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Synthesis of Enantiomerically Pure (Purin-6-yl)phenylalanines and Their Nucleosides, a Novel Type of Purine-Amino Acid Conjugates

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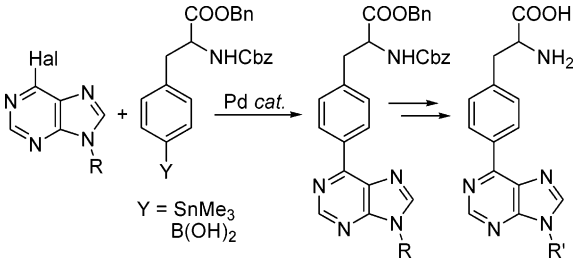

Enantiomerically or diastereomerically pure 4-(purin-6-yl)phenylalanines, a novel type of stable amino acid-purine conjugates, were synthesized by palladium-catalyzed cross-coupling reactions of protected 4-boronophenylalanines or 4-(trimethylstanyl)phenylalanines with diverse 6-halopurines (9-benzyl-6-halopurines and 9-(tetrahydropyran-2-yl)-6-halopurines as well as acyl- and silyl-protected 6-halopurine ribonucleosides and 2-deoxyribonucleosides). Free purine bases and nucleosides bearing (*S*)- or (*R*)-phenylalanine in position 6 were obtained after complete deprotection of the products of cross-coupling reactions. Reactivity trends for both of these cross-coupling and deprotection protocols have been compared in terms of practicability, efficiency, and stereoselectivity.

Purine bases and nucleosides bearing C-substituents in position 6 are known to possess cytostatic[1] or antimicrobial[2] activity, and some of them were used as artificial nucleobases in the extension of the genetic alphabet.[3] Cross-coupling reactions are a powerful tool[4] for the synthesis of these compounds but, in most cases, were used only for an introduction of simple unfunctionalized carbon substituents. On the other hand, purines bearing C-substituents containing functional groups (OH, NH_2, COOH, etc.) would provide new exploitable moieties for interactions with complementary nucleobases, enzymes, or receptors while still preserving higher stability toward enzymatic degradation due to the presence of a C−C bond in position 6. However, because of limited synthetic accessibility, such compounds are scarcely reported in the literature. Therefore, an extension of the cross-coupling methodology to functionalized C-substituents represents a useful and challenging goal. Very recently we have reported the synthesis of 6-(hydroxymethyl)purines[5] that exert cytostatic activity and inhibit adenosine deaminase. Another important subclass of these modified purines is carbon−carbon-linked conjugates of purines and amino acids. Such compounds, as hybrids between nucleobases/nucleosides and amino acids, could interact with a number of receptors or enzymes or could serve as building blocks for construction of stable conjugates of nucleic acids and peptides/proteins.[6]

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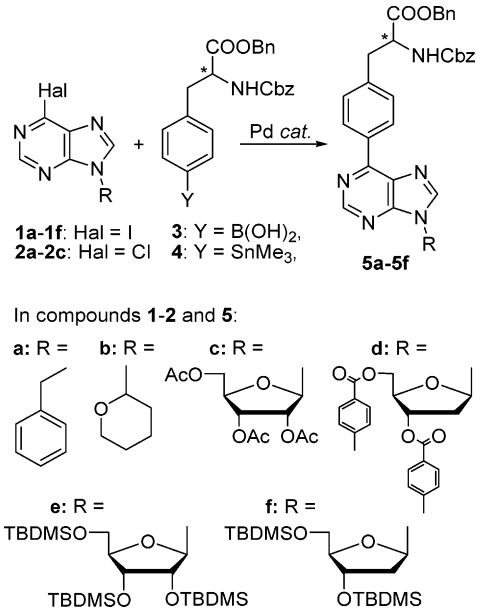
The first type of such conjugates were protected (purin-6-yl)glycines[7] prepared by Pd-catalyzed α-arylation of ethyl *N*-(diphenylmethylidene)glycinate by 6-iodopurines. Unfortunately, as a result of limited stability of the system, we were unable to cleave protective groups. We have succeeded with another type of conjugates, i.e., (purin-6-yl)alanines.[8] They were prepared by Pd(0)-catalyzed cross-coupling reactions of protected iodozincalanines with 6-iodopurines followed by a deprotection sequence. This approach allowed us a simple single-step introduction of a chiral alanine moiety to the target molecule. Enantiomericaly pure (purine-6-yl)alanines were obtained when optically pure amino acid building blocks were used. This paper reports on the synthesis of 4-(purin-6-yl)phenylalanines, the third example of this type of compounds, combining the structural features of cytostatic 6-arylpurines[1] and amino acids and having a longer and bulkier spacer between the amino acid and purine moieties.

Results and Discussion

Our approach toward the synthesis of 4-(purin-6-yl)-phenylalanines is based on palladium-catalyzed cross-coupling reactions of 6-halopurines (**1**, **2**) with organoboron reagent[9,10] (**3**) or organostannane[11] (**4**) derived from phenylalanine (Scheme 1). In general, organoboron[1,12−14] or organotin[15] compounds are established reagents for the introduction of aryl substituents into position 6 of the purine scaffold by cross-coupling reactions. Stannanes are practical because of their good accessibility and solubility in organic solvents and tolerance to most functional groups, while their major drawbacks are toxicity and complicated separation of the products. On the other hand, boronic acids, as well as byproducts of the cross-coupling reactions, are nontoxic, but in some cases there might be problems with stability of functional and/or protecting groups in the basic polar reaction media.

SCHEME 1. General Synthesis of (Purin-6-yl)phenylalanines



Therefore we have decided to explore both of these approaches and compare them in terms of practicability, efficiency, and stereoselectivity.

The starting 4-boronophenylalanine[9] **3** is known in (*S*)-enantiomeric form, and (*R*)-**3** was prepared analogously. New organostannane **4** was prepared in (*S*)- and (*R*)-forms by application of methodology reported for related Boc/Me-protected (*S*)-4-(trimethylstanyl)phenylalanine.[11] There are a few literature examples of use of 4-boronophenylalanines[16,10d−g] as well as the Boc/Me-protected analogue[11a] of organostannane **4** in cross-coupling reactions with simple aryl or hetaryl halides, but in most cases the products were not deprotected and their enantiopurity was not studied thoroughly. No example of cross-coupling reactions of these Phe-derived organometallics with highly functionalized biomolecular systems of limited stability, i.e., nucleosides, was reported so far. Apparently, suitable protecting groups both for amino acid and purine or nucleoside moieties must be selected and the reactions should be performed under mild conditions. The protecting groups must be easily introduced, survive under cross-coupling conditions, and be cleavable under mild conditions. Therefore, the groups of choice were benzyl carbamates for the amino group, benzyl esters for carboxylic function, and acyl (acetyl or 4-toluoyl) or silyl (*tert*-butyldimethylsilyl, TBDMS) ethers for sugar hydroxyl groups.

Suzuki−Miyaura Cross-Coupling Reactions. The Suzuki−Miyaura cross-coupling reactions of 4-(borono)-phenylalanines **3** with 6-halopurines **1** and **2** were investigated at first[17] (Scheme 2, Table 1). Reaction of organoboron **3** with model 6-iodopurine **1a** was performed in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in toluene

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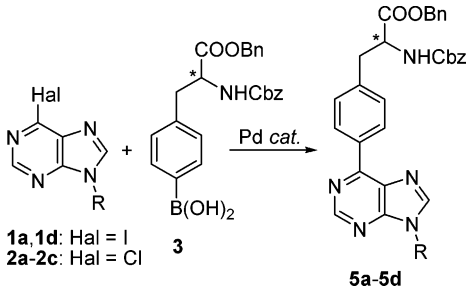
(17) Although direct use of pinacol esters of boronic acids in Suzuki−Miyaura cross-coupling reactions is well-known,[10d−g] reaction of pinacol ester of **3** with 6-iodopurine **1a** gave cross-coupling product in poor yields in preliminary experiments (for details see Supporting Information at http://pubs.acs.org). Therefore, our attention turned to more reactive free boronic acids.

TABLE 1. Cross-Coupling Reactions of 4-(Borono)phenylalanines with 6-Halopurines

entry	purine reagent	product	catalyst	additives	solvent	T [°C]	reaction time [h]	yield [%][a]
1	**1a**	**5a**	$Pd(PPh_3)_4$	K_2CO_3	toluene	100	10	25
2	**1a**	**5a**	$Pd(OAc)_2$ + 1.5 L[b]	K_3PO_4	dioxane	100	6	66
3	**2a**	**5a**	$Pd(OAc)_2$ + 1.5 L[b]	K_3PO_4	dioxane	100	6.5	67
4	**2b**	**5b**	$Pd(OAc)_2$ + 1.5 L[b]	K_3PO_4	dioxane	100	3	74 (*S*)[d]
5	**2c**	**5c**	$Pd(OAc)_2$ + 1.5 L[b]	K_3PO_4	dioxane	100	5	71 (*S*)[e] 70 (*R*)[e]
6	**1d**	**5d**	$Pd(OAc)_2$ + 1.5 L[b]	K_3PO_4	dioxane	100	4	70 (*S*)[e] 73 (*R*)[e]
7	**1a**	**5a**	$Pd(PPh_3)_4$	CuTC[c]	THF	rt	8	25

[a] If no stereochemical descriptor is given, the reactions were performed with racemic organoboron reagent. [b] L = 2-(dicyclohexylphosphino)biphenyl. [c] Copper(I) 2-thiophenecarboxylate. [d] 81% de. [e] Approximately 80% de.

SCHEME 2. Suzuki–Miyaura Cross-Coupling Reactions



(traditional conditions for the synthesis of 6-arylpurines[1,12]) to give the product **5a** in unsatisfactory yield of 25% (Table 1, entry 1). A more efficient catalytic system based on $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl ligand with K_3PO_4 base in dioxane reported by Lakshman[13] as an alternative for the synthesis of 6-phenylpurines was examined in our further experiment with 6-iodopurine **1a** to afford a good isolated yield of product **5a** (66%, entry 2). Similarly to previous findings in the Suzuki–Miyaura reactions of 6-halopurines,[1,12] the use of more readily available 6-chloropurine **2a** gave the same good yield as in the case of the 6-iodo derivative **1a** (entry 3). These conditions were found to be applicable to the cross-coupling reactions of other 9-substituted 6-halopurines (**2b**, **2c**, **1d**) affording the desired products **5b–d** in good yields (entries 4–6). Finally, we explored use of a nonbasic palladium-catalyzed copper-mediated variation of the Suzuki–Miyaura coupling reaction.[18] Reaction of 6-iodopurine **1a** with boronic acid **3** was carried out in the presence of $Pd(PPh_3)$ catalyst and 2 equiv of CuTC in DMF to furnish the product **5a** in a yield of only 25% (entry 7). These findings showed that the Lakshman's methodology[13] was superior in terms of product yields (entries 2–6).

The optical purity of product (*S*)-**5b** prepared under Lakshman's conditions (entry 4) was studied by an indirect method based on use of Marfey's derivatizating reagent (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide), a standard method for determination of optical purity used in peptide chemistry.[19] Reaction of optically pure Marfey's reagent with mixture of (*R*)- and (*S*)-enantiomers of amino acids leads to mixture of epimers. Baseline separation of these epimers by HPLC on C18 column is then used for determination of ratio of (*R*)- and (*S*)- amino acid in the original mixture. In our case, protecting groups of sample (*S*)-**5b** were cleaved by TFA and hydrogenolysis to give free (*S*)-4-(9-*H*-purin-6-yl)phenylalanine. Derivatization of this product by Marfey's reagent and following HPLC analysis showed that the diastereomerical purity of sample (*S*)-**5b** was only 81% de. Going one more step backward, we examined optical purity of starting boronic acid (*S*)-**3** by same methodology. The observed 93% ee indicated that partial racemization took place already during preparation of organoboron reagent (*S*)-**3** according to literature procedure.[20] Optical purity of (*S*)-**5b** is then the result of an accumulation of the undesired enantiomer in the two steps.

Stille Cross-Coupling Reactions. The Stille cross-coupling reactions of 4-(trimethylstanyl)phenylalanine **4** with 6-halopurines **1** and **2** (Scheme 3, Table 2) were investigated in order to develop an alternative, racemization-free route toward the protected (purin-6-yl)-phenylalanines **5**. Initial experiments with 6-iodopurine **1a** and traditional $Pd(PPh_3)_4$ as catalyst in DMF or toluene did not give any product even after 24 h of heating (Table 2, entries 1 and 2). CuI as cocatalyst in DMF (but not in toluene) resulted in formation of the desired product **5a** in low yield (entries 3 and 4). Inspired by work of Morera on the reactivity of 4-(trimethylstanyl)phenylalanines[11] and Farina's studies on positive effects of $AsPh_3$ ligand and polar solvents on Pd(0)-catalyzed Stille reactions,[21,22] we tried a catalytic system consisting of Pd_2dba_3 (0.03 equiv) and $AsPh_3$ (0.12 equiv) in DMF. However, only traces of the desired product **5a** were isolated (9%, entry 5). Then the influence of CuI as cocatalyst in the previous reaction was examined. In contrast to Morera's results,[11] where it was reported that there was virtually no influence of CuI on reactions of organotin reagent **4**, in our case the use of CuI (0.2 equiv) and Pd_2dba_3 (0.03 equiv)/$AsPh_3$ (0.12 equiv) in DMF resulted in complete consumption of the starting iodopurine **1a** after 24 h, and the cross-coupling product **5a** was isolated in 42% yield (entry 6). To verify the influence of the leaving group, the use of 6-chloropurine **2a** was examined under the same conditions. In this case (unlike with boronic acids) a significant difference in reactivity of 6-chloro- and 6-iodopurines was found. The conversion

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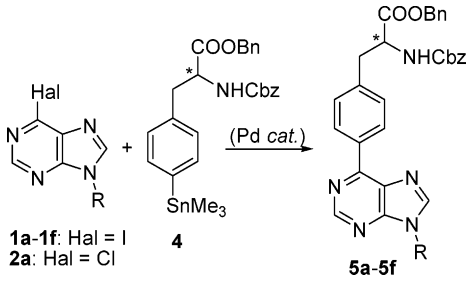
TABLE 2. Cross-Coupling Reactions of 4-(Trimethylstannyl)phenylalanines with 6-Halopurines

entry	purine	product	catalyst	additives (equiv)	T [°C]	reaction time [h]	yield [%][a]
1	**1a**	**5a**	$Pd(PPh_3)_4$	none	80	24	0
2[b]	**1a**	**5a**	$Pd(PPh_3)_4$	none	100	24	0
3	**1a**	**5a**	$Pd(PPh_3)_4$	CuI (0.2)	80	24	9
4[b]	**1a**	**5a**	$Pd(PPh_3)_4$	CuI (0.2)	100	24	0
5	**1a**	**5a**	$Pd_2dba_3 + 4AsPh_3$	none	80	24	9
6	**1a**	**5a**	$Pd_2dba_3 + 4AsPh_3$	CuI (0.2)	80	24	42
7	**2a**	**5a**	$Pd_2dba_3 + 4AsPh_3$	CuI (0.2)	80	24	3
8	**1a**	**5a**	$Pd_2dba_3 + 4AsPh_3$	CuI (0.2) + CsF (2)	80	4	68
9	**1b**	**5b**	$Pd_2dba_3 + 4AsPh_3$	CuI (0.2) + CsF (2)	80	4.5	69 (S)[c]
10	**1a**	**5a**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	80	1	70
11	**1b**	**5b**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	70	4	72 (S)[d] 69 (R)[d]
12	**1c**	**5c**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	70	2.5	72 (S)[d]
13	**1d**	**5d**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	70	2.5	74 (S)[d]
14	**1e**	**5e**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	65	1.75	63 (S)[d] 67 (R)[d]
15	**1f**	**5f**	$Pd_2dba_3 + 4AsPh_3$	CuI (1.2)	65	1.75	71 (S)[d] 66 (R)[d]

[a] If no stereochemical descriptor is given, the reactions were performed with racemic organotin reagent. [b] Experiments were performed in toluene. [c] 63% de. [d] >99.8% de.

SCHEME 3. Stille Cross-Coupling Reactions



of **2a** was very low and only traces of product formed after 24 h (entry 7).

Recently, a significant positive influence of CsF in combination with CuI on Stille coupling reactions[23] has been reported. Therefore, we have explored the effect of 2 equiv of CsF[24] and 0.2 equiv of CuI on our reaction in DMF in the presence of $Pd_2dba_3/AsPh_3$ and observed a substantial increase in reaction rate and preparative yield (68%, entry 8). Analogously, the reaction of 6-iodopurine **1b** gave product **5b** in similar yield (69%, entry 9). A sample of (S)-**5b** prepared by this method was deprotected and the free (S)-4-(9H-purine-6-yl)phenylalanine was tested by derivatization with Marfey's reagent as described above. The result showed that excess of rather basic CsF caused partial epimerization of the coupling product (63% de), and therefore this method is not suitable for the synthesis of enantiopure amino acids.

A mechanistic hypothesis on the influence of CsF assumes a reversible transmetalation between the organostannane and CuI and the role of CsF is to shift the equilibrium toward the formation of more reactive organocopper species.[23] The same Sn → Cu transmetalation in the presence of CuI and polar solvents was described by Farina.[25] The intermediate organocopper species is then involved in the second Cu → Pd transmetalation with palladium catalyst. Therefore, an experiment employing an excess of CuI (1.2 equiv, to ensure all organostannane could be transmetalated) and $Pd_2dba_3/AsPh_3$ catalyst in DMF was performed. The results (entry 10) showed a significant enhancement of reaction rate in comparison to the experiment with CsF (entry 8). These results employing CuI in DMF with $Pd_2dba_3/AsPh_3$ as catalyst (entries 6−10) are in agreement with Farina's Sn → Cu → Pd transmetalation hypothesis.[25] Analogously, another sample of (S)-**5b** was prepared by this method (entry 11) and deprotected, and its enantiopurity was determined by derivatization with Marfey's reagent. In this case, the enantiopurity of the final product was >99.8 ee, and therefore this was finally the method of choice for the synthesis of the enantiopure conjugates.

Thus a complete series of diastereomerically pure derivatives **5b**−**f** varying in substituent in position 9 and in configuration at the amino acid moiety (two sets of (R)- and (S)-epimers) was prepared by this method using 1.2 equiv of CuI and catalytic system based on $Pd_2dba_3/AsPh_3$ in DMF in yields of ca. 70% (entries 11−15).

Protecting Groups Cleavage. Having optimized reaction conditions for synthesis of optically pure protected (purin-6-yl)phenylalanines **5**, we turned our attention to cleavage of the protecting groups. As mentioned before, the deprotection sequence should ideally be carried out under mild conditions to prevent racemization of the amino acid moiety and decomposition of acid-labile nucleoside part of molecules **5c**−**f**. The diverse deprotection sequences are discussed below.

4-(9H-Purin-6-yl)phenylalanines (S)-**7** and (R)-**7** were prepared from (S)-**5b** and (R)-**5b** derivatives (Scheme 4). At first, (S)-**5b** and (R)-**5b** were treated by 10% TFA in DCM to give crystalline 9H-purines (S)-**6** and (R)-**6** in almost quantitative yield. Hydrogenolytic cleavage of benzyl ester and benzyl carbamate in DMF/H_2O provided final products (S)-**7** and (R)-**7** in very good overall yields (Scheme 4).

Free purine nucleosides **10** and **11** could be prepared both from acylated **5c** and **5d** and from silylated **5e** and **5f** nucleosides. In contrast to silyl ethers, cleaving of acyl groups requires basic hydrolysis, which could be ac-

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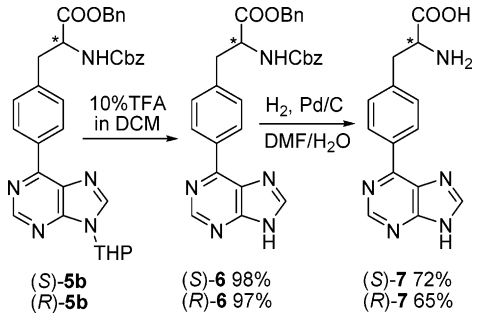
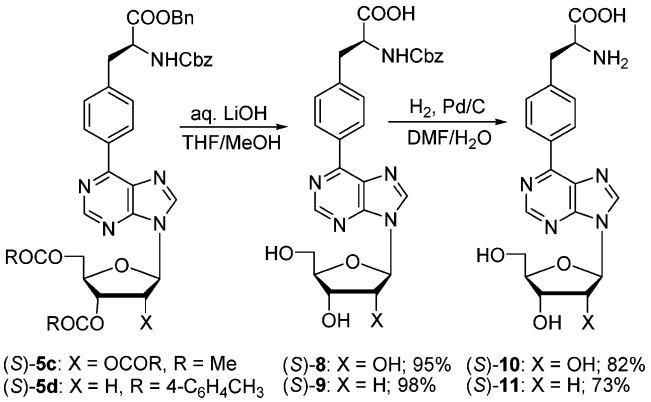
SCHEME 4. Deprotection of 5b



SCHEME 5. Deprotection of Acylated Nucleosides



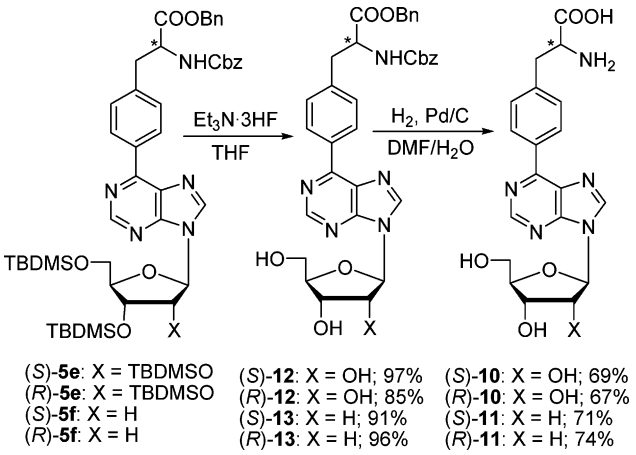
companied by partial racemization/epimerization (vide infra) of the amino acid moiety. LiOH was deemed the weakest possible base causing no racemization, yet still able to simultaneously hydrolyze all ester groups in molecule.[26] Treatment of compounds (*S*)-**5c** and (*S*)-**5d** with aqueous LiOH (0.8 equiv for one ester group) in THF/MeOH mixture at ambient temperature was performed until all esters were cleaved (Scheme 5). Then, carbamate groups of the intermediates (*S*)-**8** and (*S*)-**9** were cleaved by hydrogenolysis to give desired free nucleosides (*S*)-**10** and (*S*)-**11**. Diastereomeric purity of nucleosides was 96% and 98% de, respectively (determined by derivatization with Marfey's reagent), proving that a minute epimerization took place during the basic hydrolysis of esters. The diastereomeric purity was not improved even after employing lower concentrations of LiOH or lowering of reaction temperature to 0 °C.

Second alternative route toward nucleosides **10** and **11** started from the silyl-protected derivatives **5e** and **5f**. Treatment of **5e** and **5f** in THF by $Et_3N{\cdot}3HF$ (1.5 equiv for one silyl ether) provided the partly deprotected derivatives **12** and **13** (Scheme 6). These products were sufficiently lipophilic to allow purification by flash chromatography on silica gel column. Finally, simultaneous hydrogenolysis of benzyl esters and benzyl carbamates gave the free nucleosides (*S*)-**10**, (*R*)-**10**, (*S*)-**11**, and (*R*)-**11** in good yields. No undesired diastereomers were observed in this case (>99.8 de), showing that silyl ethers are the superior protecting groups for sugar moiety.

Biological Activity Screening. Title (purin-6-yl)-phenylalanines **7**, **10**, and **11** were subjected to biological activity screening, which comprised cytostatic effect[1a]

(26) Nicolaou, K. C.; Bella, M.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495−3499.

SCHEME 6. Deprotection of Silylated Nucleosides



(inhibition of cell growth of mouse leukemia L1210 cells (ATCC CCL 219); human promyelocytic leukemia HL60 cells (ATCC CCL 240); human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119)) and antiviral activity (HCV subgenomic replicon assay[27]). None of the tested compounds showed any considerable effect in these assays.

Conclusions

A new practical method for synthesis of enantiomerically pure (purin-6-yl)phenylalanines by palladium-catalyzed, copper-mediated Stille cross-coupling reactions of protected 4-(trimethylstanyl)phenylalanines and 6-iodopurines was developed. This method was used in the synthesis of a series of (purin-6-yl)phenylalanines (bases and nucleosides) varying in substitution in position 9 of the purine scaffold and in absolute configuration on the α-carbon of phenylalanine. For the first time, the limited applicability of the alternative routes using a Suzuki−Miyaura coupling reaction of protected 4-boronophenylalanine and CsF-mediated Stille coupling of 4-(trimethylstanyl)phenylalanines was shown as a result of partial epimerization of the amino acid moiety under the cross-coupling conditions. Furthermore, a mild, racemization-free method for cleavage of protecting groups was developed and applied to give both free (*S*)- and (*R*)-phenylalanines bearing a purine base or a purine nucleoside. These compounds may serve as building blocks for the synthesis of novel nondegradable nucleic acid/peptide conjugates.

Experimental Section

Method A. Stille Cross-Coupling Reaction of 4-(Trimethylstanyl)phenylalanine 4 with 6-Iodopurines 1a−f. DMF (15 mL) was added through a septum to an argon-purged flask containing a 6-iodopurine (1.65 mmol), 4-(trimethylstanyl)phenylalanine **4** (1.03 g, 1.87 mmol), Pd_2dba_3 (92 mg, 0.1 mmol), $AsPh_3$ (61 mg, 0.2 mmol), and CuI (380 mg, 2.0 mmol). The mixture was stirred at 65−80 °C for 1−4.5 h until consumption of starting 6-halopurine was reached according to TLC (for reaction temperature and time, see Table

(27) Stuyver, L. J.; Whitaker, T.; McBrayer, T. R.; Hernandez-Santiago, B. I.; Lostia, S.; Tharnish, P. M.; Ramesh, M.; Chu, C. K.; Jordan, R.; Shi, J. X.; Rachakonda, S.; Watanabe, K. A.; Otto, M. J.; Schinazi, R. F. *Antimicrob. Agents Chemother.* **2003,** *47*, 244−254.

2). The reaction mixture was diluted by ethyl acetate (200 mL), filtrated though a Celite pad, and washed with water (200 mL). The organic phase was evaporated and the residue was chromatographed on a silica gel column (ethyl acetate/hexane, 1:5 → 2:1) to give products **5a**−**f**.

Method B. Suzuki−Miyaura Cross-Coupling Reaction of 4-Boronophenylalanine 3 with 6-Iodopurines 1a, 1d, and 2a−c. Dioxane (6 mL) was added through a septum to an argon-purged flask containing a 6-halopurine (1.0 mmol), 4-boronophenylalanine **3** (520 mg, 1.2 mmol), and K_3PO_4 (425 mg, 2 mmol). Additionally the solution of $Pd(OAc)_2$ (23 mg, 0.1 mmol) and 2-(dicyclohexylphosphino)biphenyl (52 mg, 0.15 mmol) in dioxane (3 mL) was prepared under argon, and two drops of water (20 μL) were added. The mixture was stirred at 100 °C for 3−6 h until consumption of starting 6-halopurine was reached according to TLC (for reaction time see Table 1). The reaction mixture was filtrated though a Celite pad, evaporated in vacuo, and chromatographed on a silica gel column (ethyl acetate/hexane, 1:5 → 2:1) to give products **5a**−**d**.

Benzyl (*S*)-3-{4-[9-(Tetrahydropyran-2-yl)purin-6-yl]-phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-5b). Method A. Prepared from 9-THP-6-iodopurine (**1b**) (544 mg, 1.65 mmol) and (*S*)-4-(trimethylstannyl)phenylalanine (*S*)-**4** (1.03 g, 1.87 mmol): yield 701 mg (72%) of (*S*)-**5b**. Product was isolated as amorphous colorless solid. MS (FAB): 592 (62, M + 1); 508 (100, M − THP + 2). HRMS (FAB): for $C_{34}H_{34}N_5O_5$ calculated 592.2560, found 592.2582. ^{1}H NMR (400 MHz, $CDCl_3$): 1.64−1.89 (m, 3H, CH_2-THP); 2.04−2.23 (m, 3H, CH_2-THP); 3.18 and 3.23 (2 × dd, 2 × 1H, J_{gem} = 13.7, $J_{CH_2,CH}$ = 5.8, CH_2); 3.82 (td, 1H, J = 11.7, 2.5, bCH_2O-THP); 4.21 (ddt, 1H, J = 11.7, 4.4, 1.7, aCH_2O-THP); 4.77 (dt, 1H, $J_{CH,NH}$ = 8.3, J_{CH,CH_2} = 5.8, CH); 5.10 (s, 2H, CH_2-Cbz); 5.13 and 5.17 (2 × d, 2 × 1H, J_{gem} = 12.2, CH_2-Bn); 5.31 (d, 1H, $J_{NH,CH}$ = 8.3, NH); 5.86 (dd, 1H, J = 10.3, 2.8, CHO-THP); 7.22 (m, 2H, H-*m*-phenylene); 7.26−7.37 (m, 10H, 2 × Ph); 8.34 (s, 1H, H-8); 8.67 (m, 2H, H-*o*-phenylene); 9.01 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.8, 24.9 and 31.8 (CH_2-THP); 38.1 (CH_2); 54.7 (CH); 67.0 (CH_2-Cbz); 67.4 (CH_2-Bn); 68.9 (CH_2O-THP); 82.0 (CHO-THP); 128.1, 128.1, 128.5, 128.5, 128.6 and 128.6 (CH-Ph), 129.7 (CH-*m*-phenylene); 130.0 (CH-*o*-phenylene); 131.0 (C-5); 134.5 (C-*i*-phenylene); 135.0 (C-*i*-Ph-OBn); 136.2 (C-*i*-Ph-Cbz); 138.8 (C-*p*-phenylene); 142.0 (CH-8); 151.7 (C-4); 152.4 (CH-2); 154.5 (C-6); 155.6 (CO-carbamate); 171.1 (CO-ester). IR ($CHCl_3$): 3432, 3092, 3069, 3034, 1722, 1584, 1561, 1509, 1455, 1344, 1329, 1086, 1059, 1046, 911, 698, 647. **Method B.** Prepared from 9-THP-6-chloropurine (**2b**) (239 mg, 1.0 mmol) and (*S*)-4-(borono)phenylalanine (*S*)-**3** (520 mg, 1.2 mmol): yield 440 mg (74%) of (*S*)-**5b**.

Benzyl (*S*)-3-{4-[9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-5c). Method A. Prepared from 6-iodopurine **1c** (832 mg, 1.65 mmol) and (*S*)-4-(trimethylstannyl)phenylalanine (*S*)-**4** (1.03 g, 1.87 mmol): yield 913 mg (72%) of (*S*)-**5c**. Product was isolated as amorphous colorless solid. MS (FAB): 766 (100, M + 1); 508 (42, M − AcRf + 2). HRMS (FAB): for $C_{40}H_{40}N_5O_{11}$ calculated 766.2724, found 766.2722. ^{1}H NMR (400 MHz, $CDCl_3$): 2.10, 2.14 and 2.17 (3 × s, 3 × 3H, CH_3); 3.18 and 3.24 (2 × dd, 2 × 1H, J_{gem} = 13.9, $J_{CH_2,CH}$ = 5.9, CH_2); 4.41 (dd, 1H, J_{gem} = 12.8, $J_{5'b,4'}$ = 5.2, H-5′b); 4.45−4.52 (m, 2H, H-4′ and H-5′a); 4.77 (dt, 1H, $J_{CH,NH}$ = 8.1, J_{CH,CH_2} = 5.9, CH); 5.10 (s, 2H, CH_2-Cbz); 5.13 and 5.18 (2 × d, 2 × 1H, J_{gem} = 12.2, CH_2-Bn); 5.30 (d, 1H, $J_{NH,CH}$ = 8.1, NH); 5.72(dd, 1H, $J_{3',2'}$ = 5.6, $J_{3',4'}$ = 4.5, H-3′); 6.02 (t, 1H, $J_{2',3'}$ = 5.6, $J_{2',1'}$ = 5.3, H-2′); 6.30 (d, 1H, $J_{1'2'}$ = 5.3, H-1′); 7.23 (m, 2H, H-*m*-phenylene); 7.26−7.38 (m, 10H, 2 × Ph); 8.28 (s, 1H, H-8); 8.65 (m, 2H, H-*o*-phenylene); 9.02 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.4, 20.5 and 20.8 (CH_3); 38.1 (CH_2); 54.7 (CH); 63.0 (CH_2-5′); 67.0 (CH_2-Cbz); 67.4 (CH_2-Bn); 70.6 (CH-3′); 73.1 (CH-2′); 80.4 (CH-4′); 86.4 (CH-1′); 128.1, 128.2, 128.5, 128.6 and 128.6 (CH-Ph), 129.7 (CH-*m*-phenylene); 130.0 (CH-*o*-phenylene); 131.5 (C-5); 134.3 (C-*i*-phenylene); 134.9 (C-*i*-Ph-OBn); 136.2 (C-*i*-Ph-Cbz); 139.0 (C-*p*-phenylene); 142.4 (CH-8); 152.0 (C-4); 152.7 (CH-2); 155.0 (C-6); 155.6 (CO-carbamate); 169.4, 169.6 and 170.3 (CO−Ac); 171.1 (CO-ester). IR ($CHCl_3$): 3432, 3032, 3012, 1749, 1584, 1509, 1450, 1375, 1329, 1228, 1206, 1059, 645. $[\alpha]^{20}_D$ = −18.3 (c = 3.77, $CHCl_3$). Anal. Calcd for $C_{40}H_{39}N_5O_{11}$ (765.8): C 62.74, H 5.13, N 9.15. Found: C 62.35, H 5.13, N 8.86. **Method B.** Prepared from 6-chloropurine **2c** (413 mg, 1.0 mmol) and (*S*)-4-(borono)-phenylalanine (*S*)-**3** (520 mg, 1.2 mmol): yield 542 mg (71%) of **5c**.

Benzyl (*S*)-3-{4-[9-(3,5-Di-*O*-*p*-toluoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-5d). Method A. Prepared from 6-iodopurine **1d** (987 mg, 1.65 mmol) and (*S*)-4-(trimethylstannyl)phenylalanine (*S*)-**4** (1.03 g, 1.87 mmol): yield 1.05 g (74%) of (*S*)-**5d**. Product was isolated as amorphous colorless solid. MS (FAB): 860 (70, M + 1); 508 (68, M − ToldRf + 2); 424 (100). HRMS (FAB): for $C_{50}H_{46}N_5O_9$ calculated 860.3296, found 860.3302. ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 and 2.45 (2 × s, 2 × 3H, CH_3); 2.91 (ddd, 1H, J_{gem} = 14.2, $J_{2'b1'}$ = 5.8, $J_{2'b3'}$ = 2.2, H-2′b); 3.15−3.26 (m, CH_2 and H-2′a); 4.66−4.72 (m, 2H, H-4′ and H-5′b); 4.77 (m, 1H, CH); 4.80 (dd, 1H, J_{gem} = 13.1, $J_{5'a,4'}$ = 5.0, H-5′a); 5.10 (s, 2H, CH_2-Cbz); 5.13 and 5.18 (2 × d, 2 × 1H, J_{gem} = 12.0, CH_2-Bn); 5.29 (d, 1H, $J_{NH,CH}$ = 8.1, NH); 5.86 (dt, 1H, $J_{3'2'a}$ = 6.2, $J_{3'4'}$ = 2.2, $J_{3'2'b}$ = 2.2, H-3′); 6.65 (dd, 1H, $J_{1'2'a}$ = 8.2, $J_{1'2'b}$ = 5.7, H-1′); 7.19 (m, 2H, H-*m*-Tol); 7.22 (m, 2H, H-*m*-phenylene); 7.27−7.38 (m, 12H, H-*m*-Tol and 2 × Ph); 7.89 and 7.99 (2 × m, 2 × 2H, H-*o*-Tol); 8.29 (s, 1H, H-8); 8.62 (m, 2H, H-*o*-phenylene); 8.96 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.6 and 21.8 (CH_3); 37.9 (CH_2-2′); 38.1 (CH_2); 54.7 (CH); 64.0 (CH_2-5′); 67.0 (CH_2-Cbz); 67.4 (CH_2-Bn); 75.1 (CH-3′); 83.2 (CH-4′); 85.0 (CH-1′); 126.4 and 126.6 (C-*i*-Tol); 128.1, 128.2, 128.50, 128.57 and 128.63 (CH-Ph), 129.26 and 129.30 (CH-*m*-Tol); 129.6 (CH-*o*-Tol); 129.7 (CH-*m*-phenylene); 129.8 (CH-*o*-Tol); 130.0 (CH-*o*-phenylene); 131.6 (C-5); 134.4 (C-*i*-phenylene); 134.9 (C-*i*-Ph-OBn); 136.2 (C-*i*-Ph-Cbz); 138.9 (C-*p*-phenylene); 142.3 (CH-8); 144.2 and 144.6 (C-*i*-Tol); 151.9 (C-4); 152.4 (CH-2); 154.7 (C-6); 155.6 (CO-carbamate); 166.0 and 166.2 (CO-Tol); 171.1 (CO-ester). IR ($CHCl_3$): 3432, 3032, 3012, 1721, 1612, 1548, 1509, 1450, 1387, 1269, 1179, 1103, 1021, 926, 698, 646. $[\alpha]^{20}_D$ = −62.4 (c = 4.34, $CHCl_3$). Anal. Calcd for $C_{50}H_{45}N_5O_9$ (859.9): C 69.84, H 5.27, N 8.14. Found: C 69.73, H 5.21, N 7.99. **Method B.** Prepared from 6-iodopurine **1d** (598 mg, 1.0 mmol) and (*S*)-4-(borono)phenylalanine (*S*)-**3** (520 mg, 1.2 mmol): yield 604 mg (70%) of **5d**.

Benzyl (*S*)-3-{4-[9-(2,3,5-Tri(*tert*-butyldimethylsilyloxy)-β-D-ribofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-5e). Method A. Prepared from 6-iodopurine **1e** (1.19 g, 1.65 mmol) and (*S*)-4-(trimethylstannyl)phenylalanine (*S*)-**4** (1.03 g, 1.87 mmol): yield 1.02 g (63%) of (*S*)-**5e**. Product was isolated as amorphous colorless solid. MS (FAB): 982 (95, M + 1); 508 (100, M − TBDMSO-Rf + 2). HRMS (FAB): for $C_{52}H_{76}N_5O_8Si_3$ calculated 982.5002, found 982.5005. ^{1}H NMR (400 MHz, $CDCl_3$): −0.25, −0.03, 0.12, 0.13, 0.16 and 0.17 (6 × s, 6 × 3H, CH_3-Si); 0.79, 0.95 and 0.98 (3 × s, 3 × 9H, CH_3-*t*-Bu); 3.19 (dd, 1H, J_{gem} = 13.8, $J_{bCH_2,CH}$ = 5.6, bCH_2); 3.23 (dd, 1H, J_{gem} = 13.8, $J_{aCH_2,CH}$ = 5.7, aCH_2); 3.83 (dd, 1H, J_{gem} = 11.4, $J_{5'b,4'}$ = 2.9, H-5′b); 4.05 (dd, 1H, J_{gem} = 11.4, $J_{5'a,4'}$ = 4.1, H-5′a); 4.17 (dt, 1H, $J_{4',5'}$ = 4.1, 2.9, $J_{4',3'}$ = 3.3, H-4′); 4.35 (dd, 1H, $J_{3',2'}$ = 4.4, $J_{3',4'}$ = 3.3, H-3′); 4.75 (dd, 1H, $J_{2',1'}$ = 5.4, $J_{2',3'}$ = 4.4, H-2′); 4.77 (dt, 1H, $J_{CH,NH}$ = 8.2, J_{CH,CH_2} = 5.7, 5.6, CH); 5.11 (s, 2H, CH_2-Cbz); 5.13 and 5.19 (2 × d, 2 × 1H, J_{gem} = 12.1, CH_2-Bn); 5.28 (d, 1H, $J_{NH,CH}$ = 8.2, NH); 6.17 (d, 1H, $J_{1'2'}$ = 5.4, H-1′); 7.21 (m, 2H, H-*m*-phenylene); 7.25−7.36 (m, 10H, 2 × Ph); 8.46 (s, 1H, H-8); 8.68 (m, 2H, H-*o*-phenylene); 8.99 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): −5.4, −5.3, −5.1, −4.7, −4.6 and −4.4 (CH_3-Si); 17.8, 18.1 and 18.5 (C-*t*-Bu); 25.6, 25.8 and 26.1 (CH_3-*t*-Bu); 38.1 (CH_2); 54.7 (CH); 62.6 (CH_2-5′); 67.0 (CH_2-Cbz); 67.4 (CH_2-Bn); 72.1 (CH-3′); 75.8 (CH-2′); 85.7 (CH-4′); 88.2 (CH-1′); 128.1, 128.2, 128.50, 128.55, 128.60 and 128.62 (CH-Ph),

129.68 (CH-*m*-phenylene); 130.0 (CH-*o*-phenylene); 131.5 (C-5); 134.6 (C-*i*-phenylene); 135.0 (C-*i*-Ph-OBn); 136.1 (C-*i*-Ph-Cbz); 138.7 (C-*p*-phenylene); 143.2 (CH-8); 152.26 (CH-2); 152.29 (C-4); 154.4 (C-6); 155.6 (CO-carbamate); 171.1 (CO-ester). IR ($CHCl_3$): 3432, 3035, 2956, 2931, 1721, 1581, 1508, 1390, 1344, 1328, 1257, 1113, 1066, 839, 698, 647. $[\alpha]^{20}_D$ = −32.9 (*c* = 2.10, $CHCl_3$).

Benzyl (*S*)-3-{4-[9-(3,5-Di(*tert*-butyldimethylsilyloxy)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-5f). Method A. Prepared from 6-iodopurine **1f** (975 mg, 1.65 mmol) and (*S*)-4-(trimethylstannyl)phenylalanine (*S*)-**4** (1.03 g, 1.87 mmol): yield 1.0 g (71%) of (*S*)-**5f**. Product was isolated as amorphous colorless solid. MS (FAB): 852 (20, M + 1); 508 (100, M − TBDMSO-dRf +2). HRMS (FAB): for $C_{46}H_{62}N_5O_7Si_2$ calculated 852.4188, found 852.4226. ^{1}H NMR (400 MHz, $CDCl_3$): 0.10 and 0.12 (2 × s, 12H, CH_3-Si); 0.92 and 0.93 (2 × s, 2 × 9H, CH_3-*t*-Bu); 2.50 (ddd, 1H, J_{gem} = 13.1, $J_{2'b,1'}$ = 6.1, $J_{2'b,3'}$ = 3.7, H-2′b); 2.72 (ddd, 1H, J_{gem} = 13.1, $J_{2'a,1'}$ = 6.9, $J_{2'a,3'}$ = 5.8, H-2′a); 3.18 (dd, 1H, J_{gem} = 14.0, $J_{bCH_2,CH}$ = 6.2, bCH_2); 3.23 (dd, 1H, J_{gem} = 14.0, $J_{aCH_2,CH}$ = 5.6, aCH_2); 3.80 (dd, 1H, J_{gem} = 11.2, $J_{5'b,4'}$ = 3.2, H-5′b); 3.90 (dd, 1H, J_{gem} = 11.2, $J_{5'a,4'}$ = 4.2, H-5′a); 4.06 (dt, 1H, $J_{4',5'}$ = 4.2, 3.2, $J_{4',3'}$ = 3.2, H-4′); 4.66 (dt, 1H, $J_{3',2'}$ = 5.8, 3.7, $J_{3',4'}$ = 3.2, H-3′); 4.77 (dt, 1H, $J_{CH,NH}$ = 8.3, J_{CH,CH_2} = 6.2, 5.6, CH); 5.10 (s, 2H, CH_2-Cbz); 5.12 and 5.18 (2 × d, 2 × 1H, J_{gem} = 12.2, CH_2-Bn); 5.28 (d, 1H, $J_{NH,CH}$ = 8.3, NH); 6.58 (d, 1H, $J_{1'2'}$ = 6.9, 6.1, H-1′); 7.21 (m, 2H, H-*m*-phenylene); 7.25−7.37 (m, 10H, 2 × Ph); 8.43 (s, 1H, H-8); 8.67 (m, 2H, H-*o*-phenylene); 8.99 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): −5.5, −5.4, −4.8 and −4.7 (CH_3-Si); 18.0 and 18.4 (C-*t*-Bu); 25.8 and 26.0 (CH_3-*t*-Bu); 38.1 (CH_2); 41.2 (CH_2-2′); 54.7 (CH); 62.8 (CH_2-5′); 67.0 (CH_2-Cbz); 67.4 (CH_2-Bn); 72.0 (CH-3′); 84.5 (CH-1′); 88.0 (CH-4′); 128.09, 128.15, 128.50, 128.55, 128.59 and 128.63 (CH-Ph), 129.7 (CH-*m*-phenylene); 130.0 (CH-*o*-phenylene); 131.5 (C-5); 134.6 (C-*i*-phenylene); 135.0 (C-*i*-Ph-OBn); 136.2 (C-*i*-Ph-Cbz); 138.7 (C-*p*-phenylene); 142.7 (CH-8); 151.9 (C-4); 152.2 (CH-2); 154.4 (C-6); 155.6 (CO-carbamate); 171.1 (CO-ester). IR ($CHCl_3$): 3432, 2957, 2931, 1722, 1583, 1509, 1390, 1344, 1328, 1258, 1186, 1114, 1065, 1028, 968, 838, 698, 647. $[\alpha]^{20}_D$ = −2.9 (*c* = 2.39, $CHCl_3$).

Benzyl (*S*)-3-{4-[9-*H*-Purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-6). Compound (*S*)-**5b** (300 mg, 0.51 mmol) was dissolved in DCM (6 mL) and a solution of TFA (1.5 mL) in DCM (4.8 mL) was slowly added. The reaction mixture was stirred at ambient temperature for 1.25 h. The solution was diluted by EtOAc and washed by an aqueous solution of $NaHCO_3$. The organic part was evaporated and crude product was recrystallized from EtOAc to give (*S*)-**6** (253 mg, 98%) as white crystals, mp 168−171 °C. MS (FAB): 508 (100, M + 1); 210 (48). HRMS (FAB): for $C_{29}H_{26}N_5O_4$ calculated 508.1985, found 508.1987. ^{1}H NMR (400 MHz, DMSO-d_6): 3.02 (dd, 1H, J_{gem} = 13.7, J_{vic} = 9.9, bCH_2); 3.18 (dd, 1H, J_{gem} = 13.7, J_{vic} = 5.4, aCH_2); 4.43 (ddd, 1H, J_{CHb,CH_2} = 9.9, $J_{CH,NH}$ = 8.2, J_{Cha,CH_2} = 5.4, CH); 4.97 and 5.01 (2 × d, 2 × 1H, J_{gem} = 12.6, CH_2-Cbz); 5.13 (s, 2H, CH_2-Bn); 7.22−7.35 (m, 10H, 2 × Ph); 7.47 (bm, 2H, *m*-H-phenylene); 7.96 (d, 1H, $J_{NH,CH}$ = 8.2, NH−Cbz); 8.64 (s, 1H, H-8); 8.75 (bm, 2H, *o*-H-phenylene); 8.94 (s, 1H, H-8); 13.62 (bs, 1H, NH-9). ^{13}C NMR (100.6 MHz, DMSO-d_6): 36.6 (CH_2); 55.6 (CH); 65.6 (CH_2-Cbz); 66.3 (CH_2-Bn); 127.7, 127.9, 128.0, 128.2, 128.46 and 128.53 (CH-Ph); 129.4 (CH-*o*-phenylene); 129.6 (CH-*m*-phenylene), 129.9 (C-5); 134.2 (C-*i*-phenylene); 135.9 (C-*i*-Ph-OBn); 137.0 (C-*i*-Ph-Cbz); 140.6 (C-*p*-phenylene); 144.8 (CH-8); 152.0 (CH-2); 152.3 (C-6); 153.6 (C-4); 156.2 (CO-carbamate); 171.8 (CO-ester). IR (KBr): 3331, 3065, 2832, 1724, 1686, 1584, 1562, 1532, 1455, 1323, 1286, 1184, 1054, 922, 696, 639. $[\alpha]^{20}_D$ = −21.7 (*c* = 3.13, DMSO).

(*S*)-3-{4-[9-*H*-Purin-6-yl]phenyl}-2-aminopropanoic acid dihydrochloride ((*S*)-7). Hydrogen was bubbled through solution of (*S*)-**6** (245 mg, 0.50 mmol) in DMF (10 mL), water (5 mL), and HCl (0.2 mL, 10%) in the presence of Pd/C catalyst (10 wt %, 49 mg) for 10 h. The catalyst was filtered off on a Celite pad and the filtrate was evaporated in vacuo. Crude product was purified by preparative HPLC on C18 column with water/methanol as mobile phase. Then, 2% aqueous HCl was added to the aqueous solution of product to adjust pH to 4 and product was lyophilized from this solution to give 128 mg (72%) of (*S*)-**7** as white solid. MS (FAB): 284 (100, M + 1). HRMS (FAB): for $C_{14}H_{14}N_5O_2$ calculated 284.1148, found 284.1155. ^{1}H NMR (500 MHz, D_2O, $ref_{dioxane}$= 3.75 ppm): 3.27 (dd, 1H, J_{gem} = 14.5, $J_{bCH_2,CH}$ = 7.4, bCH_2); 3.36 (dd, 1H, J_{gem} = 14.5, $J_{aCH_2,CH}$ = 5.9, aCH_2); 4.23 (dd, 1H, J_{CH,CH_2} = 7.4, 5.9, CH); 7.44 (m, 2H, *m*-H-phenylene); 7.94 (m, 2H, *o*-H-phenylene); 8.59 (s, 1H, H-8); 8.84 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, D_2O, $ref_{dioxane}$= 67.19 ppm): 36.6 (CH_2); 55.5 (CH); 127.7 (C-5); 130.4 and 130.7 (CH-phenylene); 131.4 (C-*i*-phenylene); 139.8 (C-*p*-phenylene); 148.2 (CH-8); 150.5 (CH-2); 152.2 (C-6); 155.0 (C-4); 173.1 (CO). IR (KBr): 2912, 2866, 1739, 1616, 1595, 1565, 1516, 1387, 1320, 795, 636, 524. Anal. Calcd for $C_{14}H_{15}Cl_2N_5O_2$ (356.2): C 47.21, H 4.24, N 19.66. Found: C 47.32, H 4.61, N 16.98. $[\alpha]^{20}_D$ = −6.9 (*c* = 2.02, H_2O).

Benzyl (*S*)-3-{4-[9-(*β*-D-Ribofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-12). Et_3N·3HF (320 *μ*L, 1.95 mmol) was added to a solution of (*S*)-**5e** (380 mg, 0.39 mmol) in THF (2.5 mL), and the reaction mixture was stirred at ambient temperature for 14 h. Solvents were evaporated in vacuo and crude product was purified by flash chromatography on silica gel column with EtOAc/MeOH (95/5) eluent to give 243 mg (97%) of (*S*)-**12** as colorless amorphous solid. MS (FAB): 640 (20, M + 1); 508 (100, M − Rf +2). HRMS (FAB): for $C_{34}H_{34}N_5O_8$ calculated 640.2407, found 640.2389. ^{1}H NMR (400 MHz, DMSO-d_6): 3.03 (dd, 1H, J_{gem} = 13.8, $J_{bCH_2,CH}$ = 10.1, bCH_2); 3.19 (dd, 1H, J_{gem} = 13.8, $J_{aCH_2,CH}$ = 5.2, aCH_2); 3.61 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.9, $J_{5'b,4'}$ = 4.0, H-5′b); 3.72 (dt, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 4.0, H-5′a); 4.01 (q, 1H, $J_{4',5'}$ = 4.0, $J_{4',3'}$ = 4.0, H-4′); 4.22 (q, 1H, $J_{3',OH}$ = 5.0, $J_{3',2'}$ = 4.7, $J_{3',4'}$ = 4.0, H-3′); 4.44 (ddd, 1H, J_{CH,CH_2} = 10.1, 5.2, $J_{CH,NH}$ = 8.1, CH); 4.67 (q, 1H, $J_{2',OH}$ = 5.7, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 4.7, H-2′); 4.97 and 5.01 (2 × d, 2 × 1H, J_{gem} = 12.6, CH_2-CBz); 5.13 (s, 2H, CH_2-Bn); 5.15 (t, 1H, $J_{OH,5'}$ = 5.9, 5.3, OH-5′); 5.28 (d, 1H, $J_{OH,3'}$ = 5.0, OH-3′); 5.59 (d, 1H, $J_{OH,2'}$ = 5.7, OH-2′); 6.10 (d, 1H, $J_{1'2'}$ = 5.6, H-1′); 7.22−7.36 (m, 10H, 2 × Ph); 7.48 (m, 2H, H-*m*-phenylene); 7.97 (d, 1H, $J_{NH,CH}$ = 8.1, NH); 8.75 (m, 2H, H-*o*-phenylene); 8.93 (s, 1H, H-8); 9.01 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 36.6 (CH_2); 55.6 (CH); 61.4 (CH_2-5′); 65.6 (CH_2-Bn); 66.3 (CH_2-Cbz); 70.5 (CH-3′); 73.9 (CH-2′); 85.9 (CH-4′); 87.9 (CH-1′); 127.8, 127.95, 127.99, 128.2, 128.5 and 128.6 (CH-Ph), 129.5 (CH-*m*-phenylene); 129.7 (CH-*o*-phenylene); 130.9 (C-5); 133.8 (C-*i*-phenylene); 136.0 (C-*i*-Ph-Bn); 137.0 (C-*i*-Ph-Cbz); 141.0 (C-*p*-phenylene); 145.0 (CH-8); 152.1 (CH-2); 152.4 (C-4); 153.1 (C-6); 156.2 (CO-carbamate); 171.8 (CO-ester). IR (KBr): 3325, 3034, 1723, 1699, 1586, 1559, 1535, 1515, 1454, 1331, 1286, 1259, 1216, 1058, 800, 743, 697. $[\alpha]^{20}_D$ = −43.7 (*c* = 3.90, DMSO).

Benzyl (*S*)-3-{4-[9-(2-Deoxy-*β*-D-*erythro*-pentofuranosyl)purin-6-yl]phenyl}-2-[(benzyloxycarbonyl)amino]propanoate ((*S*)-13). Et_3N·3HF (240 *μ*L, 1.47 mmol) was added to the solution of (*S*)-**5f** (360 mg, 0.42 mmol) in THF (2.5 mL), and the reaction mixture was stirred at ambient temperature for 14 h. Solvents were evaporated in vacuo and crude product was purified by flash chromatography on silica gel column with EtOAc/MeOH (95/5) eluent to give 238 mg (91%) of (*S*)-**13** as colorless amorphous solid. MS (FAB): 624 (15, M + 1); 508 (100, M − dRf +2). HRMS (FAB): for $C_{34}H_{34}N_5O_7$ calculated 624.2458, found 624.2448. ^{1}H NMR (400 MHz, DMSO-d_6): 2.39 (ddd, 1H, J_{gem} = 13.4, $J_{2'b,1'}$ = 6.4, $J_{2'b,3'}$ = 3.6, H-2′b); 2.82 (ddd, 1H, J_{gem} = 13.4, $J_{2'a,1'}$ = 7.2, $J_{2'}$a,3′ = 6.0, H-2′a); 3.02 (dd, 1H, J_{gem} = 13.9, $J_{bCH_2,CH}$ = 10.1, bCH_2); 3.18 (dd, 1H, J_{gem} = 13.9, $J_{aCH_2,CH}$ = 5.4, aCH_2); 3.56 (dt, 1H, J_{gem} = 11.6, $J_{5'b,OH}$ = 5.5, $J_{5'b,4'}$ = 4.7, H-5′b); 3.65 (dt, 1H, J_{gem} = 11.6, $J_{5'a,OH}$ = 5.5, $J_{5'a,4'}$ = 5.0, H-5′a); 3.92 (td, 1H, $J_{4',5'}$ = 5.0, 4.7, $J_{4',3'}$ = 3.1, H-4′);

4.43 (ddd, 1H, J_{CH,CH_2} = 10.1, 5.4, $J_{CH,NH}$ = 8.1, CH); 4.47 (m, 1H, H-3′); 4.97 and 5.02 (2 × d, 2 × 1H, J_{gem} = 12.5, CH_2-CBz); 5.03 (bt, 1H, $J_{OH,5'}$ = 5.5, OH-5′); 5.13 (s, 2H, CH_2-Bn); 5.39 (bd, 1H, $J_{OH,3'}$ = 4.1, OH-3′); 6.53 (d, 1H, $J_{1'2'}$ = 7.2, 6.4, H-1′); 7.22−7.36 (m, 10H, 2 × Ph); 7.47 (m, 2H, H-*m*-phenylene); 7.96 (d, 1H, $J_{NH,CH}$ = 8.1, NH); 8.74 (m, 2H, H-*o*-phenylene); 8.89 (s, 1H, H-8); 9.99 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 36.6 (CH_2); 39.5 (CH_2-2′); 55.6 (CH); 61.7 (CH_2-5′); 65.6 (CH_2-Bn); 66.3 (CH_2-Cbz); 70.8 (CH-3′); 83.9 (CH-1′); 88.2 (CH-4′); 127.8, 127.94, 127.98, 128.2, 128.48 and 128.55 (CH-Ph), 129.5 (CH-*m*-phenylene); 129.7 (CH-*o*-phenylene); 130.9 (C-5); 133.9 (C-*i*-phenylene); 136.0 (C-*i*-Ph-Bn); 137.0 (C-*i*-Ph-Cbz); 140.9 (C-*p*-phenylene); 144.9 (CH-8); 152.0 (CH-2); 152.1 (C-4); 152.9 (C-6); 156.2 (CO-carbamate); 171.8 (CO-ester). IR (KBr): 3416, 3064, 3033, 1720, 1584, 1515, 1454, 1329, 1259, 1214, 1185, 1056, 803, 742, 645. $[\alpha]^{20}_D$ = −24.5 (*c* = 2.76, DMSO).

(*S*)-3-{4-[9-(*β*-D-Ribofuranosyl)purin-6-yl]phenyl}-2-aminopropanoic Acid Dihydrate((*S*)-10). Hydrogen was bubbled through a solution of (*S*)-**12** (210 mg, 0.33 mmol) in DMF (7 mL) and water (7 mL) in the presence of Pd/C catalyst (10 wt %, 25 mg) for 2 h. The catalyst was filtered off on a Celite pad and the filtrate was evaporated in vacuo. Crude product was purified by preparative HPLC on C18 column with water/methanol as mobile phase. Product was crystallized from water to give 103 mg (69%) of (*S*)-**10** as white crystals, mp = 208−212 °C. MS (FAB): 416 (100, M +1); 284 (97, M − Rf + 2). HRMS (FAB): for $C_{19}H_{22}N_5O_6$ calculated 416.1570, found 416.1566. ^{1}H NMR (400 MHz, D_2O, $ref_{dioxane}$ = 3.75 ppm): 3.18 (dd, 1H, J_{gem} = 14.6, $J_{bCH_2,CH}$ = 7.8, bCH_2); 3.32 (dd, 1H, J_{gem} = 14.6, $J_{aCH_2,CH}$ = 5.3, aCH_2); 3.85 (dd, 1H, J_{gem} = 12.9, $J_{5'b,4'}$ = 3.8, H-5′b); 3.94 (dd, 1H, J_{gem} = 12.9, $J_{5'a,4'}$ = 2.9, H-5′a); 4.03 (dd, 1H, J_{CH,CH_2} = 7.8, 5.3, CH); 4.28 (bq, 1H, $J_{4',3'}$ = 4.0, $J_{4',5'}$ = 3.8, 2.9, H-4′); 4.43 (dd, 1H, $J_{3',2'}$ = 5.2, $J_{3',4'}$ = 4.0, H-3′); 4.71 (t, 1H, $J_{2',1'}$ = 5.5, $J_{2',3'}$ = 5.2, H-2′); 6.09 (d, 1H, $J_{1'2'}$ = 5.5, H-1′); 7.40 (m, 2H, H-*m*-phenylene); 7.99 (m, 2H, H-*o*-phenylene); 8.55 (s, 1H, H-8); 8.66 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, $ref_{dioxane}$ = 67.19 ppm): 37.0 (CH_2); 56.4 (CH); 61.9 (CH_2-5′); 71.0 (CH-3′); 74.5 (CH-2′); 86.2 (CH-4′); 89.1 (CH-1′); 130.3 and 130.5 (CH-phenylene); 131.1 (C-5); 133.4 (C-*i*-phenylene); 139.6 (C-*p*-phenylene); 145.6 (CH-8); 151.6 (C-4); 152.2 (CH-2); 155.4 (C-6); 174.4 (CO). IR (KBr): 3240, 3112, 2926, 1613, 1587, 1561, 1516, 1451, 1399, 1330, 1215, 1101, 1057, 802, 643. $[\alpha]^{20}_D$ = −53.0 (*c* = 3.50, DMSO). Anal. Calcd for $C_{19}H_{25}N_5O_8$ (451.4): C 50.55, H 5.58, N 15.51. Found: C 50.58, H 5.68, N 15.43.

(*S*)-3-{4-[9-(2-Deoxy-*β*-D-*erythro*-pentofuranosyl)purin-6-yl]phenyl}-2- aminopropanoic Acid Dihydrate ((S)-11). Hydrogen was bubbled through a solution of (*S*)-**13** (207 mg, 0.33 mmol) in DMF (7 mL) and water (7 mL) in the presence of Pd/C catalyst (10 wt %, 25 mg) for 2 h. The catalyst was filtered off on a Celite pad and the filtrate was evaporated in vacuo. Crude product was purified by preparative HPLC on C18 column with water/methanol as mobile phase. Product was lyophilized from water to give 102 mg (71%) of (*S*)-**11** as white solid. MS (FAB): 400 (61, M + 1); 284 (100, M − dRf + 2). HRMS (FAB): for $C_{19}H_{22}N_5O_5$ calculated 400.1621, found 400.1613. ^{1}H NMR (400 MHz, D_2O, $ref_{dioxane}$ = 3.75 ppm): 2.52 (ddd, 1H, J_{gem} = 14.0, $J_{2'b1'}$ = 6.3, $J_{2'b3'}$ = 3.8, H-2′b); 2.74 (dt, 1H, J_{gem} = 14.0, $J_{2'a1'}$ = 6.5, $J_{2'a3'}$ = 6.5, H-2′a); 3.19 (dd, 1H, J_{gem} = 14.5, $J_{bCH_2,CH}$ = 7.8, bCH_2); 3.32 (dd, 1H, J_{gem} = 14.5, $J_{aCH_2,CH}$ = 5.3, aCH_2); 3.78 (dd, 1H, J_{gem} = 12.6, $J_{5'b4'}$ = 4.5, H-5′b); 3.84 (dd, 1H, J_{gem} = 12.6 $J_{5'a4'}$ = 3.4, H-5′a); 4.04 (dd, 1H, J_{CH,CH_2b} = 7.8, J_{CH,CH_2a} = 5.3, CH); 4.17 (q, 1H, $J_{4'5'b}$ = 4.5, $J_{4'3'}$ = 3.5, $J_{4'5'a}$ = 3.4, H-4′); 4.63 (dt, 1H, $J_{3'2'a}$ = 6.5, $J_{3'2'b}$ = 3.8, $J_{3'4'}$ = 3.5, H-3′); 6.40 (t, 1H, $J_{1'2'a}$ = 6.5, $J_{1'2'b}$ = 6.3, H-1′); 7.40 (m, 2H, *m*-H-phenylene); 7.98 (m, 2H, *o*-H-phenylene); 8.51 (s, 1H, H-8); 8.62 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, $ref_{dioxane}$ = 67.19 ppm): 36.9 (CH_2); 39.6 (CH_2-2′); 56.3 (CH); 62.1 (CH_2-5′); 71.6 (CH-3′); 85.2 (CH-1′); 88.0 (CH-4′); 130.3 and 130.4 (CH-phenylene); 131.0 (C-5); 133.4 (C-*i*-phenylene); 139.5 (C-*p*-phenylene); 145.3 (CH-8); 151.4 (C-4); 152.0 (CH-2); 155.1 (C-6); 174.2 (CO). IR (KBr): 3402, 3260, 3106, 2924, 1636, 1585, 1516, 1449, 1395, 1329, 1216, 1096, 1056, 802, 645. $[\alpha]^{20}_D$ = −28.1 (*c* = 5.20, DMSO). Anal. Calcd for $C_{19}H_{25}N_5O_7$ (435.4): C 52.41, H 5.79, N 16.08. Found: C 52.20, H 5.62, N 15.72.

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Supporting Information Available: General methods, synthesis of starting compounds, characterization data of compounds **5a**, (*R*)-**5b**−**f**, **9a**, (*R*)-**6**, (*R*)-**7**, (*S*)-**8**, (*S*)-**9**, (*R*)-**10**, (*R*)-**11**, (*R*)-**12**, (*R*)-**13**, and (*S*)-**4** and details about study on the reactivity of pinacol ester of 4-(borono)phenylalanines with **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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