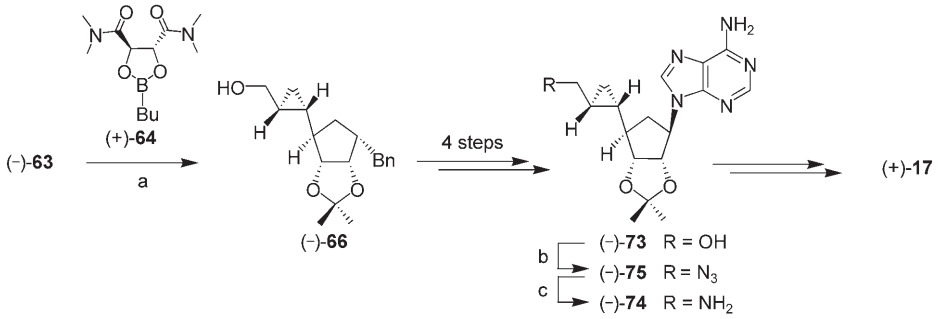


Scheme 6. Synthesis of inhibitors (+)-**15** and (+)-**16**: a) NaH, BnBr, Bu_4NI, THF, 16 h, 20 °C, 93%; b) 1. $NaIO_4$, OsO_4, MeOH/H_2O (2:1), 1 h, 0 °C, then 3 h, 20 °C; 2. $Ph_3P{=}CHCO_2Et$, toluene, 16 h, 4 °C, 64%; c) DIBAL-H, CH_2Cl_2, 3 h, −78 °C, 81%; d) (−)-**64**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, 30 min, −30 °C, then 18 h, 20 °C, quant. (97:3 d.r.); e) Ac_2O, pyridine, DMAP, 14 h, 20 °C, 83%; f) H_2, Pd/C, MeOH, 14 h, 20 °C, quant.; g) PPh_3, DIAD, 6-chloropurine, THF, 16 h, 20 °C, then 24 h, 60 °C, 40%; h) NH_3, MeOH, 14 h, 20 °C, then 24 h, 100 °C, 74%; i) PPh_3, DIAD, phthalimide, THF, 16 h, 20 °C, 68%; j) $MeNH_2$, EtOH, 16 h, 20 °C, 77%; k) 1. **27** or **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (−)-**72**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 52–57%; l) TFA/H_2O (1:1), 60 min, 0 °C, 90–98%. DME = 1,2-dimethoxyethane. DMAP = 4-(dimethylamino)pyridine.



Scheme 7. Synthesis of inhibitor (+)-**17**: a) (+)-**64**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, 30 min, −30 °C, then 18 h, 20 °C, 97% (92:8 d.r.); b) PPh_3, DIAD, $(PhO)_2PON_3$, THF, 16 h, 20 °C, 41%; c) PPh_3, dioxane, 16 h, 20 °C, then H_2O, 20 °C, 3 h, 76%.

diastereomer of (−)-**68** with the *S*,*S*-configured cyclopropane (Supporting Information) in a yield of only 49% over both steps (61% for the benzyl group removal). Compared with olefin (−)-**54**, the introduction of the purine heterocycle through Mitsunobu inversion into the secondary alcohols (−)-**68** and its diastereomer (with *S*,*S*-configured cyclopropane ring) proceeded in lower yields (40% and 39%), reflecting the increased steric requirements of the cyclopropanated linker. Following substitution of the chloride in purine (−)-**69** for an amino group and concomitant removal of the acetyl protecting group (74%), intermediate (−)-**70** was transformed via phthalimide (+)-**71** into amino-functionalized (−)-**72** (52% over two steps). In sharp contrast, the corresponding diastereomer (−)-**73** (Scheme 7) with the *S*,*S*-configured cyclopropane ring proved completely unreactive in the Mitsunobu substitution with phthalimide as a nucleophile. Therefore, (−)-**73** was converted into amine (−)-**74** by Staudinger reduction of azide (−)-**75** (31% overall). Similarly, amide coupling of (−)-**72** to give nitro- or 4-methylphenyl-substituted (+)-**76** and (−)-**77** followed by acid-catalyzed ketal deprotection provided ligands (+)-**15** and (+)-**16** with expected yields (51% over the two steps in both cases), yet the analogous synthetic operations provided (+)-**17** in an overall yield of only 13% starting from (−)-**74**. The configurational assignments for (+)-**15** and (+)-**17** on the basis of the transition-state model for the Charette cyclopropanation reaction were further supported by 2D NOESY NMR spectroscopy. The syntheses of the aristeromycin-type ligands with simple alkyl linkers, (−)-**18**, (−)-**19**, and (+)-**20** followed short, standard protocols and are described in the Supporting Information.

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In vitro biological activity

Starting from the crystal structure of the ternary complex formed between (−)-**1**, COMT, and a Mg^{2+} ion (Figure 1),[6b,c] computer simulations with MOLOC[23] suggested that enantiomerically pure ligands **1**–**12** adopt similar binding modes and geometries upon complex formation with COMT. In the predicted bisubstrate binding mode, the ribose OH groups undergo ionic hydrogen bonding and the presumably protonated NH_2 groups undergo H-bonded ion-pairing with the conformationally locked (Figure 1) side chain carboxylate of Glu 90 (Figures 3SI and 4SI, Supporting Information). According to the modeling, no substantial differences in binding affinity can be predicted between 2′-deoxy derivative (−)-**3** and its 3′-deoxy counterpart (−)-**6**.

When complexed in the bisubstrate binding mode, all ribose-modified ligands **6**–**20** are predicted to maintain the favorable interactions of the adenosine and catechol moieties with the protein and the Mg^{2+} ion that have been identified in the crystal structure of (−)-**1** complexed with COMT.[6b,c] Substitution of the ribose by the slightly larger cyclopentane ring introduces a weakly repulsive contact between the cyclopentane CH_2 residue and the CH_2 moiety of Gly 66 (predicted $d_{C\cdots C}$ = 316 pm in (−)-**13**; Figure 5SI, Supporting Information). The modeled structure of the complex with cyclopropanated ligand (+)-**15** (Figure 2) suggests additional repulsive van der Waals contacts between the cyclopropane CH_2 residue and an aromatic CH group of Trp 143 ($d_{C\cdots C}$ = 307 pm) as well as the S atom of Met 40 ($d_{C\cdots S}$ = 304 pm), and between the 3′-OH group on the cyclopentane and an aromatic CH of Tyr 95 ($d_{C\cdots C}$ = 307 pm). On the other hand, the protein structure is held rigid and not allowed to relax during the geometry optimizations of the ligand in the active site. Minor movements of the amino acid side chains lining the channel occupied by the cyclopropane linker fragment could well alleviate the predicted repulsive interactions. For example, the side chain of Trp 143 has been found to adopt substantially different orientations in two independent crystal structures.[6]

Biological activities (IC_{50} values, IC_{50} = concentration of inhibitor at which 50% maximum initial velocity is observed; Table 3) of the newly synthesized inhibitors were determined with pre-incubation by using a radiochemical assay.[6a,24] In addition, kinetic studies were performed with (−)-**6**, (−)-**7**, (+)-**10**, (−)-**11**, (−)-**12**, (+)-**15**, and (+)-**16** to determine the inhibition mechanism with respect to the cofactor binding site (Figure 3 and Supporting Information). In the experiments, the cofactor concentration was varied at saturating benzene-1,2-diol concentration for different concentrations of the inhibitor.

Table 3. In vitro biological activities of inhibitors **1**–**20**.

Compound	IC_{50} [μM][a]
(−)-**1**[6b,c]	0.009
(−)-**2**[7]	0.023
(−)-**3**[6b,c]	28
(−)-**4**[6b,c]	3
(+)-**5**[6b,c]	1
(−)-**6**	0.040
(−)-**7**	0.180
(−)-**8**	25
(+)-**9**	104
(+)-**10**	8
(−)-**11**	8
(−)-**12**	17
(−)-**13**	1000
(−)-**14**	>1000
(+)-**15**	17
(+)-**16**	9
(+)-**17**	>1000
(−)-**18**	>1000
(−)-**19**	>1000
(+)-**20**	>1000

[a] Uncertainties: ±5%.

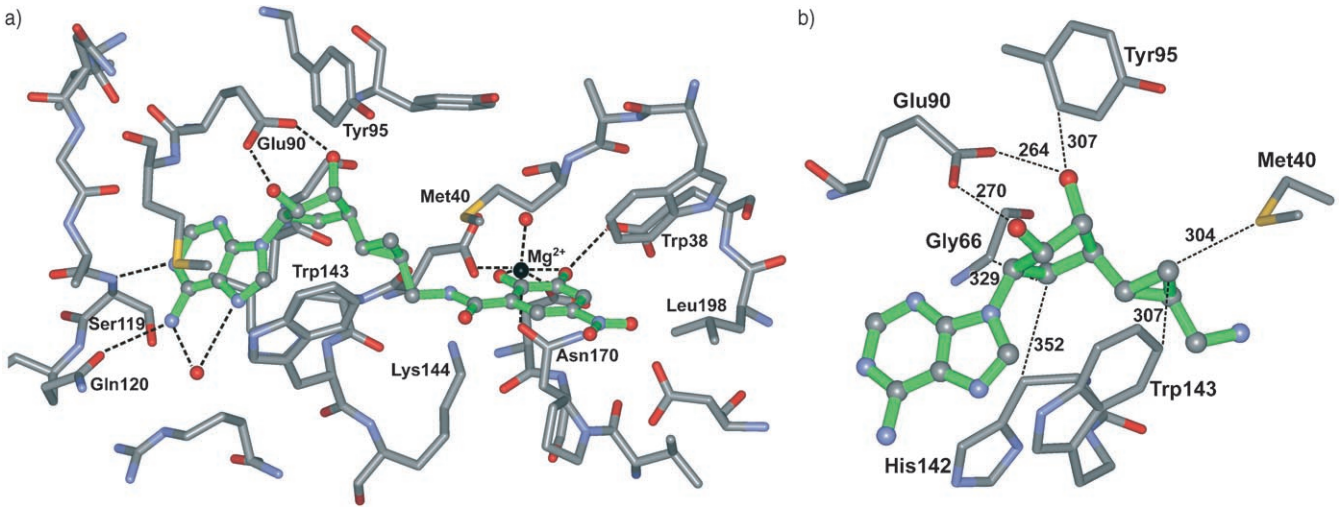

Figure 2. Computer model (MOLOC) of inhibitor (+)-**15** complexed with COMT and a Mg^{2+} ion. Ball-and-stick representation of a) the active site and of b) close contacts in the ribose binding pocket. Distances are given in pm. Color code: inhibitor skeleton, green; C atoms, gray; O atoms, red; N atoms, blue; S atoms, yellow; Mg atom, black.

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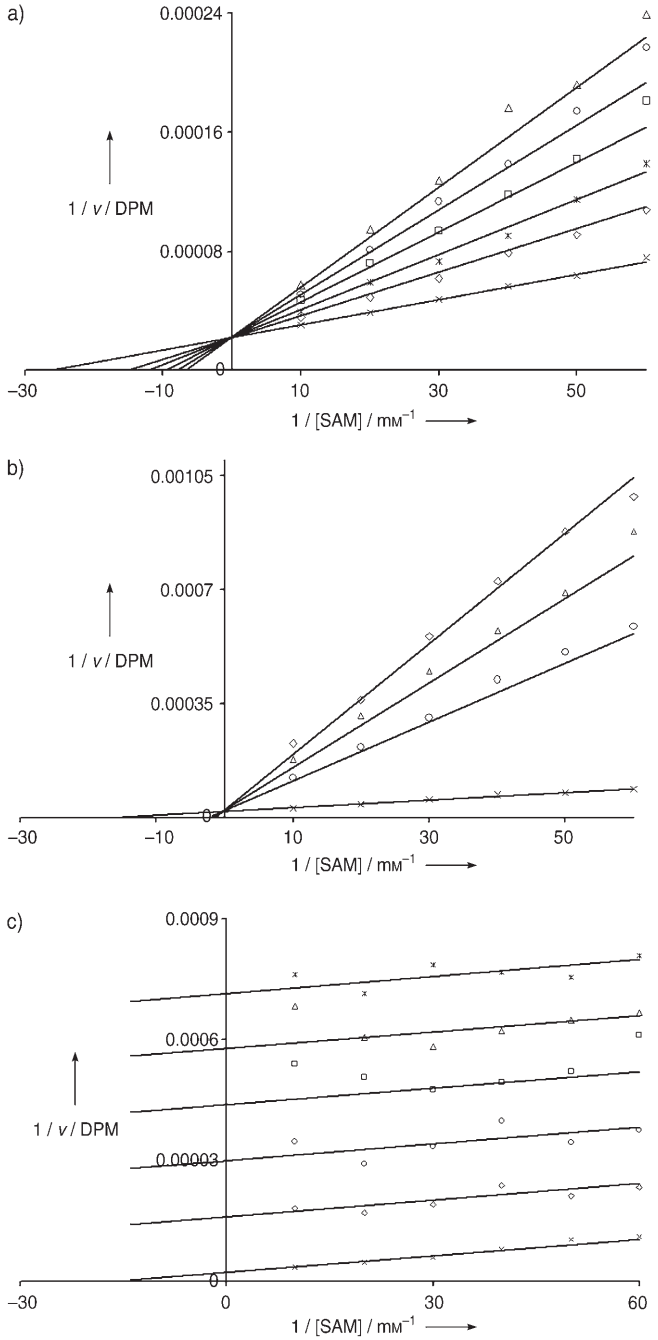

Figure 3. Lineweaver–Burk plots of reciprocal enzymatic activity as a function of the reciprocal concentration of the cofactor (SAM) for varying concentrations of inhibitors a) (−)-**6** (× 0, ◇ 50, * 80, □ 120, ○ 180, and △ 200 nM); b) (+)-**15** (× 0, ○ 30, △ 40, and ◇ 80 μM); and c) (+)-**10** (× 0, ◇ 10, ○ 20, □ 30, △ 40, and * 50 μM) at saturating benzene-1,2-diol concentrations. DMP = decays min^{-1}.

Initial velocities were determined without pre-incubation. The data were globally fitted to Equations (1), (2), or (3), which describe the cases of competitive, mixed competitive, or uncompetitive inhibition, respectively, to obtain kinetic parameters (K_i values, Table 4). In the equations, K_{ic} and K_{iu} denote the competitive and uncompetitive inhibition constants, whereas [S] and [I] are the concentrations of cofactor and inhibitor, respectively; v is the initial velocity and V the maximal velocity of the reaction. All catechol derivatives show competitive or mixed competitive binding to the (catecholic) substrate binding site, as has been previously determined.[6a]

Table 4. In vitro biological activities of newly synthesized inhibitors as obtained from kinetic measurements.

Compd	K_i [μM][a]	$-\Delta G_{inh}$ [kJ mol^{-1}][b]	Inhibition Mode
(−)-**1**[6b,c]	0.028 ± 0.002	44.8 ± 0.2	competitive
(−)-**2**[7]	0.055 ± 0.003	43.1 ± 0.1	competitive
(−)-**3**[6b,c]	14 ± 1	28.8 ± 0.2	competitive
(−)-**4**[6b,c]	2.7 ± 0.1	33.0 ± 0.1	mixed competitive
(+)-**5**[6b,c]	0.56 ± 0.03	37.1 ± 0.1	uncompetitive
(−)-**6**	0.068 ± 0.003	42.5 ± 0.1	competitive
(−)-**7**	0.176 ± 0.007	40.1 ± 0.1	competitive
(+)-**10**	1.4 ± 0.1	34.6 ± 0.2	uncompetitive
(−)-**11**	10.0 ± 1.1	29.4 ± 0.3	competitive
(−)-**12**	20.0 ± 1.1	27.7 ± 0.1	competitive
(+)-**15**	6.0 ± 0.3	30.9 ± 0.1	competitive
(+)-**16**	3.0 ± 0.5	32.4 ± 0.4	competitive

[a] K_i data refer to the inhibition of the SAM binding site. [b] ΔG_{inh} data at 310 K.

$$v = V[S]/(K_M(1 + [I]/K_{ic}) + [S]) \quad (1)$$

$$v = V[S]/(K_M(1 + [I]/K_{ic}) + [S](1 + [I]/K_{iu})) \quad (2)$$

$$v = V[S]/(K_M + [S](1 + [I]/K_{iu})) \quad (3)$$

As previously reported,[6b,c,7] the two ribose derivatives (−)-**1** (IC_{50} = 9 nM) and (−)-**2** (IC_{50} = 40 nM) are efficient bisubstrate inhibitors of COMT, binding competitively (Tables 3 and 4) to the cofactor site of the enzyme. According to X-ray analysis ((−)-**1**, Figure 1) and computer modeling (with (−)-**2**), the 2′-OH and 3′-OH groups of their ribose moieties form two short ionic hydrogen bonds to the rigidly fixed carboxylate of Glu 90.

The earlier investigations had also revealed that removal of the 2′-OH group in (−)-**1** to give (−)-**3** leads to a dramatic decrease in potency by three orders of magnitude (IC_{50} = 28 μM), although competitive inhibition kinetics with regard to SAM are still observed.[8] Most interestingly, the newly prepared 3′-deoxy derivatives (−)-**6** and (−)-**7** showed IC_{50} values in the nanomolar range (40 and 180 nM, respectively), revealing only a ≈4.5-fold decrease in biological activity relative to the parent ribose derivatives (−)-**1** and (−)-**2**. The 200-fold difference in potency (≈13.7 kJ mol^{-1}, Table 4) between the 2′-deoxy (−)-**3** and the 3′-deoxy (−)-**6** ribose derivatives is equally remarkable and unexpected. However, a literature survey showed that this is not without precedent, as the 3′-deoxy derivative of *S*-adenosylhomocysteine (SAH) retained most of the inhibitory activity of SAH towards COMT (K_i = 138 ± 31.2 μM and 36.3 ± 2.2 μM for 3′-deoxy-SAH and SAH, respectively), whereas 2′-deoxy-SAH was found to be inactive.[25] Similarly, 3′-deoxy-SAM acted as a cofactor analogue of SAM showing methyl-donor activities with a slightly higher maximal rate than that of the natural cofactor, albeit with a 30-fold lower binding affinity for COMT (K_M = 337 ± 34 and 9.66 ± 0.74 for 3′-deoxy-SAM and SAM, respectively). On the contrary, 2′-deoxy-SAM was again found to be inactive.[26]

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Several factors may contribute to this extraordinary difference between the respective pairs of 2′-deoxy- and 3′-deoxyribose derivatives: in the crystal structure of the ternary complex formed between (−)-**1**, COMT, and a Mg^{2+} ion (Figure 1), the hydrogen bond between the 2′-OH group of **1** and the side-chain carboxylate group of Glu 90 (262 pm) is 34 pm shorter than its counterpart between the same carboxylate and the neighboring 3′-OH group of the ribose (296 pm). Although this feature is not reproduced by computer modeling, the tendency of the 2′-OH group of adenosine derivatives such as SAM, sinefungin, and (−)-**1** to form shorter hydrogen bonds to Glu 90 than the 3′-OH H-bond donor, is present in all crystal structures of COMT available,[27] being most pronounced in the case of the recently published quaternary complex between the nitrocatechol inhibitor BIA 3-335, SAM, COMT, and a Mg^{2+} ion ($\Delta d_{C\cdots O} = 46$ pm). However, in contrast to all other cases, the ribose moiety in this instance adopts the unusual East (^{O}E) conformation (Figure 4).[28] This asymmetry in the bidentate H-bonding motif of the ribose hydroxy groups to the Glu 90 carboxylate may reflect an intrinsic difference in the incremental contribution of the two hydroxy groups to the free enthalpy of binding upon complexation with COMT, with the 2′-OH group being much more important than its 3′-counterpart.

On the other hand, conformational changes of the ribose pucker upon structural modification have been held responsible for differences in the binding affinity of nucleosidic inhibitors to various enzymatic targets.[29] Generally, conventional nucleosides are known to adopt one of two extreme forms of ring pucker in the crystal ("North" (N) or "South" (S), with preferred pseudorotational phase angle values *P* ranging between 0° to 36° and 144° to 180°, respectively, (Figure 4)), and to rapidly equilibrate between them in solution.[30] The occurrence of the same (or the other) conformation in the enzyme–inhibitor complex has, in the past, been related to high (or low) biological activity of the respective nucleosidic inhibitor.[31]

A survey of the solution- and solid-state conformations of 2′-deoxy-, 3′-deoxy-, and riboadenosine shows that in the crystal, the ribose moiety of 2′-deoxyadenosine monohydrate[32a] adopts the S-type conformation ($P = 194.4°$), whereas adenosine,[33] 2′-deoxyadenosine,[32b] and 3′-deoxyadenosine[34] crystallize as the N-conformer ($P = 7.1°$, 13.2°, and 4.4°, respectively). In all cases, the *anti* orientation of the purine nucleobase is present. In solution, however, adenosine and 2′-deoxyadenosine exhibit a slight preference for the S-type conformation (≈60–70%), whereas the 3′-deoxy isomer retains a strong preference for the N-type conformer (≈90%).[35] Given the fact that in the crystal structure ((−)-**1**) and the computer models ((−)-**3** and (−)-**6**) of the enzyme–inhibitor complexes the ligands adopt S-type ribose conformations ($P = 183°$, 182°, and 192°, respectively),[36] and assuming similar conformational preferences of the bisubstrate inhibitors and the parent 5′-unmodified nucleosides, differences in ribose puckering cannot be a major contributor to the observed dramatic variations in binding affinity between (−)-**3** and (−)-**6**. Rather, differences in solvation between free (−)-**1**, (−)-**3**, and (−)-**6** may play an important role in determining the measured free enthalpies of binding for the complexes with COMT.[37] The virtually identical molar hydration free energies of adenosine and 2′-deoxyadenosine monohydrate ($\Delta G^0_{m(solv)} = -10.3$ kJ mol^{-1}, with a higher enthalpic contribution $\Delta H^0_{m(solv)}$ for the deoxygenated derivative, −43.9 versus −32.0 kJ mol^{-1})[38] suggest that the desolvation penalty of the 2′-deoxy derivative (−)-**3** upon binding to the enzyme is only very poorly compensated by the establishment of one single (weak) hydrogen bond to Glu 90. In contrast, (−)-**6** may benefit from an increased gain in free enthalpy due to a much stronger H-bond formation, whereas the formation of a second hydrogen bond gives rise to the additional increase in potency for (−)-**1**.

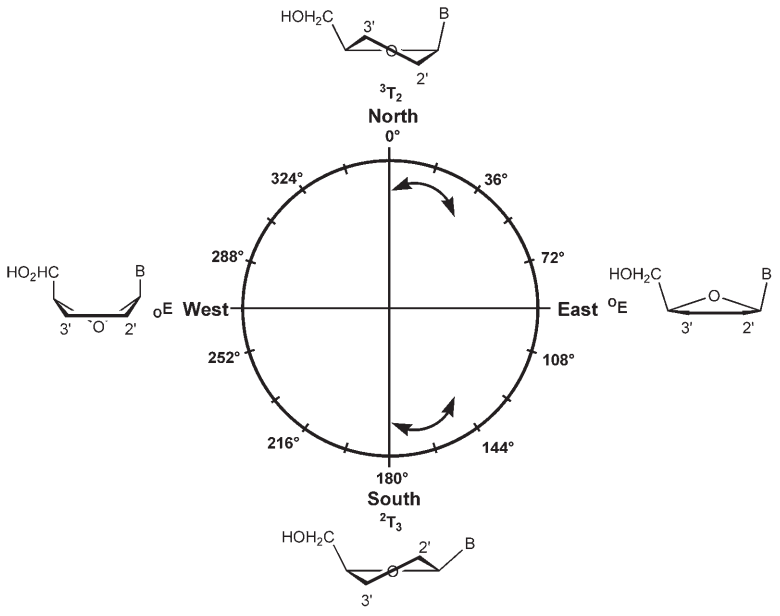

Figure 4. The pseudorotational phase cycle of the furanose ring in nucleosides. The phase angle *P* results from a mathematical expression that combines all torsional angles involved in the pseudorotation, thus allowing the circular description of the conformational space from pseudorotation. The arrows denote the preferred pseudorotational regions as observed in a CSD search;[30d] T and E denote twist and envelope conformations, respectively. Super- and subscripts denote localizations of the corresponding atoms above or below the plane defined by the three (or four in the case of only one super- or subscript) remaining atoms, respectively.

Similarly, the combined enthalpic and entropic contributions of hydrogen bonding and ion pairing between the protonated amino groups of (−)-**8**, (+)-**9**, (−)-**11**, and (−)-**12** and the carboxylate group of Glu 90 seem to be insufficient to compensate for the losses in free enthalpy associated with the desolvation of the primary ammonium residue upon binding to the active site of COMT. Thus, the 2′-aminodeoxy-3′-deoxy derivatives (−)-**11** and (−)-**12** ex-

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hibit IC_{50} values in the low micromolar range (8 μM and 17 μM, respectively) corresponding to a decrease in inhibitory activity of two orders of magnitude relative to 3′-deoxy analogues (−)-**6** and (−)-**7**. Interestingly, the trends observed for the transition from 2′-deoxy derivative (−)-**3** to its 3′-deoxy counterpart (−)-**6** are also present in the corresponding amino series, albeit with much smaller differences in binding affinities. Hence, 3′-aminodeoxy-2′-deoxy derivative (−)-**8** displays COMT inhibition with an IC_{50} value of 25 μM, whereas 2′-amino-substituted (−)-**11** exhibits a threefold higher biological activity ($IC_{50} = 8$ μM).

Notably, whereas all four ammonium derivatives show competitive inhibition kinetics with respect to SAM, the azido analogue (−)-**10** is not capable of occupying the SAM binding site and therefore only binds to the catechol site, directing the derivatized nucleoside moiety into the surrounding solution (parallel lines in the Lineweaver–Burk plot; Figure 3c). A similar noncompetitive binding had been previously observed for cyclopentane (+)-**5**, while furan (−)-**4** had shown a mixed competitive inhibition mechanism.[8]

After the results obtained with the ribose, deoxyribose, and ammonium derivatives, it came as quite a surprise that the reestablishment of both 2′-OH and 3′-OH groups in the series of carbocyclic inhibitors **13**–**20** led to completely inactive compounds in most of the cases studied (Tables 3 and 4). The seemingly conservative mutation of the ribose ether oxygen atom to a CH_2 unit leads to a dramatic decrease in inhibitory activity of five orders of magnitude (!) for carbocyclic (−)-**13** ($IC_{50} = 1$ mM) relative to the potent, low nanomolar inhibitor (−)-**1**.

At first sight, significant differences in the preferred conformations of the five-membered carbocycle in comparison with the parent ribose, combined with additional stereoelectronic effects may seem the most probable cause of these remarkably different biological activities. Indeed, the exchange of the ribose furan oxygen atom for a methylene unit in carbonucleosides abolishes the anomeric affect, as well as important *gauche* interactions between the oxygen atom and the 2′-OH and 3′-OH groups which mainly govern the preference for N- and S-type conformers in ribonucleosides.[30c] Furthermore, the basicity of the N atoms of the nucleobase heterocycle is expected to increase in the case of carbonucleosides as a consequence of the missing anomeric effect, leading to a change in the strength of hydrogen bonds formed between the nucleobase and amino acid residues of the enzyme in an enzyme–ligand complex.[39] In fact, the biological activities of most conventional carbocyclic nucleosides have been poorer than those of the corresponding ribosides,[11b] and this might be interpreted as a consequence of a combination of the above-mentioned effects. However, a survey of the literature suggests that in the case of ligands **13**–**20** the reasons for the dramatic loss in binding activity upon introduction of the carbocycle may be more complex. Thus, NMR investigations convincingly demonstrate that in analogy to adenosine, the solution conformations of aristeromycin can be described in terms of the two-state N/S equilibrium of the pseudorotational phase cycle in which the S-type conformation is adopted preferentially ($P = 130°$–$135°$),[40] roughly matching the conformation required by computer modeling for the binding of **13**–**20** to the active site of COMT ($P = 137°$–$199°$). In contrast, crystalline aristeromycin adopts an East-type conformation (^{1}aE) ($P = 89.2°$),[41] which suggests that the energy barrier of interconversion between N- and S-type conformers is easily reached at room temperature and can be overcome by crystal packing forces. Furthermore, the carbocyclic SAH analogue SAmH ("m" denotes the carbocyclic modification) was reported to possess inhibitory activity toward COMT similar to the parent natural counterpart ($K_i = 168 \pm 39$ μM and 36.3 ± 2.2 μM, for SAmH and SAH, respectively).[42] Similarly, aristeromycin-derived SAM (SAmM) was an active cofactor in COMT-catalyzed methylation reactions with an approximate 12-fold lower affinity for the enzyme ($K_M = 125 \pm 62$ μM and 9.66 ± 0.74 μM for SAmM and SAM, respectively) and an equally lowered maximal catalytic velocity relative to that of natural SAM.[43]

Therefore, in addition to conformational effects, we suggest that repulsive enzyme–ligand contacts, as indicated by computer modeling (Figure 2), in the narrow channel connecting the adenine with the catechol moiety as well as in the ribose binding site are largely responsible for the measured weak binding affinities of the carbocyclic derivatives. Despite the predicted steric congestion, however, the cyclopropanated aristeromycin analogues with an *R*,*R*-configured three-membered ring occupy the SAM binding site as demonstrated by the competitive inhibition kinetics for (+)-**15** ($IC_{50} = 17$ μM) and (+)-**16** ($IC_{50} = 8$ μM). Interestingly, this is the only case of inhibitor pairs in which the binding affinity of the derivative carrying the 4-methylphenyl substituent in position 5 of the catechol exceeds the affinity of the NO_2-substituted counterpart, albeit only by a very small margin. Steric congestion apparently increases upon changing to (−)-**17** with an *S*,*S*-configured cyclopropane ring, which shows no activity within the sensitivity limits of the assay. In case of (−)-**18**, (−)-**19**, and (+)-**20** with simple alkyl chain linkers, hydrophobic collapse of the inhibitor in the free state, which leads to a favorably solvated conformation with stacking catechol and adenine residues,[6a,c] is another factor responsible for the absence of any measurable biological affinity.

Conclusions

In vitro biological evaluation and kinetic studies on a diverse series of ribose-modified potential bisubstrate inhibitors of COMT confirm that the ribose structural unit is a key element of molecular recognition and plays a crucial role in determining both binding affinity and binding mode. However, the high potency of the 3′-deoxy derivatives (−)-**6** and (−)-**7** shows that careful and adequately placed modifications can be tolerated surprisingly well. At the same time, the dramatic difference between the isomeric 2′-deoxy and 3′-deoxy derivatives (−)-**3** and (−)-**6** convincingly illustrates the high complexity of the molecular recognition event. Apparently, the asymmetry in hydrogen bonding between the two ribose hydroxy groups and the side-chain carboxylate group of Glu 90 combined with poorly explored solvation effects gives rise to this remarkable difference. Similar effects may also stand at the

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origin of the decrease in binding affinity measured for ammonium-functionalized ligands such as (−)-**8** and (−)-**11**.

Most remarkably, the minor change from the ribose ether oxygen atom to the CH_2 unit of a carbocyclic cyclopentane core, in most cases, leads to complete loss of the binding affinity. While an adequate description of this unexpected effect in terms of molecular recognition principles remains elusive, it may be speculated that steric congestion in the ribose binding site and, in general, in the narrow channel that connects the adenine and catechol sites, as well as conformational changes upon replacement of the ribose moiety may play an important role. Thus, the preparation of ligands with smaller hydroxylated carbocyclic cores (cyclobutane, cyclopropane) may lead to potent bisubstrate inhibitors of COMT. Similarly, synthesis of C-nucleosides, obtained by introduction of a C–C bond in place of the nucleosidic C–N bond, should yield inhibitors that possess an increased stability toward acidic or enzymatic degradation. However, the above examples demonstrate that modifications of the ribose moiety in bisubstrate inhibitors of COMT are delicate and that further surprises can be expected.

Experimental Section

Materials and general methods. Solvents and reagents were purchased reagent-grade and used without further purification. Solvents for extractions and chromatography were of technical grade and were distilled prior to use. All reactions were carried out under an Ar atmosphere unless otherwise stated. THF was distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Anhydrous Me_2SO, DMF, and pyridine, stored over molecular sieves, were purchased from Fluka. The preparation of the following compounds has been reported previously: (−)-**21**,[10] **33**,[6a] **34**,[12] **35**,[5a] **36**,[44] (−)-**40**,[14] (−)-**51**,[16] **53**,[6a] (−)-**54**,[19a] (−)-**89**,[19a] (−)-**90**,[45] and (−)-**64** and (+)-**64**.[22b] The synthesis of inhibitors (−)-**1**,[6b,c] (−)-**2**,[7] (−)-**3**,[8] (−)-**4**,[8] and (+)-**5**[8] have been described previously. Protocols for the following compounds are included in the Supporting Information: (−)-**7**, (+)-**9**, (−)-**12**, (−)-**13**, (−)-**14**, (+)-**15**, (+)-**16**, (+)-**17**, (−)-**18**, (−)-**19**, (+)-**20**, **27**, (−)-**30**, (+)-**32**, **37**, (−)-**50**, (+)-**52**, (+)-**58**, (+)-**59**, (+)-**60**, (−)-**66**, (−)-**69**, (−)-**70**, (+)-**71**, (−)-**72**, (−)-**74**, (−)-**75**, (+)-**76**, (−)-**77**, (−)-**78**, (−)-**79**, (−)-**80**, (+)-**81**, (−)-**82**, (+)-**83**, (−)-**84**, (−)-**85**, (+)-**86**, (−)-**87**, and (−)-**88**. Thin-layer chromatography (TLC) was performed on aluminum-backed sheets coated with SiO_2 60 F_{254} from Macherey–Nagel. Column chromatography (CC) was performed with Fluka SiO_2 60 (230–400 mesh, 0.040–0.063 mm). Analytical HPLC was performed on a Kromasil 100 Si column (250× 4 mm, 5 μm); products were eluted with EtOAc/hexane (1:1) at a flow rate of 1 $cm^3 min^{-1}$, and detected with UV at $\lambda = 254$ nm. Analytical reversed-phase (RP) HPLC was performed on a Merck LiChrospher 100 C-18 column (250×4 mm, 5 μm, 100 Å); products were eluted with a linear gradient (5–55%) of CH_3CN in H_2O containing 0.1% TFA over 20 min with a flow rate of 1 $cm^3 min^{-1}$, and detected with UV at $\lambda = 254$ nm. Preparative HPLC was performed on a Merck LiChrosorb C-18 column (250×25 mm, 7 μm); products were eluted with a linear gradient of CH_3CN in H_2O containing 0.1% TFA with a flow rate of 10 $cm^3 min^{-1}$, and detected with UV at $\lambda = 254$ nm. Melting points (mp) were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at $\lambda = 589$ nm and are given in 10^{-1} deg $cm^2 g^{-1}$. Infrared spectra were recorded on a Perkin–Elmer 1600-FTIR spectrometer or a Perkin–Elmer Spectrum BX II. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300, Varian Mercury 300, or Bruker AMX-500 spectrometers. Chemical shifts are reported in ppm downfield of $SiMe_4$, with the residual signal of the solvent as an internal reference. Coupling constants (*J*) are given in Hz. The resonance multiplicity is described as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MALDI mass spectra were recorded on an IonSpec Ultima instrument with 2,5-dihydroxybenzoic acid or 2,4,5-trihydroxyacetophenone-diammonium citrate (2:1) as a matrix. Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich. The nomenclature was generated by using the computer program ACD-Name (ACD/Labs).

General procedure A (GP A) for the oxidation of primary alcohols and subsequent Wittig olefination to α,β-unsaturated esters. $Ph_3P{=}CHCO_2Et$ (2.5 equiv) and IBX (2.5 equiv) were added to a solution of the primary alcohol (1 equiv) in Me_2SO, and the mixture was stirred for 16–48 h at 20 °C. H_2O was added followed by extraction with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by CC.

General procedure B (GP B) for the reduction of α,β-unsaturated esters to allylic alcohols. A solution of the unsaturated ester in dry CH_2Cl_2 was cooled to −78 °C, and a 1 M solution of DIBAL-H in CH_2Cl_2 (4–6 equiv) was added dropwise by syringe. The mixture was stirred for 2–4 h at −78 °C and then quenched by the addition of a saturated solution of NH_4Cl (aq). A saturated solution of potassium sodium tartrate monohydrate (aq) was added, and the mixture was vigorously stirred at 20 °C for 16 h. The clear biphasic mixture was phase-separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure to give a residue that was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1).

General procedure C (GP C) for the Mitsunobu substitution of allylic and secondary alcohols with phthalimide or azide. DIAD (2 equiv) was added dropwise to an ice-cold solution of Ph_3P (2 equiv) in dry THF, and the mixture was stirred for 30 min at 0 °C. A solution of the alcohol (1 equiv) in THF was then added to the resulting slurry, followed by the appropriate nucleophile (phthalimide or $(PhO)_2PON_3$, 2 equiv). The mixture was stirred 16 h at 20 °C, then the solvent was evaporated in vacuo, and the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1).

General procedure D (GP D) for the cleavage of *N*-alkylated phthalimides with $MeNH_2$. The *N*-alkylated phthalimide was dissolved in a solution of $MeNH_2$ in EtOH (33%, 20 mL), and the solution was stirred for 16 h at 20 °C. *Method A*: After evaporation of the volatiles under decreased pressure, the residue was redissolved in $CHCl_3$ (60 mL) and extracted with 10% aq AcOH (5×20 mL). The combined aqueous phases were adjusted to pH > 12 by the addition of NaOH, followed by extraction with $CHCl_3$ (6×25 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. *Method B*: After evaporation of the volatiles under decreased pressure, the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 89:10:1).

General procedure E (GP E) for the reduction of azides to amines. *Method A* (Staudinger reduction): PPh_3 (2 equiv) was added to a solution of the azide in dioxane (filtered through Al_2O_3 to remove peroxides), and the mixture was stirred for 16 h at 20 °C. H_2O was added, and stirring was continued for 3 h. The mixture partitioned between a saturated solution of Na_2CO_3 (aq) and $CHCl_3$, and the aqueous phase was extracted twice with $CHCl_3$. The combined organic phases were extracted with 10% aq AcOH (5×20 mL). The combined aqueous phases were adjusted to pH > 12 by the addition of NaOH, followed by extraction with $CHCl_3$ (6×25 mL). The

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combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure. *Method B* (reduction with 1,3-propanedithiol as reducing agent): To a solution of the azide in MeOH, 1,3-propanedithiol (10 equiv) and Et_3N (10 equiv) were added and the mixture was stirred 16 h at 20 °C. Volatiles were removed under decreased pressure, and the residue was purified by RP HPLC or directly used in the next transformation.

General procedure F (GP F) for the amide coupling of primary amines with catechol carboxylic acid building blocks **27** and **28**. EDC·HCl (1.5 equiv) and *N*-hydroxysuccinimide (1.3 equiv) were added to a solution of the corresponding carboxylic acid **27** or **28** in dry CH_2Cl_2, and the mixture was stirred for 1 h at 20 °C. Following the addition of the amine building block (0.7 equiv) and Et_3N (2 equiv), stirring was continued for 16 h at 20 °C. The mixture partitioned between CH_2Cl_2 and H_2O, and the organic phase was washed with a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated under decreased pressure. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1).

General procedure G (GP G) for the acid-catalyzed deprotection of acetonide and/or diarylmethylketal protecting groups. The protected precursor was treated with a mixture of TFA/H_2O (1:1) at 0 °C for 60 min. Volatiles were removed under high vacuum at ambient temperature. The residue was redissolved in Me_2SO (2 mL) and purified by preparative RP HPLC. The product fractions were evaporated to dryness by lyophilization.

General procedure H (GP H) for the substitution of secondary alcohols by 6-chloropurine under Mitsunobu conditions. DIAD (2 equiv) was added dropwise to an ice-cold solution of Ph_3P (2 equiv) in dry THF, and the mixture was stirred for 30 min at 0 °C. A solution of the secondary alcohol (1 equiv) in THF was then added to the resulting slurry, followed by 6-chloropurine (1.6 equiv). The suspension was stirred for 16 h at 20 °C, then 24 h at 60 °C. The resulting clear solution was evaporated in vacuo, and the residue was purified by CC (SiO_2; EtOAc/hexane 1:1).

General procedure I (GP I) for the substitution of Cl for NH_2 at C6 of the purine heterocycle. A solution of the N9-alkylated chloropurine was saturated with NH_3 at 0 °C and heated at 100 °C for 24 h in a sealed stainless steel reaction vessel. Volatiles were removed under decreased pressure, and the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1→9:1).

Ethyl (2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-enoate ((−)-22): Compound (−)-**21** (200 mg, 0.8 mmol), $Ph_3P{=}CHCO_2Et$ (700 mg, 2 mmol), and IBX (560 mg, 2 mmol) were dissolved in Me_2SO (15 mL) and reacted according to *GP A*. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1→9:1) provided (−)-**22** (144 mg, 57%) as a white solid: mp: 150–151 °C; $[\alpha]_D^{20} = -63.2$ ($c = 0.75$, Me_2SO); ^{1}H NMR (300 MHz, $(CD_3)_2SO$): $\delta = 1.20$ (t, $J = 7.2$ Hz, 3H), 2.20 (dd, $J = 12.6$, 6.3 Hz, 1H), 2.39 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.72 (m, 1H), 4.95 (m, 1H), 5.82 (d, $J = 3.9$ Hz, 1H), 5.96 (d, $J = 1.8$ Hz, 1H), 5.99 (d, $J = 15.8$ Hz, 1H), 7.01 (dd, $J = 15.8$, 5.7 Hz, 1H), 7.31 (bs, 2H), 8.16 (s, 1H), 8.25 ppm (s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): $\delta = 14.1$, 40.4, 60.1, 74.4, 78.2, 90.4, 119.0, 120.9, 139.1, 147.0, 149.0, 152.7, 156.1, 165.4 ppm; IR (neat): $\tilde{\nu} = 3135$w, 1715m, 1649s, 1600s, 1571m, 1474w, 1416w, 1301m, 1205w, 1172m, 1040s, 978w, 822w, 795w, 718w, 640w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{14}H_{18}N_5O_4^+$: 320.1353; found: 320.1354 $[M+H]^+$.

Ethyl (2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-4-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-enoate ((−)-23): A solution of (−)-**22** (4.3 g, 13.5 mmol) and TBDMS-Cl (4.1 g, 27 mmol, 2 equiv) in dry pyridine (40 mL) was stirred for 16 h at 20 °C. The mixture partitioned between EtOAc and H_2O and the aqueous phase was extracted with EtOAc (2×40 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield (−)-**23** as a white solid (3.39 g, 58%): mp: 156–158 °C; $[\alpha]_D^{20} = -0.6$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.11$ (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 1.30 (t, $J = 7.1$ Hz, 3H), 2.15 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.84 (m, 1H), 5.07 (m, 1H), 5.81 (bs, 2H), 5.99 (d, $J = 1.2$ Hz, 1H), 6.14 (dd, $J = 15.7$, 1.6 Hz, 1H), 7.08 (dd, $J = 15.7$, 5.3 Hz, 1H), 7.89 (s, 1H), 8.34 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.9$, −4.6, 14.3, 18.0, 25.7, 39.1, 60.7, 76.5, 79.1, 92.6, 120.2, 122.0, 138.3, 144.8, 149.2, 152.9, 155.3, 165.8 ppm; IR (neat): $\tilde{\nu} = 3150$w, 2930w, 2856w, 1716m, 1643m, 1597m, 1470w, 1367w, 1298m, 1252m, 1174w, 1085m, 1043m, 979w, 835s, 779m, 714w, 645w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{20}H_{31}N_5NaO_4Si^+$: 434.2218; found: 434.2213 $[M+Na]^+$.

(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-ol ((−)-24): A solution of (−)-**23** (1.85 g, 4.27 mmol) in dry CH_2Cl_2 (35 mL) and DIBAL-H (26 mL of a 1 M solution in CH_2Cl_2) were reacted according to *GP B*. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (−)-**24** (1.04 g, 62%) as a colorless foam: $[\alpha]_D^{20} = -5.9$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.11 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.03 (m, 2H), 3.15 (bs, 1H), 4.23 (d, $J = 4.3$ Hz, 2H), 4.80 (m, 1H), 4.96 (dt, $J = 10.0$, 6.2 Hz, 1H), 5.99 (m, 5H), 7.92 (s, 1H), 8.32 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.8$, −4.5, 18.0, 25.8, 39.3, 62.3, 76.9, 81.0, 92.5, 120.0, 128.6, 133.4, 138.4, 149.0, 152.8, 155.2 ppm; IR (neat): $\tilde{\nu} = 3170$br, 2929w, 2856w, 1644m, 1598m, 1471w, 1413w, 1363w, 1329w, 1298m, 1250m, 1204w, 1082s, 1041w, 990w, 834s, 778s, 719w, 645w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{18}H_{30}N_5O_3Si^+$: 392.2112; found: 392.2110 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{29}N_5O_3Si$ (391.20): C 55.22, H 7.47, N 17.89; found: C 55.07, H 7.49, N 17.93.

9-[(2*R*,3*R*,5*S*)-5-[(1*E*)-3-Azidoprop-1-en-1-yl]-3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]-9*H*-purin-6-amine ((−)-25): According to *GP C*, (−)-**24** (150 mg, 0.38 mmol), DIAD (155 mg, 0.77 mmol), PPh_3 (200 mg, 0.77 mmol), and $(PhO)_2PON_3$ (210 mg, 0.77 mmol) were reacted in THF (10 mL). Solvent removal under decreased pressure and CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (−)-**25** (134 mg, 84%) as a colorless foam: $[\alpha]_D^{20} = -14.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.11$ (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 2.08 (m, 2H), 4.84 (d, $J = 5.1$ Hz, 2H), 4.84 (m, 1H), 4.96 (dt, $J = 9.4$, 6.1 Hz, 1H), 5.77 (bs, 2H), 5.95 (m, 3H), 7.90 (s, 1H), 8.34 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ −4.8, −4.5, 18.0, 25.8, 39.6, 51.9, 76.7, 80.4, 92.7, 120.3, 126.5, 133.3, 138.5, 149.2, 152.8, 155.2 ppm; IR (neat): $\tilde{\nu} = 3145$br, 2929w, 2856w, 2100m, 1644m, 1596m, 1470w, 1414w, 1364w, 1328w, 1298w, 1250m, 1206w, 1110m, 1081s, 989w, 926w, 834s, 778s, 720w, 645w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{18}H_{29}N_8O_2Si^+$: 417.2177; found: 417.2172 $[M+H]^+$.

9-[(2*R*,3*R*,5*S*)-5-[(1*E*)-3-Aminoprop-1-en-1-yl]-3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]-9*H*-purin-6-amine ((−)-26): Compound (−)-**25** (240 mg, 0.58 mmol) and PPh_3 (300 mg, 1.14 mmol) were dissolved in dioxane (10 mL) and reacted according to *GP E*, *Method A*, to yield (−)-**26** (154 mg, 69%) as a colorless foam: $[\alpha]_D^{20} = -11.4$ ($c = 0.65$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.09$ (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 1.71 (bs, 2H), 2.02 (m, 2H), 3.36 (dd, $J = 5.3$, 1.2 Hz, 2H), 4.79 (m, 1H), 4.92 (m, 1H), 5.77 (ddt, $J = 15.4$, 7.3, 1.5 Hz, 1H), 5.92 (d, $J = 1.0$ Hz,

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1H), 5.97 (dtd, J=15.4, 5.3, 0.7 Hz, 1H), 6.16 (bs, 2H), 7.91 (s, 1H), 8.31 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−5.1, −4.8, 17.9, 25.6, 39.3, 43.3, 67.0, 76.9, 81.2, 92.5, 120.3, 127.8, 135.8, 138.4, 149.1, 152.8, 155.6 ppm; IR (neat): $\tilde{\nu}$=3148br, 2928w, 2855w, 1645m, 1596m, 1470m, 1412w, 1364w, 1328w, 1296w, 1251w, 1204w, 1083s, 989w, 834s, 777s, 720w, 645w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{18}H_{31}N_6O_2Si^+$: 391.2272; found: 391.2267 $[M+H]^+$.

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxamide ((+)-29)**: Compound **27** (220 mg, 0.51 mmol), EDC·HCl (150 mg, 0.77 mmol), *N*-hydroxysuccinimide (80 mg, 0.67 mmol), and (−)-**26** (154 mg, 0.39 mmol) were reacted according to *GP F*. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (+)-**29** (216 mg, 69%) as a colorless foam: $[\alpha]_D^{20}$=+1.9 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.09 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 2.05 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 4.17 (m, 2H), 4.80 (m, 1H), 4.94 (m, 1H), 5.66 (bs, 2H), 5.93 (m, 3H), 6.90 (d, J=8.9 Hz, 2H), 6.91 (d, J=8.9 Hz, 2H), 7.13 (t, J=5.8 Hz, 1H), 7.39 (d, J=8.9 Hz, 4H), 7.82 (d, J=2.3 Hz, 1H), 7.85 (s, 1H), 8.30 (s, 1H), 8.61 ppm (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.8, −4.5, 18.0, 25.8, 39.5, 41.2, 55.4, 76.8, 80.7, 92.5, 106.6, 113.8, 114.8, 120.3, 122.3, 128.1, 129.5, 129.6, 130.6, 138.5, 142.9, 148.1, 149.2, 149.5, 152.8, 155.2, 160.9, 161.3 ppm; IR (neat): $\tilde{\nu}$=2931w, 1640m, 1609m, 1514m, 1462m, 1337m, 1246s, 1206w, 1173s, 1082w, 1026m, 1003m, 829s, 779m, 719w, 647w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{40}H_{45}N_7NaO_9Si^+$: 818.2940; found: 818.2931 $[M+Na]^+$.

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxamide ((−)-31)**: A solution of (+)-**29** (170 mg, 0.21 mmol) in THF (10 mL) was treated with nBu$_4$NF (0.64 mL of a 1 M solution) in THF. The mixture was stirred for 2 h at 20 °C, then a solution of $NaClO_4$ (aq) was added, and the resulting precipitate was removed by filtration. The residue partitioned between CH_2Cl_2 and H_2O, and the organic phase was washed with a saturated solution of NH_4Cl (aq), a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated under decreased pressure. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield amide (−)-**31** as a yellowish foam (104 mg, 72%): $[\alpha]_D^{20}$=−11.0 (c=0.5, $(CH_3)_2SO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.07 (m, 1H), 2.27 (m, 1H), 3.79 (s, 6H), 4.16 (m, 2H), 4.72 (m, 1H), 4.94 (m, 1H), 5.84 (dd, J=15.6 Hz, 6.3 Hz, 1H), 5.93 (m, 2H), 6.09 (bs, 2H), 6.90 (d, J=8.9 Hz, 4H), 7.17 (t, J=5.8 Hz, 1H), 7.39 (d, J=8.9 Hz, 4H), 7.80 (d, J=2.4 Hz, 1H), 7.93 (s, 1H), 8.28 (s, 1H), 8.59 ppm (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=37.9, 41.1, 55.4, 76.0, 80.5, 92.6, 106.6, 113.8, 114.7, 120.0, 120.3, 122.3, 128.1, 129.4, 130.7, 138.1, 142.9, 148.1, 148.6, 149.5, 152.5, 155.4, 160.9, 161.3 ppm; IR (neat): $\tilde{\nu}$=3323w, 1641m, 1609m, 1513m, 1463s, 1336m, 1245s, 1207m, 1173s, 1024m, 1003m, 827m, 742w, 718w, 647w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{34}H_{31}N_7NaO_9^+$: 704.2076; found: 704.2075 $[M+Na]^+$.

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-2,3-dihydroxy-5-nitrobenzamide ((−)-6)**: Compound (−)-**31** (65 mg, 0.1 mmol) was reacted according to *GP G* to yield deprotected (−)-**6** (44 mg, quant.) as a fluffy yellowish solid after lyophilization: $[\alpha]_D^{20}$=−6.0 (c=0.25, Me_2SO); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ=2.10 (ddd, J=13.3, 5.9, 1.7 Hz, 1H, H-C3′), 2.27 (ddd, J=13.3, 9.8, 5.4 Hz, 1H), 3.97 (d, J=5.2 Hz, 2H), 4.64 (dt, J=5.4, 1.6 Hz, 1H), 4.82 (dt, J=10.0, 5.9 Hz, 1H), 5.87 (m, 2H), 5.93 (d, J=1.6 Hz, 1H), 7.71 (d, J=2.7 Hz, 1H), 8.31 (bs, 2H), 8.32 (s, 1H), 8.37 (s, 1H), 8.44 (d, J=2.7 Hz, 1H), 9.43 (t, J=5.2 Hz, 1H), 10.41 ppm (bs, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ=40.3, 75.0, 80.2, 90.9, 112.0, 114.2, 114.5, 118.8, 130.0, 130.9, 138.4, 140.4, 146.9, 148.4, 148.7, 153.0, 156.1, 167.9 ppm; one peak missing due to signal overlap; IR (neat): $\tilde{\nu}$=3314br w, 1678m, 1549w, 1516m, 1325m, 1283m, 1197s, 1136m, 1080m, 1043m, 970m, 851w, 794w, 715m, 638w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{19}H_{19}N_7NaO_7^+$: 480.1238; found: 480.1240 $[M+Na]^+$.

Methyl 6-bromo-2,2-bis[4-(methoxy)phenyl]-1,3-benzodioxole-4-carboxylate (38): 4,4′-Dimethoxybenzophenone (737 mg, 3.04 mmol) and oxalyl chloride (0.52 mL, 6.1 mmol) were stirred at 60 °C for 30 min, then the temperature was raised to 110 °C to remove excess oxalyl chloride. Subsequently, **36** (430 mg, 1.74 mmol) was added to the mixture, and the dark-red solution was stirred at 160 °C for 40 min. After cooling, EtOAc was added to the viscous mixture, which was washed with a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated under decreased pressure. The crude product was purified by CC (SiO_2; hexane/EtOAc 19:1) to yield **38** as a white solid (722 mg, 88%): mp: 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.80 (s, 6H), 3.92 (s, 3H), 6.89 (d, J=9.0 Hz, 4H), 7.10 (d, J=2.1 Hz, 1H), 7.46 (d, J=9.0 Hz, 4H), 7.54 ppm (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.3, 55.3, 112.5, 113.6, 115.6, 119.6, 124.9, 128.1, 131.3, 147.9, 149.4, 160.4, 164.0 ppm; IR (KBr): $\tilde{\nu}$=3097w, 3014w, 2948w, 2835w, 1731s, 1612m, 1515s, 1467s, 1433m, 1345m, 1317s, 1261s, 1198s, 1169s, 1049s, 1005m, 954m, 929m, 864w, 835s, 778m, 755w, 708w, 667w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{23}H_{19}NNaO_6^+$: 493.0257; found: 493.0263 $[M+Na]^+$.

Methyl 2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxylate (39): A solution of 4-methylphenylboronic acid (245 mg, 1.8 mmol) in EtOH (2 mL) and a solution of K_2CO_3 (750 mg, 5.41 mmol) in H_2O (2 mL) were added to the green solution of **38** (425 mg, 0.86 mmol) and $[Pd(PPh_3)_4]$ (52 mg, 0.045 mmol) in toluene (10 mL). The mixture was heated at reflux for 16 h. After cooling to 20 °C, the mixture partitioned between EtOAc and H_2O. The organic layer was washed twice with a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by CC (SiO_2; hexane/EtOAc 9:1→4:1) to yield **39** as a white solid (327 mg, 79%): mp: 59–61 °C; ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ=2.32 (s, 3H), 3.76 (s, 6H), 3.88 (s, 3H), 7.00 (d, J=8.9 Hz, 4H), 7.23 (d, J=8.2, 2H), 7.43 (d, J=8.9 Hz, 4H), 7.50 (d, J=8.2, 2H), 7.52 (d, J=1.9 Hz, 1H), 7.54 ppm (d, J=1.9 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ=20.6, 52.2, 55.2, 110.9, 112.0, 113.7, 118.2, 119.8, 126.1, 127.7, 129.4, 130.8, 134.2, 135.8, 136.6, 146.5, 148.5, 159.9, 163.8 ppm; IR (neat): $\tilde{\nu}$=2952w, 1718m, 1609m, 1511m, 1469m, 1248s, 1207s, 1171s, 1028s, 1004m, 931w, 829s, 780w, 756w, 723w, 617w cm^{-1}; HR MALDI MS: m/z: calcd for $C_{30}H_{27}O_6^+$: 483.1802; found: 483.1793 $[M+H]^+$; elemental analysis calcd (%) for $C_{30}H_{26}O_6$ (482.17): C 74.67, H 5.43; found: C 74.76, H 5.51.

2,2-Bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxylic acid (28): The biphasic mixture of a solution of **39** (370 mg, 0.77 mmol) in THF (10 mL) and a solution of LiOH·H_2O (161 mg, 3.8 mmol) in H_2O (10 mL) was heated at reflux for 3 h. A saturated solution of NH_4Cl (aq) was added, and the mixture partitioned between EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc (20 mL), and the combined organic fractions were washed twice with a saturated solution of NaCl (aq) before being dried over $MgSO_4$ and evaporated in vacuo to yield **28** as a white solid (334 mg, 93%): mp: 68–70 °C; ^{1}H NMR (300 MHz, $[D_8]$THF): δ=2.33 (s, 3H), 3.76 (s, 6H), 6.89 (d, J=8.8 Hz, 4H), 7.18 (d, J=8.2, 2H), 7.29 (d, J=1.9 Hz, 1H), 7.45 (d, J=8.2, 2H), 7.49 (d, J=8.8 Hz, 4H), 7.64 ppm (d, J=1.9 Hz, 1H); ^{13}C NMR (75 MHz, $[D_8]$THF): δ=21.1, 55.5, 111.2, 114.2, 114.4, 119.4, 122.0, 127.2,

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128.9, 130.2, 133.1, 135.5, 137.5, 138.3, 148.6, 150.1, 161.5, 165.7 ppm; IR (neat): $\tilde{\nu}$ = 2835w, 1599m, 1510m, 1464m, 1416w, 1305w, 1284w, 1247s, 1205s, 1168s, 1050w, 1025s, 951w, 927w, 828s, 769m, 722w, 683w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{29}H_{25}O_6^+$: 469.1646; found: 469.1638 $[M+H]^+$.

9-{3-Deoxy-5-*O*-[(1,1-dimethylethyl)(diphenyl)silyl]-β-D-*threo*-pentofuranosyl}-9*H*-purin-6-amine ((+)-41): A solution of (−)-**40** (11.5 g, 45.77 mmol) and TBDPS-Cl (13.1 mL, 50.4 mmol, 1.1 equiv) in dry pyridine (120 mL) was stirred for 16 h at 20 °C. The solvent was evaporated under decreased pressure, and residual pyridine was removed by co-evaporation with toluene (2×30 mL). The residue partitioned between EtOAc and H_2O, and the aqueous phase was extracted with EtOAc (2×80 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1→9:1) to yield (+)-**41** as a colorless foam (16.14 g, 70%): $[\alpha]_D^{20}$ = +61.9 (*c* = 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 9H), 2.32 (ddd, *J* = 14.0, 4.7, 3.1 Hz, 1H), 2.57 (ddd, *J* = 14.0, 8.9, 5.5 Hz, 1H), 3.64 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.99 (dd, *J* = 11.4, 2.6 Hz, 1H), 4.36 (dtd, *J* = 8.9, 4.7, 2.6 Hz, 1H), 4.51 (bs, 1H), 4.87 (bs, 1H), 5.73 (bs, 2H), 6.16 (d, *J* = 3.3 Hz, 1H), 7.43 (m, 6H), 7.69 (m, 4H), 8.30 (s, 1H), 8.32 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 26.9, 34.9, 65.6, 70.8, 77.1, 86.6, 119.3, 127.8, 127.9, 130.0 (2×), 131.8, 131.9, 135.4, 135.5, 140.2, 149.5, 152.6, 155.2 ppm; IR (neat): $\tilde{\nu}$ = 3136br w, 2930w, 1640m, 1597m, 1471w, 1426w, 1332w, 1301w, 1245w, 1212w, 1110s, 999w, 971w, 824w, 797w, 741w, 700s, 648w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{26}H_{32}N_5O_3Si^+$: 490.2269; found: 490.2262 $[M+H]^+$.

9-{3-Deoxy-2-*O*-[tris(1-methylethyl)silyl]-β-D-*threo*-pentofuranosyl}-9*H*-purin-6-amine ((−)-42): TIPS-OTf (9.16 g, 29.9 mmol) was added to a solution of (+)-**41** (12.59 g, 24.9 mmol) and imidazole (2.04 g, 29.9 mmol) in dry DMF (40 mL), and the mixture was stirred for 16 h at 20 °C. The mixture partitioned between a saturated solution of $NaHCO_3$ (aq) and EtOAc, and the organic phase was washed with saturated NaCl (aq), dried over $MgSO_4$, and evaporated under decreased pressure. The residue was redissolved in MeOH (200 mL), cooled to 0 °C, and NaOH (15 g, 375 mmol) was added. The mixture was stirred for 8 h at 20 °C, then the volatiles were removed under decreased pressure, and the residue partitioned between H_2O and EtOAc. The organic phase was washed with H_2O (2×100 mL), a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield (−)-**42** as a white solid (7.34 g, 73%): mp: 217–218 °C; $[\alpha]_D^{20}$ = −22.8 (*c* = 1.23, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.86 (m, 21H, $((CH_3)_2CH)_3$–Si), 2.43 (ddd, *J* = 12.6, 9.5, 8.3 Hz, 1H, H-C3′), 2.57 (ddd, *J* = 12.6, 6.8, 6.6 Hz, 1H), 3.74 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.99 (dd, *J* = 12.2, 3.1 Hz, 1H), 4.21 (m, 1H), 4.51 (ddd, *J* = 8.3, 6.8, 5.9 Hz, 1H), 6.34 (d, *J* = 5.9 Hz, 1H), 8.17 (s, 1H), 8.44 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 13.2, 18.2, 35.9, 63.8, 74.2, 79.6, 86.2, 119.4, 142.3, 150.7, 153.4, 157.0 ppm; IR (neat): $\tilde{\nu}$ = 3110m, 2941m, 2866m, 1681s, 1607s, 1569w, 1470w, 1423w, 1376w, 1301s, 1246m, 1218w, 1134m, 1090s, 1071s, 1003m, 882m, 827m, 796w, 723w, 692s, 616w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{19}H_{34}N_5O_3Si^+$: 408.2425; found: 408.2431 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{33}N_5O_3Si$ (407.24): C 55.99, H 8.16, N 17.18; found: C 56.09, H 8.07, N 17.11.

Ethyl (2*E*)-3-[(2*S*,4*S*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-4-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-enoate ((+)-43): Compound (−)-**42** (6.8 g, 16.68 mmol), $Ph_3P{=}CHCO_2Et$ (11.63 g, 33.37 mmol), and IBX (8.14 g, 29.23 mmol) were dissolved in Me_2SO (100 mL) and reacted according to *GP A*. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (+)-**43** (7.03 g, 89%) as a white solid: mp: 156–158 °C; $[\alpha]_D^{20}$ = +2.1 (*c* = 1.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (m, 21H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.15 (ddd, *J* = 13.3, 7.3, 5.9 Hz, 1H), 2.69 (ddd, *J* = 13.3, 7.4, 6.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.75 (m, 2H), 5.70 (bs, 2H), 6.05 (dd, *J* = 15.6, 1.5 Hz, 1H), 6.39 (d, *J* = 4.9 Hz, 1H), 7.09 (dd, *J* = 15.6, 5.5 Hz, 1H), 8.06 (s, 1H), 8.34 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 14.3, 17.7, 40.4, 60.7, 72.1, 75.6, 85.1, 119.0, 121.4, 140.4, 145.8, 150.0, 152.8, 155.1, 165.7 ppm; IR (neat): $\tilde{\nu}$ = 3139w, 2941w, 2865w, 1708m, 1677m, 1602s, 1571w, 1471w, 1424w, 1367w, 1305s, 1272w, 1241w, 1211w, 1178s, 1096m, 1075m, 1044m, 995m, 977m, 884m, 825m, 797w, 682s, 650m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{23}H_{38}N_5O_4Si^+$: 476.2688; found: 476.2683 $[M+H]^+$; elemental analysis calcd (%) for $C_{23}H_{37}N_5O_4Si$ (475.26): C 58.08, H 7.84, N 14.72; found: C 57.84, H 7.70, N 14.48.

(2*E*)-3-[(2*S*,4*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-ol ((−)-44): A solution of (+)-**43** (7.0 g, 14.72 mmol) in dry CH_2Cl_2 (120 mL) and DIBAL-H (120 mL of a 1 M solution in CH_2Cl_2) were reacted according to *GP B*. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (−)-**44** (5.38 g, 86%) as a colorless solid: mp: 206–208 °C; $[\alpha]_D^{20}$ = −1.9 (*c* = 1.06, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.87 (m, 21H), 2.15 (dt, *J* = 12.6, 8.4 Hz, 1H), 2.69 (dt, *J* = 12.6, 6.2 Hz, 1H), 4.09 (d, *J* = 4.3 Hz, 2H), 4.60 (m, 1H), 4.91 (m, 1H), 5.94 (m, 2H), 6.33 (d, *J* = 5.7 Hz, 1H), 8.16 (s, 1H), 8.18 ppm (s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ = 11.3, 17.5, 60.6, 72.0, 76.9, 83.0, 118.0, 128.6, 133.5, 139.7, 149.5, 152.2, 155.6 ppm; one peak missing due to overlap with the solvent signal; IR (neat): $\tilde{\nu}$ = 3305w, 3129w, 2943w, 2866w, 1662m, 1602m, 1573w, 1469w, 1424w, 1374w, 1299w, 1253w, 1210w, 1147w, 1094s, 1064s, 993w, 946w, 927w, 885m, 834w, 796w, 681m, 645m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{21}H_{36}N_5O_3Si^+$: 434.2587; found: 434.2580 $[M+H]^+$; elemental analysis calcd (%) for $C_{21}H_{35}N_5O_3Si$ (433.25): C 58.17, H 8.14, N 16.15; found: C 58.43, H 7.93, N 15.86.

2-{(2*E*)-3-[(2*S*,4*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((+)-45): Compound (−)-**44** (2 g, 4.61 mmol), DIAD (1.4 g, 6.92 mmol), PPh_3 (1.82 g, 6.92 mmol), and phthalimide (1.21 g, 6.92 mmol) in THF (60 mL) were reacted according to *GP C*. Solvent removal under decreased pressure and CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (+)-**45** (2 g, 77%) as a colorless foam: $[\alpha]_D^{20}$ = +4.1 (*c* = 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (m, 21H), 2.08 (ddd, *J* = 13.2, 7.7, 6.4 Hz, 1H), 2.57 (dt, *J* = 13.2, 6.4 Hz, 1H), 4.31 (d, *J* = 5.8 Hz, 2H), 4.54 (q, *J* = 6.4 Hz, 1H), 4.91 (q, *J* = 6.4 Hz, 1H), 5.71 (bs, 2H), 5.83 (dtd, *J* = 15.3, 5.7, 0.7 Hz, 1H), 5.97 (ddt, *J* = 15.3, 6.4, 1.0 Hz, 1H), 6.31 (d, *J* = 5.1 Hz, 1H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 8.02 (s, 1H), 8.30 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 17.7, 38.8, 40.3, 72.3, 76.8, 84.7, 119.0, 123.3, 126.2, 131.9, 132.8, 133.9, 140.5, 150.0, 152.7, 155.1, 167.6 ppm; IR (neat): $\tilde{\nu}$ = 3357br w, 2942w, 2865w, 1711s, 1645m, 1597m, 1468w, 1423w, 1393m, 1331w, 1298w, 1244w, 1058m, 939w, 882w, 829w, 796w, 721m, 685m, 652m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{29}H_{39}N_6O_4Si^+$: 563.2797; found: 563.2788 $[M+H]^+$.

2-{(2*E*)-3-[(2*S*,4*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((+)-46): A solution of (+)-**45** (1.5 g, 2.67 mmol) in dry THF (20 mL) was cooled to 0 °C and treated with nBu_4NF (3.2 mL of a 1 M solution in THF). After stirring for 5 min at 0 °C, the reaction was quenched by the addition of a saturated solution of NH_4Cl (aq, 10 mL) and the mixture partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with H_2O (40 mL), a saturated solution of NaCl (aq, 40 mL), dried over $MgSO_4$, and evaporated under decreased pres-

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sure. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield (+)-**46** as a colorless foam (970 mg, 90%): $[\alpha]_D^{20} = +20.7$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.00$ (ddd, $J = 13.3$, 7.6, 6.4 Hz, 1H), 2.57 (dt, $J = 13.3$, 6.7 Hz, 1H), 4.30 (dd, $J = 5.6$, 0.8 Hz, 2H), 4.59 (m, 2H), 5.83 (dtd, $J = 15.5$, 5.5, 0.7 Hz, 1H), 6.03 (ddt, $J = 15.5$, 6.9, 1.3 Hz, 1H), 6.19 (d, $J = 5.0$ Hz, 1H), 7.79 (m, 2H), 7.85 (m, 2H), 8.15 (s, 1H), 8.18 ppm (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta =$ 39.7, 39.8, 72.2, 78.8, 86.9, 119.5, 124.1, 127.5, 133.2, 134.0, 135.2, 141.9, 150.4, 153.4, 156.9, 169.1 ppm; IR (neat): $\tilde{\nu} = 3133$br w, 1704s, 1635m, 1597m, 1469w, 1394m, 1332w, 1298w, 1244w, 1210w, 1055m, 941w, 797w, 718m, 648w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{20}H_{18}N_6NaO_4^+$: 429.1282; found: 429.1288 $[M+Na]^+$.

2-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((−)-47): Compound (+)-**46** (200 mg, 0.98 mmol), DIAD (200 mg, 0.98 mmol), PPh_3 (260 mg, 0.98 mmol), and $(PhO)_2PON_3$ (270 mg, 0.98 mmol) were reacted according to *GP C*. Solvent removal under decreased pressure and CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (−)-**47** (152 mg, 72%) as a colorless foam: $[\alpha]_D^{20} = -37.3$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 2.28$ (m, 2H), 4.33 (dd, $J = 4.3$, 0.8 Hz, 2H), 4.83 (m, 2H), 5.90 (m, 2H), 5.96 (d, $J = 1.7$ Hz, 1H), 6.00 (bs, 2H), 7.72 (dd, $J = 5.5$, 3.1 Hz, 2H), 7.86 (dd, $J = 5.5$, 3.1 Hz, 2H), 7.90 (s, 1H), 8.30 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 35.9$, 38.8, 65.5, 80.4, 89.9, 120.2, 127.9, 131.3, 131.8, 134.0, 138.5, 148.9, 153.0, 155.4, 167.6 ppm; IR (neat): $\tilde{\nu} = 3168$br w, 2106m, 1706s, 1634m, 1597m, 1469w, 1426w, 1394m, 1329m, 1294m, 1246m, 1047m, 951w, 797w, 719m, 648w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{20}H_{18}N_9O_3^+$: 432.1527; found: 432.1521 $[M+H]^+$.

9-{(2*R*,3*R*,5*S*)-5-[(1*E*)-3-Aminoprop-1-en-1-yl]-3-azidotetrahydrofuran-2-yl}-9*H*-purin-6-amine ((−)-48): Reaction of (−)-**47** (200 mg, 0.46 mmol) with $MeNH_2$ (15 mL of an 8 M solution in EtOH) and purification according to *GP D*, *Method B*, afforded (−)-**48** (100 mg, 72%) as a colorless foam: $[\alpha]_D^{20} = -52.1$ ($c = 0.72$, $(CH_3)_2SO$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.55$ (bs, 2H), 2.28 (m, 2H), 3.37 (dd, $J = 5.2$, 1.6 Hz, 2H), 4.85 (m, 2H), 5.74 (ddt, $J = 15.3$, 7.4, 1.6 Hz, 1H), 5.98 (m, 4H), 7.03 (s, 1H), 8.34 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 36.2$, 43.3, 65.7, 81.3, 90.0, 120.3, 126.8, 136.7, 138.5, 148.9, 153.0, 155.4 ppm; IR (neat): $\tilde{\nu} = 3311$w, 3157w, 2101s, 1644s, 1597s, 1574m, 1473w, 1418w, 1364w, 1330w, 1297w, 1250m, 1054w, 971w, 910w, 798w, 730m, 646w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{12}H_{16}N_9O^+$: 302.1472; found: 302.1470 $[M+H]^+$.

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-2-[3-(methoxy)phenyl]-2-[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxamide ((−)-49)**: Amide coupling of (−)-**48** (100 mg, 0.33 mmol) with **27** (183 mg, 0.43 mmol), using EDC·HCl (124 mg, 0.65 mmol) and *N*-hydroxysuccinimide (56 mg, 0.56 mmol) according to *GP F* yielded (−)-**49** (145 mg, 62%) as a yellowish foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1): $[\alpha]_D^{20} = -20.6$ ($c = 0.63$, $(CH_3)_2SO$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 4.16 (m, 2H), 4.84 (m, 2H), 5.72 (bs, 2H), 5.84 (dd, $J = 15.5$, 6.7 Hz, 1H), 5.95 (d, $J = 1.8$ Hz, 1H), 5.96 (dt, $J = 15.5$, 5.4 Hz, 1H), 6.90 (dd, $J = 8.9$, 2.3 Hz, 4H), 7.13 (t, $J = 5.8$ Hz, 1H), 7.39 (d, $J = 8.9$ Hz, 4H), 7.81 (d, $J = 2.5$ Hz, 1H), 7.86 (s, 1H), 8.29 (s, 1H), 8.60 ppm (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 36.2$, 41.1, 55.4, 65.5, 80.6, 89.9, 106.6, 113.5, 113.8, 114.7, 120.3, 122.3, 128.1, 129.4, 129.6, 130.5, 138.6, 142.9, 148.1, 149.0, 149.5, 153.1, 155.3, 160.9, 161.3 ppm; IR (neat): $\tilde{\nu} = 3323$w, 2932w, 2106m, 1643m, 1608m, 1513m, 1463m, 1336m, 1244s, 1208m, 1173s, 1024m, 1003m, 828m, 742w, 647w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{34}H_{30}N_{10}NaO_8^+$: 729.2140; found: 729.2150 $[M+H]^+$.

(2*R*,3*R*,5*S*)-2-(6-Amino-9*H*-purin-9-yl)-5-[(1*E*)-3-{[(2,3-dihydroxy-5-nitrophenyl)carbonyl]amino}prop-1-en-1-yl]tetrahydrofuran-3-aminium trifluoroacetate ((−)-11): Reaction of (−)-**49** (75 mg, 0.106 mmol) with 1,3-propanedithiol (115 mg, 1.06 mmol) and Et_3N (110 mg, 1.06 mmol) in MeOH (5 mL) according to *GP E*, *Method B*, followed by acid-catalyzed ketal deprotection according to *GP G* and subsequent purification by RP HPLC (0.1% TFA in H_2O/CH_3CN) yielded (−)-**11** (48 mg, 80%) as a fluffy yellow solid after lyophilization: $[\alpha]_D^{20} = -13.8$ ($c = 0.69$, $(CD_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): $\delta = 2.34$ (ddd, $J = 13.7$, 6.5, 3.3 Hz, 1H), 2.54 (m, 1H), 3.95 (m, 2H), 4.55 (m, 1H), 4.85 (m, 1H), 5.81 (m, 2H), 6.14 (d, $J = 3.8$ Hz, 1H), 7.71 (d, $J = 2.7$ Hz, 1H), 7.83 (bs, 1H), 8.22 (s, 1H), 8.41 (s, 1H), 8.42 (d, $J = 2.7$ Hz, 1H), 8.52 (bs, 2H), 9.43 (t, $J = 5.6$ Hz, 1H), 10.46 ppm (bs, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): $\delta = 35.3$, 42.3, 54.1, 78.9, 86.2, 112.0, 114.3, 114.5, 118.9, 129.6, 129.9, 138.3, 140.4, 147.0, 148.9, 151.1, 154.8, 156.2, 167.8 ppm; IR (neat): $\tilde{\nu} = 3091$br w, 1668s, 1513m, 1433w, 1335m, 1286m, 1183s, 1130s, 970w, 838w, 798m, 721m, 641w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{19}H_{21}N_8O_6^+$: 457.1579; found: 457.1573 $[M+H]^+$.

***N*-{(2*E*)-3-[(2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-2,3-dihydroxy-5-nitrobenzamide ((+)-10)**: Compound **53** (84 mg, 0.28 mmol) was added to a solution of (+)-**52** (85 mg, 0.28 mmol) and Et_3N (0.3 mL) in DMF (4 mL) and the mixture was stirred for 16 h at 20 °C. Purification by RP HPLC (0.1% HCO_2H in H_2O/CH_3CN) yielded (+)-**10** (120 mg, 88%) as a fluffy yellowish solid: $[\alpha]_D^{20} = +2.9$ ($c = 0.79$, $(CD_3)_2SO$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$): $\delta = 2.55$ (m, 1H), 3.01 (ddd, $J = 13.4$, 7.2, 5.1 Hz, 1H), 3.96 (m, 2H), 4.37 (m, 1H), 4.61 (q, $J = 6.8$ Hz, 1H), 5.89 (m, 2H), 6.14 (dd, $J = 7.3$, 5.1 Hz, 1H), 7.45 (bs, 2H), 7.69 (d, $J = 2.7$ Hz, 1H), 8.11 (s, 1H), 8.35 (s, 1H), 8.43 (d, $J = 2.7$ Hz, 1H), 9.51 (t, $J = 5.4$ Hz, 1H), 10.40 ppm (bs, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): $\delta = 35.6$, 38.7, 63.4, 82.4, 83.7, 111.6, 114.0, 114.6, 119.0, 128.6, 130.7, 137.9, 139.7, 146.8, 148.7, 151.8, 155.3, 156.5, 167.7 ppm; IR (neat): $\tilde{\nu} = 3344$w, 3092br w, 2105m, 1642m, 1513m, 1471m, 1331s, 1246s, 1085w, 970w, 796w, 742w, 705w, 646w cm^{-1}; HR ESI MS: *m/z*: calcd for $C_{19}H_{19}N_{10}O_6^+$: 483.1484; found: 483.1489 $[M+H]^+$.

(2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2-[(1*E*)-3-{[(2,3-dihydroxy-5-nitrophenyl)carbonyl]amino}prop-1-en-1-yl]tetrahydrofuran-3-aminium formate ((−)-8): Compound (+)-**10** (90 mg, 0.186 mmol) was reacted with 1,3-propanedithiol (202 mg, 1.86 mmol) and Et_3N (190 mg, 1.86 mmol) in MeOH (7 mL) according to *GP E*, *Method B*. Purification by RP HPLC (0.1% HCO_2H in H_2O/CH_3CN) yielded (−)-**8** (53 mg, 57%) as a fluffy white solid: $[\alpha]_D^{20} = -31.8$ ($c = 1.0$, $(CD_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): $\delta = 2.57$ (ddd, $J = 13.5$, 7.1, 6.3 Hz, 1H), 3.01 (ddd, $J = 13.5$, 8.0, 5.7 Hz, 1H), 3.98 (t, $J = 5.0$ Hz, 2H), 4.08 (dt, $J = 8.0$, 6.3 Hz, 1H), 4.47 (t, $J = 6.3$ Hz, 1H), 5.80 (ddt, $J = 15.5$, 6.3, 1.3 Hz, 1H), 5.89 (dt, $J = 15.5$, 5.0 Hz, 1H), 6.42 (dd, $J = 7.1$, 5.7 Hz, 1H), 7.24 (d, $J = 3.2$ Hz, 1H), 7.31 (bs, 2H), 8.15 (s, 1H), 8.33 (s, 1H), 8.33 (d, $J = 3.2$ Hz, 1H), 10.89 ppm (t, $J = 5.7$ Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): $\delta = 35.0$, 39.0, 53.7, 82.2, 82.6, 104.1, 114.3, 119.1, 120.7, 126.4, 129.3, 132.7, 139.5, 148.9, 149.0, 152.7, 156.0, 163.0, 168.3 ppm; IR (neat): $\tilde{\nu} = 3170$br m, 1598m, 1475m, 1240s, 1078m, 983w, 798w, 703w, 647w cm^{-1}; HR ESI MS: *m/z*: calcd for $C_{19}H_{21}N_8O_6^+$: 457.1579; found: 457.1571 $[M+H]^+$.

6-Chloro-9-[(3a*S*,4*R*,6*R*,6a*R*)-6-ethenyl-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]-9*H*-purine ((+)-55): Compound (−)-**54** (1.09 g, 5.92 mmol), DIAD (2.67 g, 12.42 mmol), PPh_3 (3.26 g, 12.42 mmol), and 6-chloropurine (1.46 g, 9.47 mmol) in dry THF (20 mL) were reacted according to *GP H*. Solvent removal under decreased pressure and CC (SiO_2; EtOAc/hexane 1:1) provided (+)-**55** (1.44 g, 76%) as a white solid: mp: 65–66 °C; $[\alpha]_D^{20} = +9.4$ ($c = 0.63$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H), 1.59 (s, 3H),

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2.54 (m, 2H), 2.85 (m, 1H), 4.66 (dd, $J=7.3$, 6.3 Hz, 1H), 4.85 (ddd, $J=10.8$, 7.7, 5.2 Hz, 1H), 5.08 (dd, $J=7.3$, 5.2 Hz, 1H), 5.16 (dt, $J=10.3$, 1.3 Hz, 1H), 5.21 (dt, $J=17.2$, 1.3 Hz, 1H), 5.95 (ddd, $J=17.2$, 10.3, 7.0 Hz, 1H), 8.16 (s, 1H), 8.75 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.0$, 27.4, 36.2, 47.8, 62.1, 83.3, 83.8, 114.2, 116.3, 132.3, 137.2, 144.5, 151.3, 151.6, 151.7 ppm; IR (neat): $\tilde{\nu}=3072$w, 2981w, 2927w, 1746w, 1642w, 1597s, 1557s, 1491w, 1436w, 1436w, 1402m, 1378m, 1344m, 1304w, 1258m, 1198s, 1066s, 936m, 916s, 864s, 839s, 790w, 689w, 637s cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{15}H_{18}ClN_4O_2^+$: 321.1113; found: 321.1112 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{17}ClN_4O_2$ (320.10): C 56.17, H 5.34, N 17.47; found: C 56.13, H 5.31, N 17.37.

(2*E*)-3-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]prop-2-en-1-ol ((+)-56): $NaIO_4$ (1.33 g, 6.22 mmol) and OsO_4 (11 mg, 0.042 mmol) were added to a solution of (+)-**55** (1.33 g, 4.15 mmol) in MeOH (20 mL) and H_2O (10 mL) at 0 °C. The resulting suspension was stirred for 1 h at 0 °C, then for 3 h at 20 °C. The white precipitate was removed by filtration, and volatiles were evaporated under decreased pressure at 20 °C. The residue partitioned between H_2O and CH_2Cl_2, and the organic phase was washed with a saturated solution of NaCl (aq), dried over $MgSO_4$, and evaporated under decreased pressure at 20 °C. To an ice-cold solution of the residue in dry toluene (25 mL), Ph_3P=CHCHO (2.53 g, 8.3 mmol) was added, and the mixture was stirred for 16 h at 4 °C. The reaction was quenched by the addition of H_2O (25 mL), and the mixture partitioned between H_2O and EtOAc. The organic phase was dried over $MgSO_4$, evaporated under decreased pressure, and the residue was redissolved in MeOH (20 mL). $CeCl_3\cdot 7H_2O$ (3.1 g, 8.3 mmol) was added to the solution at 0 °C, followed by $NaBH_4$ (314 mg, 8.3 mmol) over 15 min. The mixture was stirred for 20 min at 20 °C, quenched by the addition of H_2O, and extracted with CH_2Cl_2 (3× 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (+)-**56** (600 mg, 41%) as a colorless foam: $[\alpha]_D^{20}=+12.2$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.23$ (s, 3H), 1.50 (s, 3H), 2.46 (m, 2H), 2.78 (m, 2H), 4.10 (m, 2H), 4.59 (t, $J=7.0$ Hz, 1H), 4.81 (ddd, $J=10.9$, 7.4, 5.2 Hz, 1H), 5.01 (dd, $J=7.0$, 5.2 Hz, 1H), 5.76 (m, 2H), 8.17 (s, 1H), 8.66 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=24.9$, 27.2, 36.4, 46.5, 61.9, 62.8, 83.1, 83.7, 114.1, 130.1, 131.1, 132.0, 144.6, 151.0, 151.4, 151.5 ppm; IR (neat): $\tilde{\nu}=3380$br w, 2984w, 1591s, 1558s, 1492w, 1399m, 1336s, 1201s, 1151m, 1067s, 942s, 862s, 791w, 647s cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{16}H_{20}ClN_4O_3^+$: 351.1218; found: 351.1212 $[M+H]^+$.

(2*E*)-3-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]prop-2-en-1-ol ((+)-57): A solution of (+)-**56** (580 mg, 1.65 mmol) in MeOH (20 mL) was saturated with NH_3 at 0 °C and reacted according to *GP I*. Solvent removal and CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (+)-**57** (430 mg, 79%) as a colorless foam: $[\alpha]_D^{20}=+30.4°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.27$ (s, 3H), 1.54 (s, 3H), 2.44 (m, 2H), 2.78 (m, 1H), 4.14 (d, $J=2.9$ Hz, 2H), 4.61 (t, $J=7.0$ Hz, 1H), 4.73 (ddd, $J=11.2$, 7.0, 5.1 Hz, 1H), 5.05 (dd, $J=7.0$, 5.1 Hz, 1H), 5.79 (m, $J=3.1$ Hz, 2H), 6.38 (bs, 2H), 7.81 (s, 1H), 8.28 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=24.9$, 27.3, 36.6, 46.6, 61.2, 62.3, 83.2, 83.7, 113.7, 119.7, 130.1, 130.9, 139.4, 149.2, 152.3, 155.6 ppm; IR (neat): $\tilde{\nu}=3322$m, 3177m, 2986w, 2930w, 1639s, 1597s, 1476m, 1415w, 1375m, 1300w, 1248m, 1206m, 1156m, 1063s, 971m, 858m, 798m, 648m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{16}H_{22}N_5O_3^+$: 332.1717; found: 332.1713 $[M+H]^+$.

(3a*R*,4*R*,6*S*,6a*S*)-4-Ethenyl-2,2-dimethyl-6-[(phenylmethyl)oxy]tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole ((−)-61): NaH (1.96 g, 48.9 mmol, 60% in mineral oil) was added to an ice-cold solution of (−)-**54** (4.5 g, 24.44 mmol) in dry THF (280 mL). The mixture was stirred for 30 min at 0 °C, then nBu$_4$NI (4.51 g, 12.22 mmol) and benzyl bromide (12.54 g, 73.33 mmol) were added. Stirring was continued for 16 h at 20 °C, then the reaction was quenched by the addition of a saturated solution of NH_4Cl (aq, 200 mL). The aqueous phase was extracted with EtOAc (2×200 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure. CC (SiO_2; hexane/EtOAc 6:1) yielded (−)-**61** (6.18 g, 93%) as a colorless oil: $[\alpha]_D^{20}=-61.2$ ($c=0.82$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.33$ (s, 3H), 1.54 (s, 3H), 1.82 (ddt, $J=12.3$, 5.9, 0.9 Hz, 1H), 2.12 (m, 1H), 2.68 (t, $J=6.6$ Hz, 1H), 3.81 (dt, $J=10.3$, 5.2 Hz, 1H), 4.41 (d, $J=5.5$ Hz, 1H), 4.56 (t, $J=5.5$ Hz, 1H), 4.58 (d, $J=12.3$ Hz, 1H), 4.70 (d, $J=12.3$ Hz, 1H), 5.99 (dt, $J=10.2$, 1.3 Hz 1H), 5.00 (dt, $J=17.7$, 1.3 Hz, 1H), 5.68 (ddd, $J=17.7$, 10.2, 6.6 Hz, 1H), 7.33 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=24.3$, 26.2, 31.9, 44.0, 71.7, 77.8, 78.2, 83.8, 110.7, 114.7, 127.4, 127.6, 128.1, 138.1, 138.3 ppm; IR (neat): $\tilde{\nu}=2981$s, 2931s, 1638w, 1496w, 1373s, 1252w, 1208s, 1164w, 1114s, 1044s, 915m, 886m, 739s, 699s cm^{-1}; HR EI MS: *m/z*: calcd for $C_{17}H_{22}O_3^+$: 274.1564; found: 274.1563 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{22}O_3$ (274.16): C 74.42, H 8.08; found: C 74.13, H 8.10.

Ethyl (2*E*)-3-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-dimethyl-6-[(phenylmethyl)oxy]-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}prop-2-enoate ((−)-62): $NaIO_4$ (7.0 g, 32.75 mmol) and OsO_4 (56 mg, 0.218 mmol) were added to a solution of (−)-**61** (5.98 g, 21.83 mmol) in MeOH (100 mL) and H_2O (50 mL) at 0 °C. The resulting suspension was stirred for 1 h at 0 °C, then for 2 h at 20 °C. The white precipitate was removed by filtration, and the filtrate partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (4× 150 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure at 20 °C. Ph_3P=$CHCO_2Et$ (15.21 g, 43.67 mmol) was added to an ice-cold solution of the residue in dry toluene (200 mL), and the mixture was stirred for 16 h at 4 °C. The reaction was quenched by the addition of H_2O (200 mL), and the mixture partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (3×200 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated under decreased pressure. CC (SiO_2; hexane/EtOAc 5:1) yielded (−)-**62** (4.82 g, 64%) as a colorless oil: $[\alpha]_D^{20}=-44.9$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.27$ (t, $J=7.1$ Hz, 3H), 1.32 (s, 3H), 1.53 (s, 3H), 1.82 (ddt, $J=11.9$, 5.2, 1.2 Hz, 1H), 2.16 (m, 1H), 2.81 (td, $J=7.2$, 1.2 Hz, 1H), 3.79 (dt, $J=10.4$, 5.2 Hz, 1H), 4.17 (q, $J=7.1$ Hz, 2H), 4.43 (d, $J=5.7$ Hz, 1H), 4.56 (d, $J=12.0$ Hz, 1H), 4.56 (t, $J=5.7$ Hz, 1H), 4.69 (d, $J=12.0$ Hz, 1H), 5.78 (dd, $J=15.8$, 1.7 Hz, 1H), 6.79 (dd, $J=15.8$, 7.2 Hz, 1H), 7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=14.1$, 24.2, 26.1, 32.1, 43.4, 60.3, 71.9, 77.7, 78.2, 83.2, 111.3, 121.6, 127.6, 127.7, 128.3, 138.1, 148.0, 166.1 ppm; IR (neat): $\tilde{\nu}=2981$m, 1718s, 1651w, 1452w, 1372m, 1268w, 1169m, 1113m, 1039m, 868w, 739w, 699w cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{20}H_{26}NaO_5^+$: 369.1672; found: 369.1666 $[M+Na]^+$.

(2*E*)-3-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-[(phenylmethyl)oxy]tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}prop-2-en-1-ol ((−)-63): A solution of (−)-**62** (4.45 g, 12.9 mmol) in dry CH_2Cl_2 (150 mL) and DIBAL-H (51 mL of a 1 M solution in CH_2Cl_2) were reacted according to *GP B*. Workup followed by CC (SiO_2; EtOAc/hexane 1:1) provided (−)-**63** (3.17 g, 81%) as a colorless oil: $[\alpha]_D^{20}=-52.2$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.33$ (s, 3H), 1.53 (s, 3H), 1.80 (ddt, $J=12.2$, 5.4, 0.9 Hz, 1H), 2.12 (ddd, $J=12.2$, 10.6, 7.4 Hz, 1H), 2.69 (t, $J=6.0$ Hz, 1H), 3.81 (dt, $J=10.6$, 5.4 Hz, 1H), 4.07 (t, $J=4.7$ Hz, 2H), 4.39 (d, $J=5.6$ Hz, 1H), 4.56 (t, $J=5.6$ Hz, 1H), 4.58 (d, $J=12.2$ Hz, 1H), 4.70 (d, $J=12.2$ Hz, 1H), 5.51 (dd, $J=15.7$, 6.0 Hz, 1H),

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5.60 (dt, $J=15.7$, 4.7 Hz, 1H), 7.33 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=24.5$, 26.4, 43.3, 63.5, 72.0, 78.1, 78.5, 84.5, 111.3, 127.8, 128.0, 128.5, 129.8, 132.3, 138.6 ppm; IR ($CHCl_3$): $\tilde{\nu}=3618$m, 3458w, 3007s, 2963s, 2930s, 2873s, 1455m, 1374m, 1163m, 1106s, 1046s, 876m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{18}H_{24}NaO_4^+$: 327.1572; found: 327.1553 $[M+Na]^+$; elemental analysis calcd (%) for $C_{18}H_{24}O_4$ (304.17): C 71.03, H 7.95; found: C 71.00, H 7.97.

[(1*R*,2*R*)-2-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-[(phenylmethyl)oxy]-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}cyclopropyl]methanol ((−)-65): Et_2Zn (23 mL of a 1 M solution in hexane) was slowly added to a solution of DME (2.4 g, 26.7 mmol) in dry CH_2Cl_2 (17 mL) at −25 °C (internal temperature), followed by CH_2I_2 (4.22 mL, 52.4 mmol). This mixture was stirred for 20 min at −25 °C before being slowly transferred by cannula to a solution of (−)-**64** (2.24 g, 8.2 mmol) and (−)-**63** (1.40 g, 4.6 mmol) in dry CH_2Cl_2 (14 mL) at −30 °C, while maintaining the internal temperature between −30 °C and −25 °C. The mixture was stirred for 18 h at 20 °C, then the reaction was quenched by the addition of a saturated solution of NH_4Cl (aq) and partitioned between H_2O and Et_2O. The aqueous phase was extracted with Et_2O (2×100 mL), and the combined organic fractions were concentrated to ≈200 mL. A solution of KOH (5 M, 200 mL) was added, and the biphasic mixture was vigorously stirred for 6 h at 20 °C. The organic phase was washed with a saturated solution of NaCl (aq), dried over $MgSO_4$, and concentrated in vacuo. The diastereomeric ratio was determined by analytical HPLC (97:3 d.r.). CC (SiO_2; EtOAc/hexane 1:2) with analytical HPLC to verify the purity of the product fractions yielded (−)-**65** (1.46 g, quant.) as a colorless oil: $t_R=8.7$ min; $[\alpha]_D^{20}=-39.0$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.40$ (m, 3H), 0.88 (m, 1H), 1.33 (m, 4H), 1.50 (s, 3H), 1.77 (m, 1H), 2.07 (m, 1H), 3.44 (m, 2H), 3.90 (dt, $J=10.7$, 5.5 Hz, 1H), 4.41 (d, $J=5.5$ Hz, 1H), 4.63 (m, 3H), 7.34 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=9.9$, 20.0, 21.5, 24.3, 26.3, 33.3, 45.9, 66.4, 71.8, 78.3, 78.5, 84.3, 111.0, 127.7, 128.0, 128.4, 138.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=3685$w, 3619w, 2927m, 2930s, 1521m, 1423m, 1374m, 1107m, 1106s, 1046s, 929s, 627m cm^{-1}; HR MALDI MS: *m/z*: calcd for $C_{19}H_{26}NaO_4^+$: 341.1723; found: 341.1724 $[M+Na]^+$.

[(1*R*,2*R*)-2-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-[(phenylmethyl)oxy]-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}cyclopropyl]methyl acetate ((−)-67): Ac_2O (4.75 mL, 50.3 mmol) and DMAP (30 mg, 0.5 mmol) were added to a solution of (−)-**65** (1.6 g, 5.0 mmol) in dry pyridine (25 mL). The mixture was stirred for 14 h at 20 °C and subsequently partitioned between H_2O and EtOAc. The organic phase was washed with a saturated solution of $KHCO_3$ (aq, 2× 50 mL) and a saturated solution of NH_4Cl (aq, 2×50 mL) before being dried over $MgSO_4$ and evaporated under decreased pressure. CC (SiO_2; EtOAc/hexane 1:2) yielded (−)-**67** (1.41 g, 83%) as a colorless oil: $[\alpha]_D^{20}=-31.5$ ($c=1.11$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.45$ (m, 3H), 0.91 (m, 1H), 1.30 (m, 4H), 1.48 (s, 3H), 1.74 (dd, $J=12.1$, 6.0 Hz, 1H), 2.03 (m, 4H), 3.74 (dd, $J=11.3$, 7.9 Hz, 1H), 3.90 (m, 2H), 4.38 (d, $J=5.4$ Hz, 1H), 4.58 (d, $J=12.1$ Hz, 1H), 4.59 (t, $J=5.4$ Hz, 1H), 4.69 (d, $J=12.1$ Hz, 1H), 7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.2$, 17.6, 20.5, 20.9, 24.2, 26.1, 33.0, 45.7, 67.8, 71.6, 78.1, 78.2, 84.0, 110.7, 127.5, 127.7, 128.2, 138.2, 170.9 ppm; IR (neat): $\tilde{\nu}=2933$w, 1735s, 1454w, 1369m, 1236s, 1164w, 1115m, 1034m, 819m, 739m, 701w, 631m cm^{-1}; HR EI MS: *m/z*: calcd for $C_{21}H_{28}O_5^+$: 360.1932; found: 360.1931 $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{28}O_5$ (360.19): C 69.98, H 7.83; found: C 69.91, H 8.12.

{(1*R*,2*R*)-2-[(3a*R*,4*R*,6*S*,6a*S*)-6-Hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methyl acetate ((−)-68): Pd/C (10%, 140 mg) was added to a solution of (−)-**67** (1.4 g, 3.88 mmol) in MeOH (30 mL), and the mixture was stirred for 14 h at 20 °C under an atmosphere of H_2. Filtration of the mixture over celite and concentration under decreased pressure provided (−)-**68** (1.05 g, quant.) as a colorless oil: $[\alpha]_D^{20}=-16.8$ ($c=0.58$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.47$ (m, 3H,), 0.94 (m, 1H), 1.32 (s, 3H), 1.39 (m, 1H), 1.45 (s, 3H), 1.81 (m, 2H), 2.04 (s, 3H), 3.74 (dd, $J=11.5$, 8.0 Hz, 1H), 3.97 (dd, $J=11.5$, 6.6 Hz, 1H), 4.12 (dt, $J=8.5$, 5.7 Hz, 1H), 4.46 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.3$, 17.4, 20.1, 21.1, 24.3, 26.0, 36.9, 45.6, 68.0, 71.4, 79.0, 84.3, 111.3, 170.9 ppm; IR (neat): $\tilde{\nu}=3484$br w, 2989s, 2937w, 1735s, 1370m, 1236s, 1209s, 1162w, 1094m, 1039m, 969w, 878w, 633w cm^{-1}; HR EI MS: *m/z*: calcd for $C_{14}H_{22}O_5^+$: 270.1462; found: 270.1461 $[M]^+$.

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Keywords: aristeromycin analogues · bisubstrate inhibitors · catechol *O*-methyltransferase · medicinal chemistry · structure-based design

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