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Enantiodivergent Synthesis of Cyclohexenyl Nucleosides

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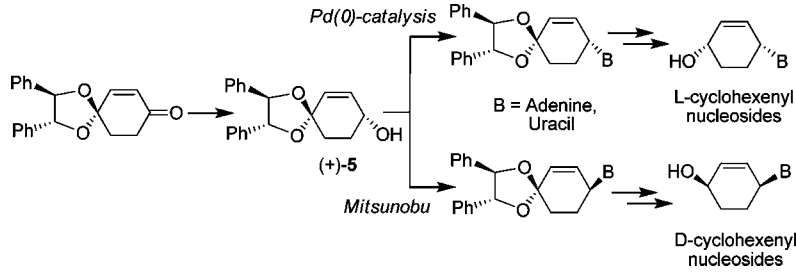

An enantiodivergent synthesis of several cyclohexenyl nucleosides has been efficiently completed starting from the enantiopure hydrobenzoin-derived monoketal of cyclohex-2-en-1,4-dione, (+)-**5**. Stereodiversity was accomplished on the base coupling step. This methodology has proved to be useful for the synthesis of enantiopure pyrimidine and purine nucleoside analogues, which anti-HIV activity has been evaluated.

Introduction

The considerable attention focused on finding new antiviral and antitumor therapeutic agents has been rewarded with the discovery of a variety of carbanucleosides exhibiting potent and selective biological activity.[1] The cyclopentenyl nucleosides (-)-carbovir, **1**,[2] and abacavir, **2**,[3] are among the earlier examples (Figure 1). These analogues are more resistant to hydrolytic processes and have enhanced lipophilicity compare to regular nucleosides, favoring absorption and penetration through the cell membrane. Fewer efforts have been directed toward the synthesis of six-membered carbocyclic analogues.[4] However, cyclohexenyl nucleosides are a promising class of antiviral compounds, wherein replacement of the oxygen atom of the furanose ring by a double bond induces annular flexibility, similar to that of a natural furanose nucleoside.[5] Recently, it has been described that both enantiomers of cyclohexenylguanine **3** display potent and selective anti-herpesvirus activity (HSV-1, HSV-2, VZV, CMV).[6]

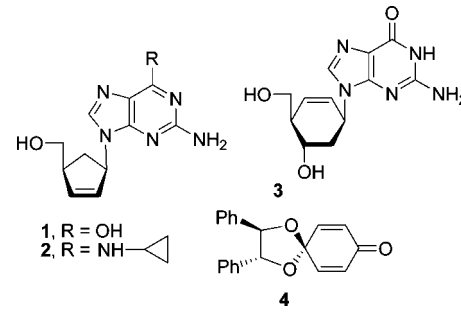

FIGURE 1. Several biological active carbocyclic nucleosides **1**−**3** and chiral *p*-benzoquinone monoketal **4**.

It is well-known that opposite enantiomers can display different pharmacological and toxicological properties.[7] Hence,

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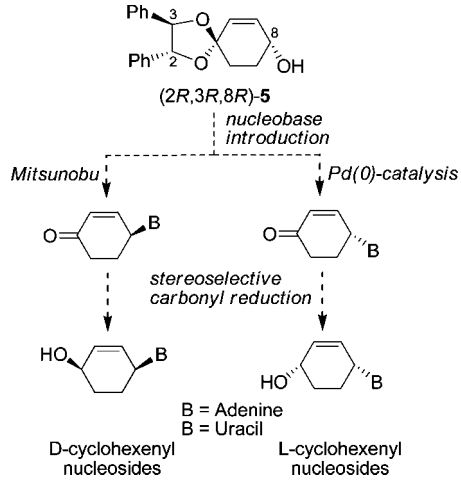
SCHEME 1. Synthetic Strategy



the synthesis of enantiomerically pure nucleoside analogues is required. During the past years our research group has developed efficient methodologies for the preparation of enantiomerically pure cyclohexane compounds. As part of this research, we have prepared a series of *p*-benzoquinone monoketals derived from chiral C_2-symmetric diols (e.g., **4**),[8] which have been successfully used as building blocks in the synthesis of several bioactive products containing a cyclohexane unit in their structure.[9]

This former experience, along with the reported activity of the six-membered carbocyclic nucleosides such as **3**, prompted us to plan the synthesis of enantiopure cyclohexenyl nucleoside analogues designed as potential antiviral agents. Herein we report an enantiodivergent approach to D- and L-4-hydroxycyclohexenyl nucleosides, starting from the common intermediate **5**, which bears a hydrobenzoin moiety as the chiral auxiliary (Scheme 1). We have designed a divergent synthesis that involves two main transformations: (i) introduction of the nucleobase with either inversion (Mitsunobu methodology) or retention (Pd-catalyzed coupling reaction) of configuration, followed by removal of the chiral auxiliary and (ii) stereoselective reduction of the carbonyl group to deliver the target cyclohexene nucleosides with the *cis* relative configuration.

Results and Discussion

The enantiopure allylic alcohol (2*R*,3*R*,8*R*)-**5** was previously synthesized in our laboratory from *p*-benzoquinone in three steps involving selective ketalization with (*R*,*R*)-hydrobenzoin (81% yield), partial hydrogenation using Wilkinson's catalyst (41% yield), and reduction with $NaBH_4$ (67% yield).[10] With the aim of skipping the low-yielding hydrogenation step, we have now set up a more practical and multigram preparation of **5** starting from 1,4-cyclohexandione, **6** (Scheme 2).

SCHEME 2. Synthesis of Key Intermediate (+)-(2*R*,3*R*,8*R*)-5

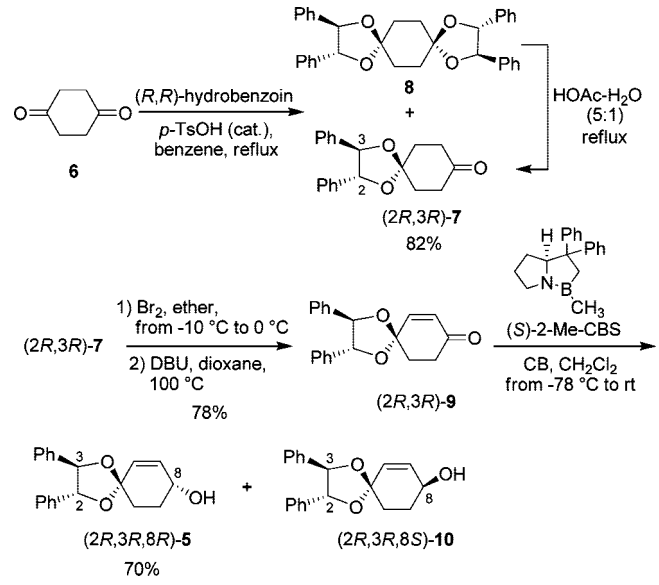


TABLE 1. Reduction of Ketone 9

entry	reducing agent	conditions	yield (%)	**5**:**10**
1	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	MeOH, −78 °C	93	4:1
2	DIBAL-H	THF, −78 °C	71	4:1
3	L-Selectride	THF, −78 °C	63	4:1
4	catecholborane	CH_2Cl_2, −78 °C	33	3:1
5	catecholborane, (*S*)-2-Me-CBS	CH_2Cl_2, −78 °C	90	8:1
6	catecholborane, (*R*)-2-Me-CBS	CH_2Cl_2, −78 °C	95	1:1

Thus, treatment of **6** with (*R*,*R*)-hydrobenzoin in benzene at reflux temperature afforded the monoketal (2*R*,3*R*)-**7** along with the corresponding bisketal **8** in 54% and 46% yield, respectively. Monohydrolysis of **8** furnished an additional amount of (2*R*,3*R*)-**7**, the overall yield for the conversion of **6** into **7** then being 82%. Sequential bromination of the ketone **7** with Br_2 at −5 °C and dehydrobromination, using DBU in dioxane at reflux, afforded the enone (2*R*,3*R*)-**9** in 78% overall yield. Other oxidant methodologies, using IBX[11] or Mukaiyama protocol,[12] proved to be less efficient for this transformation.

The efficiency of the synthesis of the key allylic alcohol (2*R*,3*R*,8*R*)-**5** depends on the diastereoselectivity of the reduction of the carbonyl group of (2*R*,3*R*)-**9**. Hence, we proceeded to study this reaction using different reducing agents (Table 1).

Initially, reduction of ketone **9** was performed using $NaBH_4$ in MeOH in the presence of $CeCl_3$ at −78 °C, affording a ca. 4:1 mixture of (2*R*,3*R*,8*R*)-**5** and (2*R*,3*R*,8*S*)-**10** in 93% yield (entry 1). Similarly, when other reducing agents based on aluminum (entry 2) or boron (entry 3) were employed, values of diastereoselectivity around 4:1 were achieved. When catecholborane (CB) was used in the reaction, a ca. 3:1 mixture of isomers was again obtained albeit in low yield (entry 4).

Better selectivity was achieved by using catecholborane paired with (*S*)-2-Me-CBS (entry 5).[13] In this case a ca. 8:1 mixture of **5** and **10** was obtained in 90% yield, from which the major

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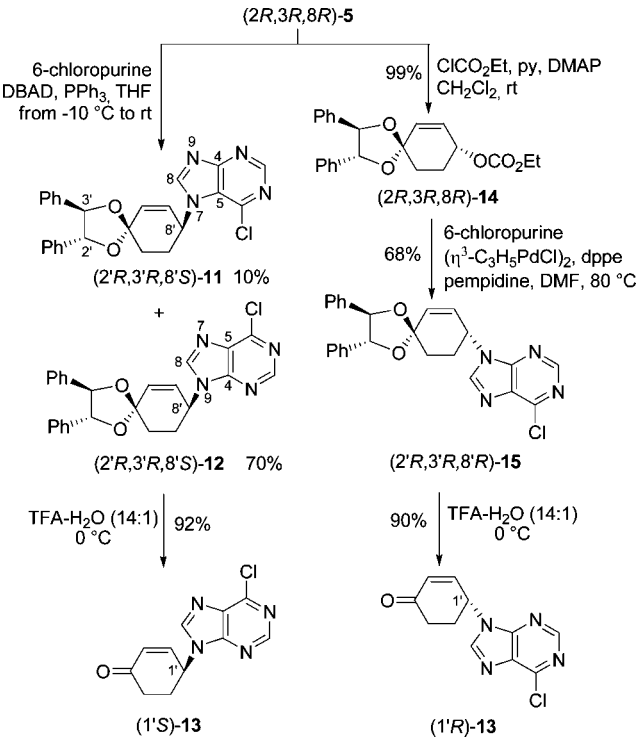
SCHEME 3. Synthesis of (1′*S*)- and (1′*R*)-13

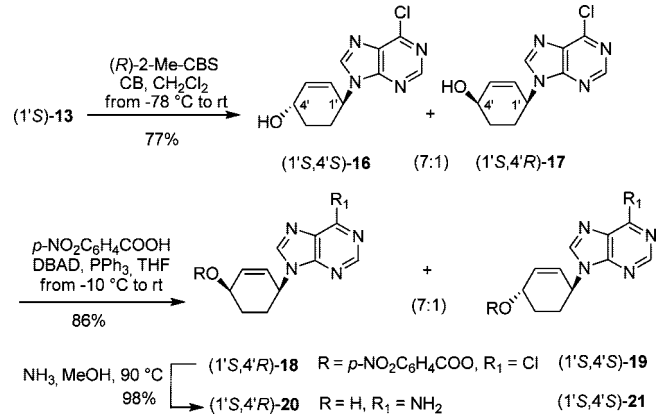


diastereoisomer **5** was isolated by crystallization in 70% yield. Remarkably, reduction with catecholborane paired with the (*R*)-enantiomer of 2-Me-CBS (entry 6) yielded a 1:1 mixture of both diastereoisomers in 95% yield, showing a clear example of mismatching between the sense of chirality of the reducing agent and that of the substrate.

With (2*R*,3*R*,8*R*)-**5** in hand, we assayed the introduction of a purine base by a Mitsunobu type reaction, which has been shown to give carbocyclic nucleosides with inversion of configuration.[14] Thus, the allylic alcohol **5** was reacted with 6-chloropurine in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine to provide the desired *N*9-regioisomer (2′*R*,3′*R*,8′*S*)-**12** in 70% yield, along with the *N*7-coupled product (2′*R*,3′*R*,8′*S*)-**11** in10% yield (Scheme 3). The attachment site of the purine base was deduced from the ^{1}H and ^{13}C NMR spectra wherein the H-8 proton signal and the C-4, C-8, and C-8′ signals of the *N*9-isomer **12** (δ 8.21, 151.4, 153.7, and 49.8) are shifted highfield compared to that of the *N*7-isomer **11** (δ 8.37, 162.4, 147.5, and 51.9). These data agree with those reported in the literature.[15] Removal of the chiral auxiliary from **12** was readily achieved by treatment with a mixture of trifluoroacetic acid−H_2O (14:1), furnishing the cyclohexenone (*1′S*)-**13** in 92% yield, $[\alpha]_D = -73.3$ (*c* 1.35, $CHCl_3$).

Next, the synthesis of the antipode (1′*R*)-**13** was targeted for attention. Trost palladium-catalyzed coupling of allylic carbonates with heterocyclic bases, which proceeds with retention of configuration, has proven to be efficient for the synthesis of carbanucleosides.[16,17] The allylic carbonate (2*R*,3*R*,8*R*)-**14** was prepared quantitatively by reaction of **5** with ethyl chloroformate, pyridine, and DMAP in CH_2Cl_2 and was coupled with 6-chloropurine in the presence of $[\eta^3$-$C_3H_5PdCl]_2$, 1,2-bis(diphenylphosphino)ethane (dppe) and 1,2,2,6,6-pentamethylpiperidine (pempidine) in DMF to afford exclusively the *N*9-isomer (2′*R*,3′*R*,8′*R*)-**15** in 68% yield. In this case, the *N*7 coupling product regioisomer was not detected. The subsequent hydrolysis of the ketal delivered (1′*R*)-**13** in 90% yield, $[\alpha]_D = +70.6$ (*c* 1.35, $CHCl_3$).

SCHEME 4. Synthesis of D-Cyclohexenyl Adenine Nucleoside



Having a convenient methodology for the supply of both enantiomers of **13**, the synthesis of D-*cis*-1-(4-hydroxy-2-cyclohexenyl) adenine was undertaken (Scheme 4). The first step is the reduction of the carbonyl group of the enone (1′*S*)-**13**, wherein β-oriented OH at C-4′ is required. Assayed reductions with available achiral reagents ($NaBH_4-CeCl_3\cdot 7H_2O$, $LiBH_4-ZnCl_2$) produced chromatographically inseparable mixtures of both isomers (1′*S*,4′*S*)-**16** and (1′*S*,4′*R*)-**17** in good yields, with the *trans*-isomer **16** being predominant in all cases (ca. 3:1). A reagent-controlled stereoselective reduction with catecholborane in the presence of (*R*)-2-Me-CBS increased notably the proportion of the *trans* alcohol, delivering a 7:1 mixture of **16** and **17** in 77% global yield. Interestingly, when the reaction was performed with the opposite enantiomer of the catalyst, (*S*)-2-Me-CBS, the *trans*:*cis* ratio dropped to 2:1. Its relative configuration was established by detailed 1D and 2D NMR experiments. The 1,4-*trans* relationship of the major isomer **16** was assigned from the coupling constants observed in the ^{1}H NMR spectrum. For H-1′ a large coupling constant (10.6 Hz) with H-6ax and a smaller coupling constant (5.2 Hz) with H-6eq were detected. Similarly, H-4′ showed coupling constants of 9.7 and 4.7 Hz with H-5ax and H-5eq, respectively. Altogether these coupling constants indicate that both the nucleobase on C-1 and the hydroxyl group on C-4′ occupy pseudoequatorial positions and are arranged in a 1,4-*trans* relationship.

According to these results, we decided to assay the inversion of the hydroxyl group in **16** through a Mitsunobu reaction, using *p*-nitrobenzoic acid as the nucleophile. In the event, a 7:1 mixture of alcohols (1′*S*,4′*S*)-**16** and (1′*S*,4′*R*)-**17** delivered a 7:1 mixture of the inverted nitrobenzoates (1′*S*,4′*R*)-**18** and (1′*S*,4′*S*)-**19** in 86% yield. A final ammonolysis removed the nitrobenzoates and converted the chloropurine derivatives to a 7:1 mixture of the adenine analogues (1′*S*,4′*R*)-**20** and (1′*S*,4′*S*)-**21** in 98% yield, with the total yield from **5** being 42%. Unfortunately, we were unable to separate these isomers, and all attempts to obtain a pure sample of the targeted D-

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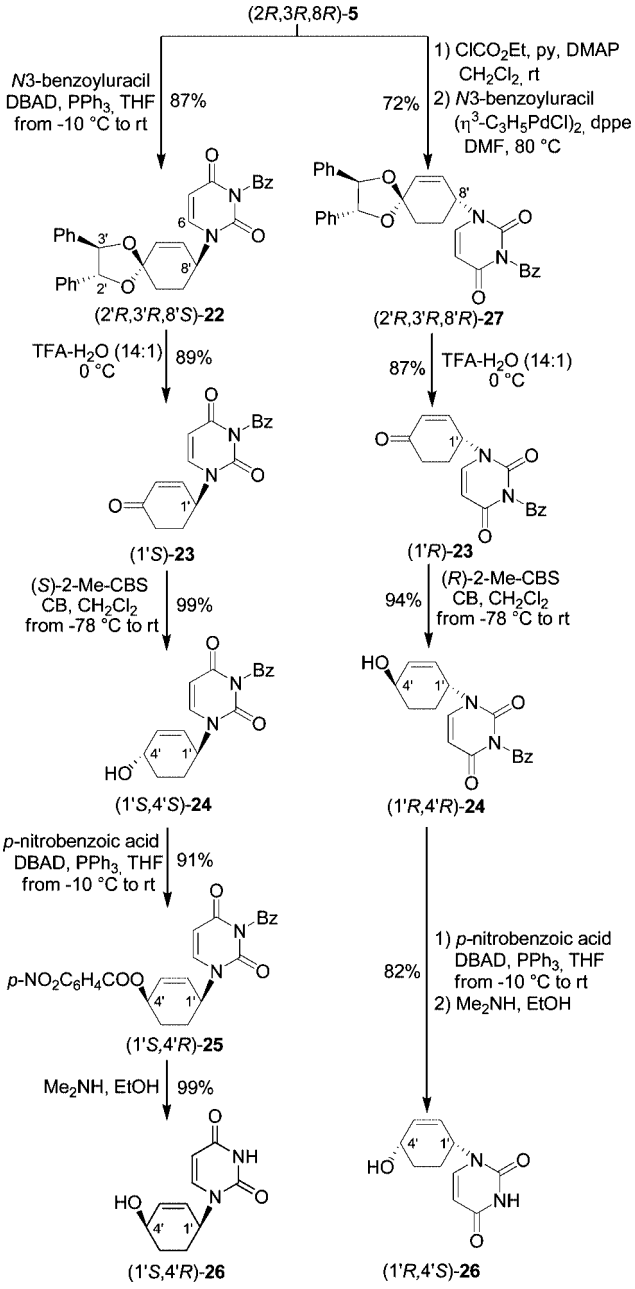
SCHEME 5. Synthesis of D- and L-Cyclohexenyl Uracil Nucleosides



cyclohexenyl adenine **20** met with failure. The *cis*-1,4-substitution of the major isomer **20** was confirmed by comparing its NMR spectra with those previously reported in the literature for racemic **20**.[18]

We then turned our attention to the synthesis of uracil cyclohexenyl nucleoside analogues, following the same strategy as above (Scheme 5). First, a Mitsunobu reaction was applied for introducing the base moiety. Thus, coupling of (2*R*,3*R*,8*R*)-**5** with *N*3-benzoyluracil[19] gave only the *N*1-alkylated derivative (2′*R*,3′*R*,8′*S*)-**22** in good yield.[20] The *O*-alkyl compound, a common byproduct of this reaction, was not detected in the NMR spectra of the reaction crude. The attachment site of the pyrimidine base was established by an HMBC experiment that showed correlation between H-8′ and C-6.

Acidic hydrolysis followed by stereoselective CBS-catalyzed reduction of (1′*S*)-**23** generated exclusively the *trans* alcohol (1′*S*,4′*S*)-**24** in 88% yield for the two steps, $[\alpha]_D = +13.2$ (*c* 0.8, $CHCl_3$). The *trans*-1,4-substitution pattern of **24** was established in a similar way as for the purine derivative by detailed 1D and 2D NMR analyses and was further confirmed from the value of the coupling constants observed in the ^{1}H NMR spectrum of its cyclohexanyl derivative **28**, easily obtained by an hydrogenation reaction. Thus, in the ^{1}H NMR spectrum of **28** H-1′ resonates at δ 4.44 and appears as a triplet of triplets with coupling constants $J_{1',2'ax} \approx J_{1',6'ax} = 11.9$ Hz and $J_{1',2'eq} \approx J_{1',6'eq} = 3.6$ Hz. A similar pattern is observed for H-4′, appearing as a triplet of triplets at δ 3.66 with large diaxial coupling constants ($J_{4',5'ax} \approx J_{4',3'ax} = 11.1$ Hz) and small coupling constants ($J_{4',5'eq} \approx J_{4',3'eq} = 4.3$ Hz). These data suggest a chair conformation with both the heterocyclic base moiety and the hydroxyl group in equatorial orientations, which is possible only in a 1,4-*trans* relationship. As above, the corresponding *cis*-1,4 compound was obtained by using a second Mitsunobu-type reaction between the allylic alcohol (1′*S*,4′*S*)-**24** and *p*-nitrobenzoic acid, furnishing the nitrobenzoate (1′*S*,4′*R*)-**25**, which was treated with methylamine in ethanol solution[21] to provide the target *cis*-1,4-hydroxy-2-cyclohexenyl uracil, (1′*S*,4′*R*)-**26**, in 90% yield for the two steps, $[\alpha]_D = +73.0$ (*c* 1.0, MeOH).

The synthesis of its enantiomer (1′*R*,4′*S*)-**26** was carried out via the palladium-catalyzed coupling reaction of the previously described allylic carbonate (2*R*,3*R*,8*R*)-**14** with *N*3-benzoyluracil, which afforded the uracil derivative (2′*R*,3′*R*,8′*R*)-**27** in 72% yield.[22] Acid treatment and subsequent diastereoselective reduction furnished (1′*R*,4′*R*)-**24** in 82% yield, $[\alpha]_D = +12.4$ (*c* 1.0, $CHCl_3$). Finally, Mitsunobu-type reaction and simultaneous removal of the ester protecting groups gave access to the cyclohexenyl uracil analogue (1′*R*,4′*S*)-**26** in 82% yield for the two steps, $[\alpha]_D = -72.2$ (*c* 1.1, MeOH). Thus, the synthesis of both enantiomers (1′*R*,4′*S*)- and (1′*S*,4′*R*)-**26** has been successfully accomplished from the common intermediate (2*R*,3*R*,8*R*)-**5** in 68% and 47% yield, respectively.

As a preliminary test, the new synthesized nucleoside analogues were evaluated on MT4 cells for anti-HIV-1 activity against wild-type NL4-3 strain as well as cytotoxicity using AZT and AMD3100 as the positive control. The results are summarized in Table 2. Unfortunately, although a weak anti-HIV activity was found for **11**, **12**, (1′*S*)-**13**, (1′*R*)-**13**, **15**, (1′*R*)-**23**, and (1′*S*)-**23**, it was not separate from cytotoxicity.

Conclusions

In summary, an enantiodivergent synthesis of adenine and uracil cyclohexenyl nucleosides has been developed from the unique chiral precursor (2*R*,3*R*)-**9**, bearing a dihydrobenzoin

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TABLE 2. Anti-HIV-1 Activity against Wild-Type NL4-3 Strain and Cytotoxicity of the Synthesized Cyclohexenyl Nucleosides in Comparison with AZT and AMD3100, used as Reference Drugs[a]

compd	EC_{50}[b]	CC_{50}[c]
11	>2.4	2.4
12	>6.8	6.8
(1′*S*)-**13**	>0.5	0.5
(1′*R*)-**13**	>13.5	13.5
15	>6.4	6.4
20, **21**	>25	>25
22	>25	>25
27	>25	>25
(1′*S*)-**23**	>4.3	4.3
(1′*R*)-**23**	>10.1	10.1
(1′*S*,4′*S*)-**24**	>25	>25
(1′*R*,4′*R*)-**24**	>25	>25
(1′*S*,4′*R*)-**26**	>25	>25
(1′*R*,4′*S*)−**26**	>25	>25
AZT	0.0010	>0.1
AMD3100	0.0015	>0.1

[a] All values are in μg/mL. Data represent mean values of at least two experiments. [b] EC_{50}: effective concentration 50 or needed concentration to inhibit 50% HIV-induced cell death, evaluated with the MTT method in MT-4 cells. [c] CC_{50}: cytotoxic concentration 50 or needed concentration to induce 50% death of noninfected cells, evaluated with the MTT method in MT-4 cells.

moiety as the chiral auxiliary. Alternative introduction of the base via a Mitsunobu reaction or a Pd(0)-promoted coupling provided the means for enantiodivergency. The synthetic sequences are short and well yielding, and the methodology has proved to be useful for the preparation of pyrimidine as well as purine nucleosides.

Experimental Section

General experimental details are provided in Supporting Information.

(2*R*,3*R*,8*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]decan-6-ene-8-ol (5). To a stirred solution of cyclohexenone **9** (5.80 g, 18.93 mmol) in dry CH_2Cl_2 (130 mL) at −78 °C was added (*S*)-Me-CBS 1.0 M in toluene (3.8 mL, 3.79 mmol) under argon atmosphere. Then, catecholborane 1.0 M in THF (42 mL, 41.65 mmol) was slowly added over 2 h, by means of a syringe pump, and the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by adding saturated aqueous NH_4Cl (150 mL). Phases were separated and the aqueous was then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography (hexanes−EtOAc, 4:1) to provide a 8:1 diastereomeric mixture of cyclohexenols **5** and **10** (5.25 g, 17.04 mmol, 90% yield) as a white solid. Recrystallization in diethyl ether-pentane furnished pure cyclohexenol **5** (4.09 g, 13.25 mmol, 70% overall yield). **5**: mp 116−117 °C (*n*-pentane−ethyl ether) {lit.[10] 117−119 °C (*n*-pentane−ethyl ether)}; $[\alpha]^{20}_D$ = +55.0 (*c* 0.6, CH_2Cl_2), {lit.[10] $[\alpha]^{20}_D$ = +49.2 (*c* 0.6, CH_2Cl_2)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 6H, H-Ar), 7.26.-7.17 (m, 4H, H-Ar), 6.05 (ddd, $J_{6,7}$ = 10.1 Hz, $J_{6,8}$ = 2.3 Hz, $J_{6,10}$ = 1.2 Hz, 1H, H-6), 5.92 (dt, $J_{7,6}$ = 10.1 Hz, $J_{7,8}$ = $J_{7,9}$ = 1.5 Hz, 1H, H-7), 4.79 (d, $J_{3,2}$ = 8.5 Hz, 1H, H-3), 4.69 (d, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 4.29 (ddt, $J_{8,9ax}$ = 9.0 Hz, $J_{8,9eq}$ = 4.3 Hz, $J_{8,7}$ = $J_{8,6}$ = 2.0 Hz, 1H, H-8), 2.29−2.18 (m, 2H, H-9, H-10), 2.11−2.01 (m, 1H, H-9/H-10), 1.93−1.80 (m, 1H, H-9/H-10); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.3, 136.2, 135.7, 129.5, 128.5, 128.4, 128.3, 126.8, 126.6, 105.7, 85.5, 85.1, 66.6, 32.8, 31.0.

6-Chloro-9-[(2′*R*,3′*R*,8′*S*)-2′,3′-diphenyl-1′,4′-dioxaspiro[4.5]decan-6′-ene-8′-yl]purine (12) and its N7-Isomer (11). A solution of DBAD (761 mg, 3.24 mmol) in anhydrous THF (6 mL) was added dropwise over 10 min to a −10 °C stirred suspension of **5** (500 mg, 1.62 mmol), 6-chloropurine (505 mg, 3.24 mmol) and triphenylphosphine (858 mg, 3.24 mmol) in anhydrous THF (10 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. The organic solvent was removed under vacuum, and the resulting oil was purified by flash chromatography (hexanes−EtOAc, 4:1) to afford the *N*9-isomer **12** (505 mg, 1.13 mmol, 70% yield) and the corresponding *N*7-isomer **11** (75 mg, 0.16 mmol, 10% yield) both as white solids. **11** (*N*7-isomer): mp 196−198 °C (ethyl ether); $[\alpha]^{20}_D$ = +44.0 (*c* 0.25, $CHCl_3$); IR (ATR) ν 3027, 2880, 1597, 1380, 1210, 1051, 1018, 971, 694, 621 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.91 (s, 1H, H-2), 8.37 (s, 1H, H-8), 7.38−7.28 (m, 6H, H-Ar), 7.28−7.18 (m, 4H, H-Ar), 6.49 (dd, $J_{6′,7′}$ = 10.0 Hz, $J_{6′,8′}$ = 1.8 Hz, 1H, H-6′), 6.19 (dd, $J_{7′,6′}$ = 10.0 Hz, $J_{7′,8′}$ = 3.9 Hz, 1H, H-7′), 5.73 (m, 1H, H-8′), 4.89 (d, $J_{3′,2′}$ = 8.6 Hz, 1H, H-3′), 4.79 (d, $J_{2′,3′}$ = 8.6 Hz, 1H, H-2′), 2.71−2.55 (m, 1H, H-9′), 2.35−2.15 (m, 3H, H-9′,2H-10′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.4, 152.6, 147.5, 142.9, 136.1, 135.7, 135.5, 128.7, 128.6, 128.3, 126.7, 126.6, 126.5, 122.1, 104.3, 85.8, 85.2, 51.9, 30.7, 29.0; HRMS (ESI+) calcd for $C_{25}H_{21}ClN_4O_2Na$ 467.1245 [M + Na]$^+$, found 467.1243. **12** (*N*9-isomer): mp 197−199 °C (ethyl ether); $[\alpha]^{20}_D$ = −20.0 (*c* 0.25, $CHCl_3$); IR (ATR) ν 3064, 3027, 1597, 1566, 1446, 1396, 1089, 933, 768, 695 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.78 (s, 1H, H-2), 8.21 (s, 1H, H-8), 7.38−7.29 (m, 6H, H-Ar), 7.29−7.20 (m, 4H, H-Ar), 6.44 (dd, $J_{6′,7′}$ = 10.0 Hz, $J_{6′,8′}$ = 1.9 Hz, 1H, H-6′), 6.14 (dd, $J_{7′,6′}$ = 10.0 Hz, $J_{7′,8′}$ = 3.6 Hz, 1H, H-7′), 5.45 (m, 1H, H-8′), 4.90 (d, $J_{3′,2′}$ = 8.5 Hz, 1H, H-3′), 4.82 (d, $J_{2′,3′}$ = 8.5 Hz, 1H, H-2′), 2.63−2.48 (m, 1H, H-9′), 2.35−2.22 (m, 3H, H-9′, 2H-10′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.9, 151.4, 151.2, 143.7, 135.8, 135.7, 135.3, 132.0, 128.7, 128.6, 127.7, 126.7, 126.6, 104.4, 85.8, 85.2, 49.8 31.8, 27.8; HRMS (ESI+) calcd for $C_{25}H_{21}ClN_4O_2Na$ 467.1245 [M + Na]$^+$, found 467.1233.

6-Chloro-9-[(1′*S*)-4′-oxo-cyclohex-2′-ene-1′-yl]purine [(1′*S*)-13]. To a 14:1 mixture of trifluoroacetic acid (10 mL) and water (0.7 mL) at 0 °C was added the 6-chloropurine derivate **12** (450 mg, 1.01 mmol) in one portion. After 40 min of stirring at 0 °C, CH_2Cl_2 (10 mL) and water (10 mL) were added, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude material by flash chromatography (EtOAc) yielded cyclohexenone (1′*S*)-**13** (231 mg, 0.93 mmol, 92% yield) as a white solid: mp 124−126 °C (ethyl ether); $[\alpha]^{20}_D$ = −73.3 (*c* 1.35, $CHCl_3$); IR (ATR) ν 3061, 2957, 1682, 1589, 1401, 1332, 1145, 937, 826, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, H-2), 8.17 (s, 1H, H-8), 6.95 (ddd, $J_{2′,3′}$ = 10.2 Hz, $J_{2′,1′}$ = 2.5 Hz, $J_{2′,6′}$ = 1.4 Hz, 1H, H-2′), 6.34 (ddd, $J_{3′,2′}$ = 10.2 Hz, $J_{3′,1′}$ = 2.6 Hz, $J_{3′,5′}$ = 0.6 Hz, 1H, H-3′), 5.68 (m, 1H, H-1′), 2.74−2.63 (m, 2H, H-5′), 2.63−2.48 (m, 2H, H-6′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.0, 152.2, 151.7, 151.3, 145.0, 142.9, 132.8, 131.8, 51.3, 35.8, 30.4; HRMS (ESI+) calcd for $C_{11}H_9ClN_4ONa$ 271.0357 [M + Na]$^+$, found 271.0351.

(2*R*,3*R*,8*R*)-2,3-Diphenyl-8-ethoxycarbonate-1,4-dioxaspiro[4.5]-decan-6-ene (14). To a mixture of alcohol **5** (300 mg, 0.97 mmol) and DMAP (24 mg, 0.19 mmol) in dry CH_2Cl_2 (9 mL) were added, under argon atmosphere, pyridine (235 μL, 2.92 mmol) and, dropwise, ethyl chloroformate (288 μL, 2.92 mmol). The reaction mixture was stirred at room temperature for 4 h, quenched with 1 M aqueous hydrochloric acid (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic fractions were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes−EtOAc, 4:1) to furnish carbonate **14** (366 mg, 0.96 mmol, 99% yield) as a colorless syrup: $[\alpha]^{20}_D$ = +69.2 (*c* 2.5, $CHCl_3$); IR (ATR) ν 1729, 1495, 1372, 1262, 1116, 952, 793, 698 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36−7.27 (m, 6H, H-Ar), 7.27−7.16 (m, 4H, H-Ar), 6.05 (s, 2H, H-7, H-6), 5.23 (br t, *J* = 5.4 Hz, 1H, H-8), 4.79 (d, $J_{3,2}$ = 8.7 Hz, 1H, H-3), 4.72 (d, $J_{2,3}$ = 8.7 Hz, 1H, H-2), 4.22 (q, *J* = 7.4 Hz, 2H, -CH_2-), 2.37−2.45 (br dd, *J* = 11.1 Hz, *J* = 2.5 Hz, 2H, H-10,

H-9), 2.18−2.01 (m, 2H, H-10, H-9), 1.32 (t, J = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.9, 136.3, 136.2, 131.9, 130.6, 128.5, 128.4, 126.7, 126.7, 126.6, 105.3, 85.7, 85.2, 72.1, 64.1, 32.4, 27.1, 14.3; HRMS (ESI+) calcd for $C_{23}H_{24}O_5Na$ 403.1516 $[M + Na]^+$, found 403.1520.

6-Chloro-9-[(2′*R*,3′*R*,8′*R*)-2′,3′-diphenyl-1′,4′-dioxaspiro[4.5]decan-6′-ene-8′-yl]purine (15). To a mixture of carbonate **14** (105 mg, 0.28 mmol), 6-chloropurine (65 mg, 0.41 mmol), allylpalladium chloride dimer (3 mg, 0.01 mmol), and 1,4-bis(diphenylphosphino)ethane (10 mg, 0.03 mmol) in anhydrous DMF (2.5 mL) was added dropwise 1,2,2,6,6-pentamethylpiperidine (150 μL, 0.83 mmol) under argon atmosphere. The solution was stirred at 80 °C overnight. Then, the reaction mixture was passed through a Celite pad, and the organic layer was concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (hexanes−EtOAc, from 4:1 to 2:1) to provide **15** (84 mg, 0.19 mmol, 68% yield) as a white solid: mp 96−98 °C (ethyl ether); $[\alpha]^{20}_D$ = +16.0 (*c* 0.25, $CHCl_3$); IR (ATR) υ 3061, 2924, 2876, 1588, 1399, 1195, 961, 793, 697, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H, H-2), 8.23 (s, 1H, H-8), 7.37−7.28 (m, 6H, H-Ar), 7.28−7.18 (m, 4H, H-Ar), 6.32 (dd, $J_{6',7'}$ = 10.1 Hz, $J_{6',8'}$ = 2.2 Hz, 1H, H-6′), 6.07 (d, $J_{7',6'}$ = 10.1 Hz 1H, H-7′), 5.46 (br m, 1H, H-8′), 4.88 (d, $J_{3',2'}$ = 8.5 Hz, 1H, H-3′), 4.74 (d, $J_{2',3'}$ = 8.5 Hz, 1H, H-2′), 2.55−2.43 (m, 1H, H-9′), 2.37−2.22 (m, 3H, H-9′, H-10′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.0, 151.4, 151.2, 143.4, 135.7, 135.6, 134.2, 131.8, 129.0, 128.7, 128.5, 126.9, 126.7, 126.5, 104.5, 85.7, 85.3, 50.8, 33.0, 29.1; HRMS (ESI+) calcd for $C_{25}H_{21}ClN_4O_2Na$ 467.1245 $(M + Na)^+$, found 467.1247.

6-Chloro-9-[(1′*R*)-4′-oxo-cyclohex-2′-ene-1′-yl]purine [(1′*R*)-13]. To a 14:1 solution of trifluoroacetic acid (2.7 mL) and water (0.2 mL) at 0 °C was added the 6-chloropurine derivate **15** (120 mg, 0.27 mmol) in one portion. After 40 min of stirring at 0 °C, CH_2Cl_2 (3 mL) and water (3 mL) were added, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 3 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude material by flash chromatography (EtOAc) yielded cyclohexenone (1′*R*)-**13** (60 mg, 0.24 mmol, 90% yield) as a white solid: $[\alpha]^{20}_D$ = +70.6 (*c* 1.35, $CHCl_3$). The other physical and spectral data are identical of those reported for its enantiomer (1′*S*)-**13**.

***trans*-6-Chloro-9-[(1′*S*,4′*S*)-4′-hydroxy-cyclohex-2′-ene-1′-yl]purine (16) and its *cis*-Isomer (17).** To a stirred solution of cyclohexenone (1′*S*)-**13** (120 mg, 0.48 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C was added (*R*)-Me-CBS 1.0 M in toluene (97 μL, 0.097 mmol) under argon atmosphere. Then, catecholborane 1.0 M in THF (1.1 mL, 1.11 mmol) was slowly added by means of a syringe pump (addition time 2 h), and the mixture was stirred during 16 h, allowing it to warm to room temperature. Then, the reaction was quenched by adding of saturated aqueous NH_4Cl (6 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 8 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (CH_2Cl_2−MeOH, from 50:1 to 25:1) to afford an unseparable 7:1 mixture of the *trans*- and *cis*-cyclohexenols **16** and **17** (93 mg, 0.37 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 87% *trans*-isomer **16**) δ 8.73 (d, J = 0.7 Hz, 1H, H-2), 8.11 (s, 1H, H-8), 6.24 (dtt, $J_{3',2'}$ = 10.1 Hz, $J_{3',4'} = J_{3',1'}$ = 2.9 Hz, $J_{3',5'} = J_{3',5'}$ = 0.9 Hz, 1H, H-3′), 5.86 (dqt, $J_{2',3'}$ = 10.0 Hz, $J_{2',1'} = J_{2',4'} = J$ = 1.9 Hz, $J_{2',6'} = J$ = 1.0 Hz, 1H, H-2′), 5.37 (ddt, $J_{1',6'ax}$ = 10.6 Hz, $J_{1',6'eq}$ = 5.2 Hz, $J_{1',3'} = J_{1',2'}$ = 2.6 Hz, 1H, H-1′), 4.47 (ddt, $J_{4',5'ax}$ = 9.7 Hz, $J_{4',5'eq}$ = 4.7 Hz, $J_{4',3'} = J_{4',2'}$ = 2.2 Hz, 1H, H-4′), 2.47−2.38 (br dd, J = 8.4 Hz, $J_{6',5'}$ = 5.8 Hz, 1H, H-6′), 2.19−2.10 (br dd, J = 11.7 Hz, $J_{5',6'}$ = 5.8 Hz, 1H, H-5′), 1.96−1.86 (m, 1H, H-6′), 1.82−1.71 (m, 1H, H-5′); (ca. 13% *cis*-isomer **17**, observable signals) δ 8.74 (s, 1H, H-2), 8.24 (s, 1H, H-8), 6.30 (m, 1H, H-3′), 5.88 (br d, 1H, H-2′), 5.27 (m, 1H, H-1′), 4.37 (m, 1H, H-4′); ^{13}C NMR (62.5 MHz, $CDCl_3$) (major *trans*-isomer **16**) δ 152.0, 151.6, 151.2, 143.4, 137.2, 131.7, 125.9, 64.9, 50.9, 30.1, 28.0; (minor *cis*-isomer **17**) δ 151.9, 151.7, 151.3, 144.1, 136.8, 131.8, 125.7, 63.9, 50.2, 28.0, 25.7; HRMS (ESI+) calcd for $C_{11}H_{11}ClN_4ONa$ 273.0514 $[M + Na]^+$, found 273.0512.

***cis*-6-Chloro-9-[(1′*S*,4′*R*)-4′-(*p*-nitrobenzoyloxy)-cyclohex-2′-ene-1′-yl]purine (18) and its *trans*-Isomer (19).** A solution of DBAD (155 mg, 0.66 mmol) in dry THF (1.5 mL) was added dropwise over 10 min to a −10 °C stirred suspension of a 7:1 mixture of *trans*- and *cis*-cyclohexenols **16** and **17** (83 mg, 0.33 mmol), *p*-nitrobenzoic acid (111 mg, 0.66 mmol) and triphenylphosphine (175 mg, 0.66 mmol) in anhydrous THF (2 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The organic solvent was removed under vacuum and the resulting oil was purified by flash chromatography (hexanes−EtOAc, 2:1) furnishing an unseparable ca. 7:1 mixture of *cis*- and *trans*-*p*-nitrobenzoates **18** and **19** (114 mg, 0.26 mmol, 86% yield). IR (ATR) υ 1722, 1588, 1522, 1436, 1332, 1270, 1117, 998, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 87% *cis*-isomer **18**) δ 8.78 (s, 1H, H-2), 8.31 (d, J = 8.7 Hz, 2H, *Ph*-NO_2), 8.25 (s, 1H, H-8), 8.24 (d, J = 8.7 Hz, 2H, *Ph*-NO_2), 6.40 (ddd, $J_{3',2'}$ = 10.0 Hz, $J_{3',4'}$ = 3.4 Hz, J = 2.0 Hz, 1H, H-3′), 6.16 (br dd, $J_{2',3'}$ = 10.0 Hz, $J_{2',1'}$ = 2.6 Hz, 1H, H-2′), 5.65 (br, 1H, H-4′), 5.40 (br, 1H, H-1′), 2.33 (m, 1H, H-6′), 2.22 (m, 2H, H-5′), 2.07 (m, 1H, H-6′); (ca. 13% *trans*-isomer **19**, observable signals) δ 8.78 (s, 1H, H-2), 8.17 (s, 1H, H-8), 6.35 (m, 1H, H-3′), 6.11 (br d, 1H, H-2′), 5.79 (br, 1H, H-4′), 5.49 (br, 1H, H-1′).

***cis*-9-[(1′*S*,4′*R*)-4′-Hydroxy-cyclohex-2′-ene-1′-yl]adenine (20) and its *trans*-Isomer (21).** A pressure flask was charged with a 7:1 mixture of *p*-nitrobenzoates **18** and **19** (25 mg, 0.06 mmol) in MeOH (3 mL) and the solution was saturated with ammonia. Then, the pressure flask was closed, heated up to 90 °C and stirred at this temperature for 48 h. Once the excess of ammonia was eliminated (by passing through a stream of nitrogen), the volatiles were removed under reduced pressure and the remaining colorless oil was purified by flash chromatography (CH_2Cl_2−MeOH, from 20:1 to 9:1) to provide an inseparable mixture of adenine derivates **20** and **21** (14 mg, 0.06 mmol, 98% yield) in a 7:1 diastereomeric ratio. ^{1}H NMR (400 MHz, d_6-DMSO) (ca. 87% *cis*-isomer **20**) δ 8.14 (s, 1H, H-2), 8.04 (s, 1H, H-8), 7.24 (br, 2H, -NH_2), 6.08 (ddd, $J_{3',2'}$ = 10.1 Hz, $J_{3',4'}$ = 3.2 Hz, $J_{3',1'}$ = 2.0 Hz, 1H, H-3′), 5.82 (ddd, $J_{2',3'}$ = 10.1 Hz, $J_{2',1'}$ = 3.5 Hz, $J_{2',4'}$ = 1.5 Hz, 1H, H-2′), 5.04 (dddd, $J_{1',6'ax}$ = 7.5 Hz, $J_{1',6'eq}$ = 5.5 Hz, $J_{1',2'}$ = 3.6 Hz, $J_{1',3'}$ = 1.9 Hz, 1H, H-1′), 4.95 (d, $J_{OH,1'}$ = 6.6 Hz, 1H, -O*H*), 4.08 (qdd, $J_{4',5'ax} = J_{4',5'eq} = J_{4',0H}$ = 6.6 Hz, $J_{4',3'}$ = 3.2 Hz, $J_{4',2'}$ = 1.8 Hz, 1H, H-4′), 1.97 (m, 2H, H-5′), 1.82 (m, 1H, H-6′), 1.55 (m, 1H, H-6′); (ca. 13% *trans*-isomer **21**, observable signals) δ 8.13 (s, 1H, H-2), 5.97 (br d, 1H, H-3′), 5.72 (br d, 1H, H-2′), 5.13 (ddt, 1H, H-1′), 4.23 (ddq, 1H, H-4′), 2.16 (m, 1H, H-5′); ^{13}C NMR (90 MHz, d_6-DMSO) (*cis*-isomer **20**) δ 156.1, 152.4, 149.1, 139.1, 136.7, 125.7, 119.0, 63.3, 48.6, 28.1, 25.8; (*trans*-isomer **21**, observable signals) δ 126.4, 64.2, 50.2, 30.7; HRMS (ESI+) calcd for $C_{11}H_{13}N_5ONa$ 254.1012 $[M + Na]^+$, found 254.1011.

***N*3-Benzoyl-1-[(2′*R*,3′*R*,8′*S*)-2′,3′-diphenyl-1′,4′-dioxaspiro[4.5]decan-6′-ene-8′-yl]uracil (22).** A solution of DBAD (457 mg, 1.94 mmol) in dry THF (2.5 mL) was added dropwise over 10 min to a −10 °C stirred suspension of **5** (300 mg, 0.97 mmol), *N*3-benzoyluracil (420 mg, 1.94 mmol), and triphenylphosphine (515 mg, 1.944 mmol) in anhydrous THF (4 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. The organic solvent was removed under vacuum, and the resulting oil was purified by flash chromatography (hexanes−EtOAc, 4:1) to furnish **22** (428 mg, 0.85 mmol, 87% yield) as a white solid: mp 110−112 °C (ethyl ether); $[\alpha]^{20}_D$ = +50.0 (*c* 0.5, $CHCl_3$); IR(ATR) υ 2923, 1744, 1702, 1660, 1437, 1360, 1247, 1120, 788, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 6.4 Hz, J = 1.3 Hz, 2H:H-Bz), 7.66 (tt, J = 6.9 Hz, J = 1.1 Hz, 1H, H-Bz), 7.51 (tt, J = 8.2 Hz, J = 1.6 Hz, 2H, H-Bz), 7.40 (d, $J_{6,5}$ = 8.2 Hz, 1H, H-6), 7.34 (m, 6H, H-Ar), 7.23 (m, 4H, H-Ar), 6.40 (ddd, $J_{7',6'}$ = 11.8 Hz, $J_{7',8'}$ = 2.3 Hz, $J_{7',9'}$ = 1.6 Hz, 1H, H-7′), 5.90 (dd, $J_{6',7'}$ = 9.9 Hz, $J_{6',8'}$ = 3.1 Hz, 1H,

H-6′), 5.82 (d, $J_{5,6}$ = 7.9 Hz, 1H, H-5), 5.30 (m, 1H, H-8′), 4.85 (d, $J_{3′,2′}$ = 8.7 Hz, 1H, H-2′/H-3′), 4.83 (d, $J_{2′,3′}$ = 8.7 Hz, 1H, H-2′/3′), 2.43−2.35 (m, 1H, H-10′), 2.33−2.25 (td, *J* = 13.8 Hz, *J* = 3.7 Hz, 1H, H-9′), 2.16 (td, *J* = 10.2 Hz, *J* = 2.9 Hz, 1H, H-9′), 2.11−2.01 (m, 1H, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.2, 150.0, 141.2, 136.2, 136.0, 136.0, 135.2, 131.6, 130.6, 129.3, 129.1, 128.8, 128.7, 128.7, 126.8, 126.7, 104.5, 102.6, 86.0, 85.5, 51.6, 32.6, 27.3; HRMS (ESI+) calcd for $C_{31}H_{26}N_2O_5Na$ 529.1734 $[M + Na]^+$, found 529.1726.

***N*3-Benzoyl-1-[(1′*S*)-4′-oxo-cyclohex-2′-ene-1′-yl]uracil [(1′*S*)-23].** To a 14:1 solution of trifluoroacetic acid (8 mL) and water (0.6 mL) at 0 °C was added the *N*3-benzoyluracil derivate **22** (330 mg, 0.65 mmol) in one portion. After 40 min of stirring at 0 °C, CH_2Cl_2 (8 mL) and water (8 mL) were added, phases were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 8 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude material by flash chromatography (EtOAc) provided ketone (1′*S*)-**23** (179 mg, 0.58 mmol, 89% yield) as a white solid: mp 86−88 °C (CH_2Cl_2−ethyl ether); $[\alpha]^{20}_D$ = +12.9 (*c* 2.0, $CHCl_3$); IR (ATR) *υ* 3088, 2933, 1742, 1701, 1655, 1439, 1376, 851, 791, 683, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2 Hz, *J* = 1.2 Hz, 2H, H-Bz), 7.68 (tt, *J* = 7.4 Hz, *J* = 1.3 Hz, 1H, H-Bz), 7.52 (tt, *J* = 7.4 Hz, 2H, H-Bz), 7.26 (d, $J_{6,5}$ = 8.1 Hz, 1H, H-6), 6.80 (dt, $J_{2′,3′}$ = 10.3 Hz, $J_{2′,1′}$ = 2.1 Hz, $J_{2′,6′}$ = 2.1 Hz, 1H, H-2′), 6.27 (ddd, $J_{3′,2′}$ = 10.3 Hz, $J_{3′,1′}$ = 2.8 Hz, $J_{3′,5′}$ = 0.5 Hz, 1H, H-3′), 5.90 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-5), 5.56 (ddt, $J_{1′,6′ax}$ = 10.2 Hz, $J_{1′,6′eq}$ = 4.9 Hz, $J_{1′,2′}$ = $J_{1′,3′}$ = 2.5 Hz, 1H, H-1′), 2.66−2.42 (m, 3H, H-6′, 2H-5′), 2.24−2.10 (m, 1H, H-6′); ^{13}C NMR (90 Hz, $CDCl_3$) δ 196.1, 168.4, 161.7, 149.6, 146.2, 140.1, 135.3, 133.5, 131.3, 130.5, 129.3, 103.6, 52.7, 36.0, 30.0; HRMS (ESI+) calcd for $C_{17}H_{14}N_2O_4Na$ 333.0846 $[M + Na]^+$, found 333.0838.

***N*3-Benzoyl-1-[(1′*S*,4′*S*)-4′-hydroxy-cyclohex-2′-ene-1′-yl]-uracil [(1′*S*,4′*S*)-24].** To a stirred solution of cyclohexenone (1′*S*)-**23** (179 mg, 0.58 mmol) in dry CH_2Cl_2 (6 mL) at −78 °C was added (*S*)-Me-CBS 1 M in toluene (115 μL, 0.115 mmol) under argon atmosphere. Then, catecholborane 1.0 M in THF (1.15 mL, 1.15 mmol) was slowly added over 2 h, by means of a syringe pump, and the mixture was allowed to warm to room temperature and stirred for 16 h. At this time, saturated aqueous NH_4Cl (6 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (CH_2Cl_2−MeOH, from 50:1 to 25:1) to provide the cyclohexenol (1′*S*,4′*S*)-**24** (178 mg, 0.57 mmol, 99% yield) as a white solid: mp 64−66 °C (CH_2Cl_2−ethyl ether); $[\alpha]^{20}_D$ = −13.2 (*c* 0.8, $CHCl_3$); IR (ATR) *υ* 3386, 2930, 1741, 1698, 1646, 1440, 1364, 953, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 2H, H-Bz), 7.66 (tt, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H, H-Bz), 7.50 (tt, *J* = 9.2 Hz, *J* = 1.6 Hz, 2H, H-Bz), 7.26 (d, $J_{6,5}$ = 8.1 Hz, 1H, H-6), 6.18 (dtd, $J_{3′,2′}$ = 10.2 Hz, $J_{3′,4′}$ = $J_{3′,1′}$ = 2.4 Hz, $J_{3′,5′}$ = 1.3 Hz, 1H, H-3′), 5.83 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-5), 5.64 (dtd, $J_{2′,3′}$ = 10.3 Hz, $J_{2′,1′}$ = $J_{2′,4′}$ = 2.4 Hz, $J_{2′,5′}$ = 1.8 Hz, 1H, H-2′), 5.24 (ddt, $J_{1′,6′ax}$ = 11.4 Hz, $J_{1′,6′eq}$ = 5.3 Hz, $J_{1′,3′}$ = $J_{1′,2′}$ = 2.6 Hz, 1H, H-1′), 4.37 (ddt, $J_{4′,5′ax}$ = 10.4 Hz, $J_{4′,5′eq}$ = 4.4 Hz, $J_{4′,3′}$ = $J_{4′,2′}$ = 2.6 Hz, 1H, H-4′), 2.31 (m, 1H, H-6′), 2.17 (m, 1H, H-5′); 1.72−1.54 (m, 2H, H-6′, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.2, 149.9, 140.6, 138.4, 135.2, 131.6, 130.8, 129.1, 126.7, 102.7, 65.8, 52.4, 31.1, 27.8; HRMS (ESI+) calcd for $C_{17}H_{16}N_2O_4Na$ 335.1002 $[M + Na]^+$, found 335.1010.

***trans*-*N*3-Benzoyl-1-[4′-hydroxy-cyclohexan-1′-yl]uracil (28).** A stirred solution of cyclohexenol (1′*S*,4′*S*)-**24** (10 mg, 0.03 mmol) in absolute EtOH (1 mL) at room temperature was hydrogenated in the presence of 10% Pd/C (3 mg) at 15 psi for 16 h. Then, the solvent was evaporated under reduced pressure, and the resulting oil was purified by flash column chromatography (CH_2Cl_2−MeOH, 100:1) affording the cyclohexane derivate **28** (10 mg, 0,03 mmol, 100% yield) as a colorless syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 2H, H-Bz), 7.65 (tt, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H, H-Bz), 7.50 (tt, *J* = 9.1 Hz, *J* = 1.5 Hz, 2H, H-Bz), 7.29 (d, $J_{6,5}$ = 8.0 Hz, 1H, H-6), 5.83 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-5), 4.44 (tt, $J_{1′,2′ax} \approx J_{1′,6′ax}$ = 11.9 Hz, $J_{1′,2′eq} \approx J_{1′,6′eq}$ =3.6 Hz, 1H, H-1′), 3.66 (tt, $J_{4′,3′ax} \approx J_{4′,5′ax}$ = 11.1 Hz, $J_{4′,3′eq} \approx J_{4′,5′eq}$ = 4.3 Hz, 1H, H-4′), 2.13 (m, 2H, H-5′eq, H-3′eq), 2.00 (m, 2H, H-6′eq, H-2′eq), 1.63 (m, 2H, H-6′ax, H-2′ax), 1.48 (m, 2H, H-5′ax, H-3′ax); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.0, 150.0, 140.2, 135.2, 131.6, 130.5, 129.3, 102.5, 69.4, 54.7, 34.3 (2 × C), 29.6 (2 × C); HRMS (ESI+) calcd for $C_{17}H_{19}N_2O_4$ 315.1339 $[M + H]^+$, found 315.1332.

***N*3-Benzoyl-1-[(1′*S*,4′*R*)-4′-(*p*-nitrobenzoyloxy)-cyclohex-2′-ene-1′-yl]uracil (25).** A solution of DBAD (165 mg, 0.70 mmol) in dry THF (1.5 mL) was added dropwise over 10 min to a −10 °C stirred suspension of cyclohexenol (1′*S*,4′*S*)-**24** (110 mg, 0.35 mmol), *p*-nitrobenzoic acid (118 mg, 0.704 mmol), and triphenylphosphine (186 mg, 0.704 mmol) in anhydrous THF (2 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The organic solvent was removed under vacuum, and the resulting oil was purified by flash chromatography (hexanes−EtOAc, 2:1) furnishing the *p*-nitrobenzoate derivative**25** (148 mg, 0.32 mmol, 91% yield) as a pale yellow oil: IR (ATR) *υ* 2939, 1738, 1699, 1660, 1523, 1439, 1101, 722, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 9.1 Hz, *J* = 2.4 Hz, 2H, H-*Ph*-NO_2), 8.20 (dt, *J* = 8.9 Hz, *J* = 2.0 Hz, 2H, H-*Ph*NO_2), 7.93 (dd, *J* = 8.3 Hz, *J* = 1.0 Hz, 2H, H-Bz), 7.65 (tt, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H, H-Bz), 7.49 (tt, *J* = 9.3 Hz, *J* = 1.6 Hz, 2H, H-Bz), 7.39 (d, $J_{6,5}$ = 8.1 Hz, 1H, H-6), 6.36 (ddd, $J_{3′,2′}$ = 10.1 Hz, $J_{3′,4′}$ = 4.2 Hz, $J_{3′,1′}$ = 2.4 Hz, 1H, H-3′), 5.95 (ddt, $J_{2′,3′}$ = 10.1 Hz, $J_{2′,1′}$ = 2.8 Hz, $J_{2′,4′}$ = $J_{2′,6′}$ = 0.9 Hz, 1H, H-2′), 5.86 (d, $J_{5,6}$ = 8.1 Hz, 1H, H-5), 5.53 (qt, $J_{4′,3′}$ = $J_{4′,5′}$ = $J_{4′,5′}$ = 4.3 Hz, $J_{4′,2′}$ = *J* = 1.2 Hz, 1H, H-4′), 5.22 (br, 1H, H-1′), 2.21−2.13 (m, 1H, H-6′), 2.13−2.03 (br t, *J* = 4.5 Hz, 2H, H-5′), 1.97−1.81 (m, 1H, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 164.1, 162.2, 150.8, 149.9, 141.0, 135.5, 135.3, 131.8, 131.5, 131.2, 130.9, 130.5, 129.3, 123.7, 102.7, 67.2, 52.0, 25.8, 25.1; HRMS (ESI+) calcd for $C_{24}H_{19}N_3O_7Na$ 484.1115 $[M + Na]^+$, found 484.1105.

1-[(1′*S*,4′*R*)-4′-Hydroxy-cyclohex-2′-ene-1′-yl]uracil [(1′*S*,4′*R*)-26]. A solution of *p*-nitrobenzoate **25** (112 mg, 0.24 mmol) in a 33% solution of $MeNH_2$ in EtOH (3 mL) was stirred at room temperature for 1 h. The volatiles were removed under vacuum, and the remaining oil was purified by flash chromatography (CH_2Cl_2−MeOH, from 40:1 to 20:1) provide the uracil nucleoside derivative (1′*S*,4′*R*)-**26** (50 mg, 0.24 mmol, 99% yield) as a white solid: mp 55−57 °C (MeOH); $[\alpha]^{20}_D$ = +73.0 (*c* 1.0, MeOH); IR (ATR) *υ* 3349, 3178, 2927, 2858, 1662, 1459, 1041, 806, 644 cm^{-1}; ^{1}H NMR (360 MHz, d_6-DMSO) δ 11.26 (br s, 1H, -N*H*), 7.48 (d, $J_{6,5}$ = 7.9 Hz, 1H, H-6), 6.08 (ddd, $J_{3′,2′}$ = 10.4 Hz, $J_{3′,4′}$ = 3.7 Hz, $J_{3′,1′}$ = 2.4 Hz, 1H, H-3′), 5.62 (d, $J_{5,6}$ = 7.9 Hz, 1H, H-5), 5.60 (dd, $J_{2′,3′}$ = 10.4 Hz, $J_{2′,1′}$ = 2.4 Hz, 1H, H-2′), 4.91 (br d, $J_{OH,4′}$ = 6.4 Hz, 2H, H-1′, -O*H*), 3.99 (br, 1H, H-4′), 1.74 (m, 3H, 2H-6′, H-5′), 1.55 (m, 1H, H-5′); ^{13}C NMR (90 MHz, d_6-DMSO) δ 163.4, 150.8, 142.1, 136.8, 126.7, 101.1, 62.1, 50.4, 28.3, 24.3; HRMS (ESI+) calcd for $C_{10}H_{12}N_2O_3Na$ 231.0740 $[M + Na]^+$, found 231.0738.

***N*3-Benzoyl-1-[(2′*R*,3′*R*,8′*R*)-2′,3′-diphenyl-1′,4′-dioxaspiro[4.5]-decan-6′-ene-8′-yl]uracil (27).** A mixture of carbonate **14** (154 mg, 0.41 mmol), *N*3-benzoyluracil (131 mg, 0.61 mmol), allylpalladium chloride dimer (4.4 mg, 0.01 mmol), and 1,4-bis(diphenylphosphino)ethane (14.5 mg, 0.04 mmol) in anhydrous DMF (4 mL) was and stirred overnight at 80 °C. The reaction mixture was passed through a Celite pad, and the organic layer was concentrated under vacuum. The resulting oil was purified by flash chromatography (hexanes−EtOAc, 4:1) to afford **27** (147 mg, 0.29 mmol, 72% yield) as a white solid: mp 99−101 °C (CH_2Cl_2−ethyl ether); $[\alpha]^{20}_D$ = −38.3 (*c* 1.2, $CHCl_3$); IR (ATR) *υ* 2873, 1744, 1702, 1660, 1439, 1360, 1248, 1122, 761, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.3 Hz, *J* = 1.3 Hz, 2H, 2H-Bz), 7.66 (tt, *J* = 7.0

Hz, $J = 1.1$ Hz, 1H, H-Bz), 7.51 (tt, $J = 9.2$ Hz, $J = 1.6$ Hz, 2H, 2H-Bz), 7.38−7.34 (m, 4H, H-6, 3H-Ar), 7.34−7.29 (m, 3H, H-Ar), 7.29−7.23 (m, 2H, H-Ar), 7.23−7.17 (m, 2H, H-Ar), 6.29 (ddd, $J_{7',6'} = 10.1$ Hz, $J_{7',8'} = 2.4$ Hz, $J_{7',9'} = 1.5$ Hz, 1H, H-7′), 5.87 (dd, $J_{6',7'} = 10.1$ Hz, $J_{6',8'} = 1.5$ Hz, 1H, H-6′), 5.85 (d, $J_{5,6} = 7.9$ Hz, 1H, H-5), 5.35 (m, 1H, H-8′), 4.86 (d, $J_{3',2'} = 8.5$ Hz, 1H, H-3′), 4.71 (d, $J_{2',3'} = 8.5$ Hz, 1H, H-2′), 2.39−2.25 (m, 2H, H-9′, H-10′), 2.21 (td, $J = 13.0$ Hz, $J = 3.9$ Hz, 1H, H-9′), 1.98 (m, 1H, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.2, 150.0, 141.1, 135.8, 135.3, 135.2, 131.6, 130.6, 129.8, 129.3, 128.9, 128.8, 128.7, 128.6, 127.1, 126.6, 104.6, 102.9, 85.8, 85.3, 52.2, 33.3, 28.3; HRMS (ESI+) calcd for $C_{31}H_{26}N_2O_5Na$ 529.1734 $[M + Na]^+$, found 529.1721.

***N*3-Benzoyl-1-[(1′*R*)-4′-oxo-cyclohex-2′-ene-1′-yl]uracil [(1′*R*)-23].** To a 14:1 solution of trifluoroacetic acid (3 mL) and water (0.2 mL) at 0 °C was added the *N*3-benzoyluracil derivate **27** (150 mg, 0.29 mmol) in one portion. After 40 min of stirring at 0 °C, CH_2Cl_2 (5 mL) and water (5 mL) were added, the phases were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude material by flash chromatography (EtOAc) yielded ketone (1′*R*)-**23** (80 mg, 0.257 mmol, 87% yield) as a white solid: $[\alpha]^{20}_D = -11.7$ (*c* 1.0, $CHCl_3$). The other physical and spectral data are identical of those reported for its enantiomer (1′*S*)-**23.**

***N*3-Benzoyl-1-[(1′*R*,4′*R*)-4′-hydroxy-cyclohex-2′-ene-1′-yl]-uracil [(1′*R*,4′*R*)-24].** To a stirred solution of cyclohexenone (1*R*)-**23** (40 mg, 0.129 mmol) in dry CH_2Cl_2 (1.3 mL) at −78 °C was added (*R*)-Me-CBS 1 M in toluene (26 μL, 0.026 mmol) under argon atmosphere. Then, catecholborane 1.0 M in THF (258 μL, 0.258 mmol) was slowly added by means of a syringe pump over 2 h, and the mixture was stirred during 16 h, allowing it to warm to room temperature. At this time, saturated aqueous NH_4Cl (6 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (CH_2Cl_2−MeOH, from 50:1 to 25:1) to provide the cyclohexenol (1′*R*,4′*R*)-**24** (38 mg, 0.122 mmol, 94% yield) as a white solid: $[\alpha]^{20}_D = +12.4$ (*c* 1.0, $CHCl_3$). The other physical and spectral data are identical of those reported for its enantiomer (1′*S*,4′*S*)-**24**.

1-[(1′*R*,4′*S*)-4′-Hydroxy-cyclohex-2′-ene-1′-yl]uracil [(1′*R*,4′*S*)-26). A solution of DBAD (148 mg, 0.63 mmol) in dry THF (1.5 mL) was added dropwise over 10 min to a −10 °C stirred suspension of cyclohexenol (1′*R*,4′*R*)-**24** (99 mg, 0.32 mmol), *p*-nitrobenzoic acid (106 mg, 0.63 mmol), and triphenylphosphine (167 mg, 0.63 mmol) in anhydrous THF (2 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The organic solvent was removed under vacuum, and the resulting oil was purified by flash chromatography (hexanes−EtOAc, 2:1) furnishing the corresponding *p*-nitrobenzoate derivate (129 mg, 0.279 mmol, 88% yield) as a pale yellow solid. A solution of the previously synthesized *p*-nitrobenzoate (90 mg, 0.19 mmol) in a 33% solution of $MeNH_2$ in EtOH (2 mL) was stirred at room temperature for 2 h. The volatiles were removed under vacuum, and the remaining oil was purified by flash chromatography (CH_2Cl_2−MeOH, 40:1 to 20:1) to furnish the uracil nucleoside derivate (1′*R*,4′*S*)-**26** (38 mg, 0.182 mmol, 94% yield) as a white solid: $[\alpha]^{20}_D = -72.2$ (*c* 1.1, MeOH). The other physical and spectral data are identical of those reported for its enantiomer (1′*S*,4′*R*)-**26**.

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Supporting Information Available: General experimental procedures, experimental details and characterization data for compounds **7** and **9**, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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