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Asymmetric Synthesis of Cyclohexene Nucleoside Analogues

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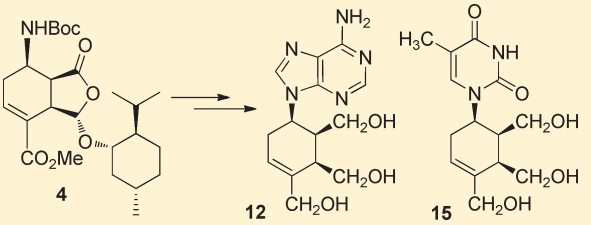
Supporting Information

ABSTRACT: The asymmetric synthesis of novel cyclohexene nucleoside analogues **12** and **15** is described. An enantiospecific Diels−Alder reaction between (*E*,*E*)-diene **2** and (+)-5-(D-mentyloxy)-2(5*H*)-furanone **3** provided the cycloadduct isomer **4**. Three additional steps yielded amine **8** allowing the constructions of the thymine and adenine moieties to afford intermediates **11** and **14**, respectively. Amination or cyclization and removal of the protecting groups occurred in one step in the presence of ammonia, giving the target six-membered ring nucleosides.



Interest in the six-membered ring nucleosides started in 1993, when a series of anhydrohexitols were reported as potent antiviral agents against acquired immune deficiency syndrome (AIDS).[1] The alteration of the sugar moiety of nucleosides lies therefore in the production of enzymatically stable derivatives without disrupting their ability to interact with complementary nucleosidic natural partners. Besides modification of the ribosyl ring by various five-membered carbasugars,[2] increasing attention has been directed toward carbocyclic derivatives for the treatment of several viruses, in particular, Herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein−Barr virus (EBV). Despite the difficulty in producing large quantities of chiral cyclohexene derivatives in high enantiomeric excess, the syntheses of enantiomerically pure cyclohexenyl[3] and cyclohexanyl[4] nucleoside analogues have been challenging in order to optimize their activities, especially when incorporated in an oligonucleotidic sequence for antisense and antigene therapy strategies.[5] Along this line, several major modifications have been made on the carba-sugar moiety leading to mono-, di-, and trihydroxylated nucleoside analogues (Figure 1). During the course of our research program on carbocyclic nucleoside analogues,[6] we previously prepared original 4,5,6-tris(hydroxymethyl)cyclohex-3-en-1-yl] compounds in racemic form,[6e] and we wish to report here the synthesis of the latter cyclohexenyl nucleoside analogues in enantiomerically pure forms.

The (*E*,*E*)-diene **2**, previously obtained in our group from lactam **1**[7] in two steps,[6e,8] was reacted in a Diels−Alder cycloaddition with chiral (+)-5-(D-mentyloxy)-2(5*H*)-furanone **3**[9] providing only one endo cycloadduct diastereoisomer **4** in which the double bond is conjugated with the ester function (Scheme 1). However, in our preliminary experiments, this reaction proved to be poorly reproducible and led either to the target molecule **4** or to the nonisomerized cycloadduct **5** in variable yield (10−20%).

When the reaction was carried out in the presence of a catalytic amount of lithium hydroxide (20%), the cycloadduct **4** was obtained as the sole product in 72% yield. To the best of our knowledge, no Diels−Alder cycloaddition reaction was reported in the presence of lithium hydroxide. We suppose that LiOH acts as a basic catalyst and leads to isomerization of the initial product **5** into the most stable cyloadduct diastereoisomer **4**.

Structure elucidation of **4** (7*R*,7a*S*,3a*S*) was carried out by means of NMR experiments. The regioselectivity was deduced from $^{1}H/^{1}H$ correlations and HMBC experiments. The endoselectivity was attributed by a phase-sensitive NOESY experiment that showed correlations between H-7/H-7a, H-7/H-3a, and H-7a/H-3a, in agreement with proximity of protons H-7, H-7a, and H-3a. The relative stereochemical relationships were assigned by single-crystal X-ray diffraction (see the Supporting Information) (Figure 2). The structure of the cycloadduct **4** was thus fully established.

During the Diels−Alder reaction both π-facial and endo selectivity are controlled. The dienophile **3** approches from the sterically less hindered face exclusively, leading to enantiomerically pure Diels−Alder cycloadduct **4** (Figure 3).

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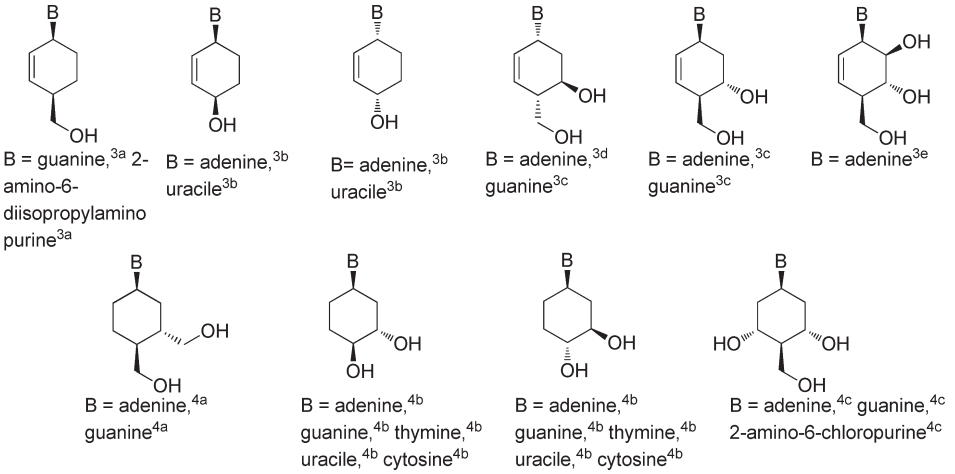
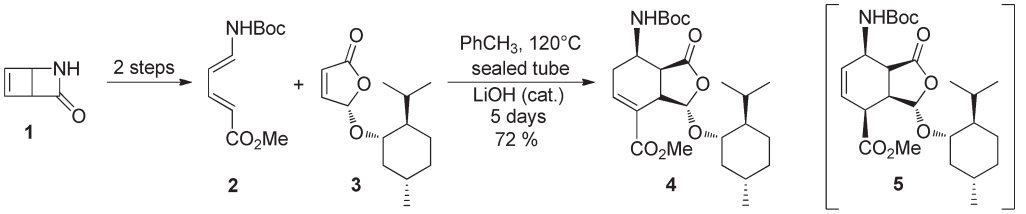


Figure 1. Examples of enantiomerically pure cyclohexenyl and cyclohexanyl nucleoside analogues.

Scheme 1. Diels−Alder Reaction



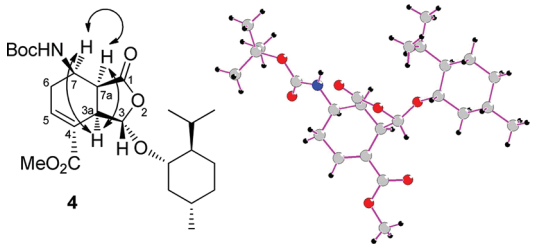


Figure 2. ORTEP analysis of (3*S*,3a*S*,7*R*,7a*S*)-methyl 7-((*tert*-butoxycarbonyl)amino)-3-(((1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl)oxy)-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carboxylate (+)-**4**.

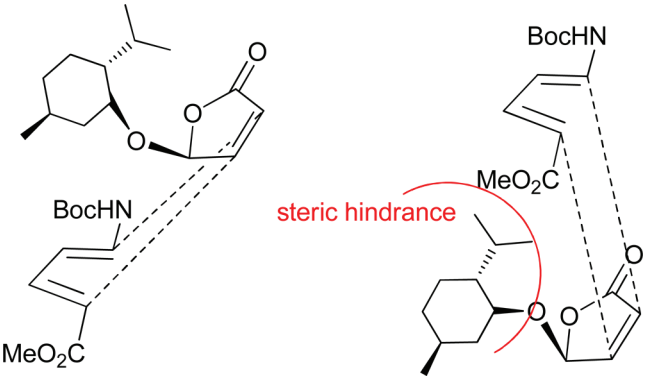


Figure 3. Proposed transition state for the π-face-selective cycloaddition.

Reduction of the anhydro **4** with $LiAlH_4$ in the conditions described by Feringa et al. (3 equiv in THF, 0 °C to rt, 16 h)[10] led to the triol **6** in low yield (15−30%). Hence, we examined the results with different reducing agents. Reduction with AlH_3 (3 equiv) and $LiBHEt_3$ (6 equiv), under similar conditions, yielded a mixture of unidentified products, while the starting material remained untouched in the presence of $LiBH_4$ (3 equiv) at reflux of THF. The use of $NaBH_4$ (3 equiv) in MeOH did not solve the problem. However, the use of diisobutylaluminium hydride (6 equiv) in toluene at −78 °C improved the formation of the desired triol **6** in satisfying yield (57% of the crude product).

The subsequent acetylation, run without purification of the crude mixture, provided compound **7** that was isolated in 51% yield over two steps (Scheme 2).

Removal of the Boc protecting group, in the presence of TMSOTf (2 equiv) at 0 °C in CH_2Cl_2, gave the free amine precursor **8** (1*R*,5*R*,6*S*) in 95% yield. The latter was readily engaged in the following step without purification to avoid a possible migration of the acetate moieties.

A purine nucleoside was first synthesized using the modified methodology developed by Harnden et al.[11] Coupling of amine **8** with 4,6-dichloro-5-formamidopyrimidine **9** in dioxane, in the presence of triethylamine, yielded compound **10** that was directly converted to the 6-chloropurine derivative **11** by heating in diethoxymethylacetate after the removal of dioxane. The treatment of unpurified intermediate **11** with ammonia in methanol under pressure yielded adenine nucleoside analogue **12** (1*R*,5*R*,6*S*), isolated as a yellow solid in 20% overall yield from **8** (Scheme 3). This sequence has the advantage to afford, easily and quickly, nucleoside analogue without purification of the intermediates.

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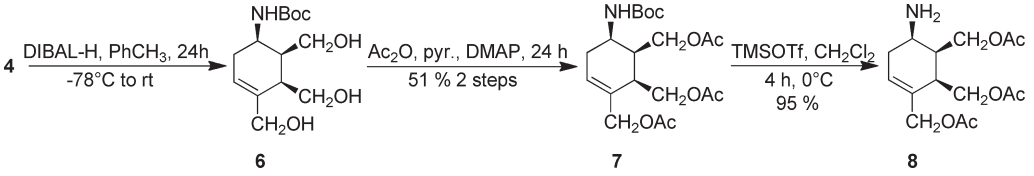
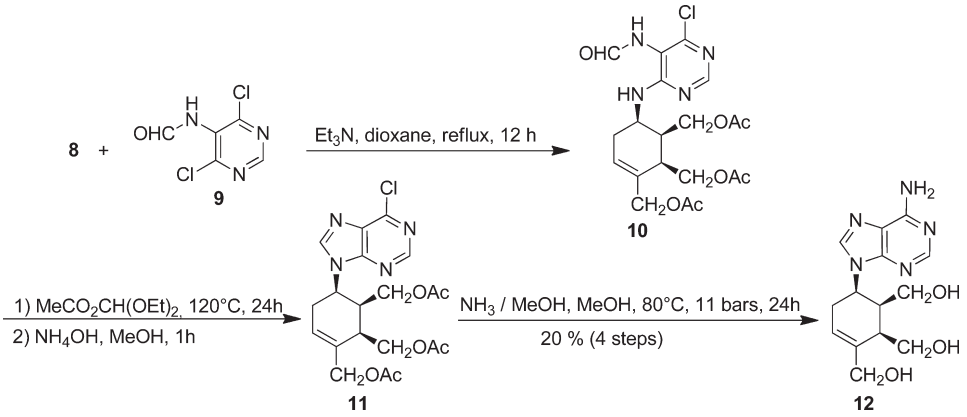
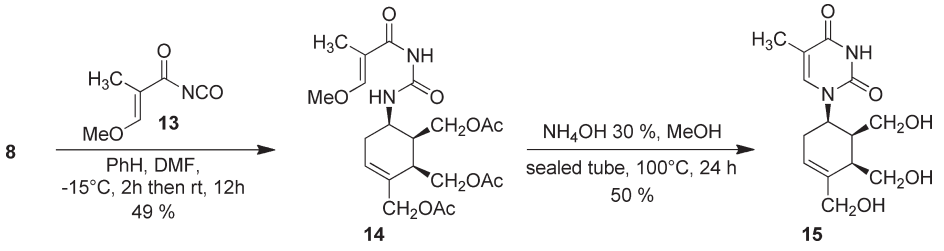
Scheme 2. Access to the Key Amine Intermediate 8



Scheme 3. Synthesis of the Adenine Nucleoside 12



Scheme 4. Synthesis of the Thymine Nucleoside 15



A synthesis of pyrimidine nucleoside was also performed according to the conditions described by Shaw and Warrener.[12] The reaction of amine **8** with β-methoxy-α-methylacrylolyl isocyanate **13** gave the intermediate urea **14** in moderate yield (40%). Cyclization of **14** into the thymine heterocycle and removal of the protecting groups were both carried out with aqueous ammonia in methanol under pressure to give the pyrimidinic cyclohexene nucleoside analogue **15** (1*R*,5*R*,6*S*) isolated as colorless oil in 24% overall yield from **8** (Scheme 4).

In summary, we have developed an efficient approach for the preparation of enantiomerically pure cyclohexene nucleoside analogues, with a *cis* relationship between the two hydroxyl substituents on the constraint carbocycle and the base moiety in both pyrimidine and purine series. The key step was the enantioselective access to the cycloadduct **4** by an univocal Diels—Alder cycloaddition. The key aminocylohex-3-ene intermediate **8**, obtained in 48% overall yield over three reaction steps from **4**, was easily converted into (+)-[(1*R*,5*R*,6*S*)-4,5,6-tris(hydroxymethyl)cyclohex-3-en-1-yl]adenine (+)-**12** and [(1*R*,5*R*,6*S*)-4,5,6-tris(hydroxymethyl)cyclohex-3-en-1-yl]thymine (+)-**15** nucleoside analogues after building the nucleotidic base by convenient procedures described in the literature. Their evaluation as antitumor and antiviral agents is in progress.

EXPERIMENTAL SECTION

Commercially available reagents and solvents were purified and dried, when necessary, by standard methods prior to use. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm. TMS was used as the internal standard for $CDCl_3$. ^{13}C NMR spectra were recorded at 100.6 MHz with complete proton decoupling. ^{1}H and ^{13}C assignments were based on both COSY and ^{1}H—^{13}C HSQC experiments. The purity of the compounds was confirmed by elemental analysis or HRMS. Optical rotations were measured in $CHCl_3$ or MeOH at room temperature. Analytical thin-layer chromatography was performed on precoated silica gel 60-F_{254} plates.

(3*S*,3a*S*,7*R*,7a*S*)-Methyl 7-((*tert*-Butoxycarbonyl)amino)-3-(((1*S*,2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl)oxy)-1-oxo-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-carboxylate ((+)-4). A solution of diene **2** (0.95 g, 4.15 mmol), compound (+)-**3**[7] (1.00 g, 4.15 mmol), and LiOH (0.02 g, 0.84 mmol) in toluene (10 mL) was heated at 120 °C in a sealed tube for 5 days. The mixture was concentrated and filtered through silica gel (EtOAc/CH_2Cl_2 1/1).

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The yellow oil was then recrystallized in petroleum ether to afford compound (+)-**4** (1.37 g, 2.95 mmol, 72%) as a white powder. Recrystallization from ethanol afforded the pure product as a solid: mp 152−154 °C; $[\alpha]^{20}_{D}$ +85 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.11 (m, 1H, H-5), 6.05 (d, 1H, NH, *J* = 9.6 Hz), 5.53 (s, 1H, H-3), 4.02 (m, 1H, H-7), 3.79 (s, 3H, OCH_3), 3.45 (m, 2H, H-3a, H-1 menthyl), 3.32 (m, 1H, H-7a), 2.56 (m, 1H, H-6), 2.22−2.08 (m, 2H, menthyl), 2.03 (m, 1H, H-6′), 1.72−1.59 (m, 3H, menthyl), 1.40−1.22 (m, 2H, menthyl), 1.45 (s, 9H, $C(CH_3)_3$), 1.04−0.97 (m, 2H, menthyl), 0.95 (d, 3H, menthyl, *J* = 6.5 Hz), 0.89 (d, 3H, menthyl, *J* = 6.5 Hz), 0.76 (d, 3H, menthyl, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7 (C═O), 165.6 (C═O), 155.2 (C═O), 141.7 (C-5), 126.3 (C-4), 103.2 (C-1), 79.7 ($C(CH_3)_3$ Boc), 52.0 (OCH_3), 47.6 (C-1 menthyl), 44.7 (C-3a), 43.5 (C-7), 40.8 (C-7a), 39.5 (CH_2 menthyl), 34.2 (CH_2 menthyl), 31.3 (CH Menthyl), 28.9 (C-6), 28.3 ($C(CH_3)_3$ Boc), 25.5 (CH menthyl), 23.0 (CH_2 menthyl), 22.2 ($CH(CH_3)_2$), 20.8 ($CH(CH_3)_2$), 15.9 (CH_3 menthyl). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.29; H, 8.75; N, 2.97.

***N*-tert-Butoxycarbonyl((1*R*,5*R*,6*S*)-4,5,6-tris(hydroxymethyl)-cyclohex-3-en-1-yl)amine (6).** To a stirred, cooled (−78 °C) solution of adduct (+)-**4** (1.56 g, 3.35 mmol) in dry toluene (8 mL) was added dropwise DIBAL-H (1 M in toluene, 29 mL, 29.00 mmol) under argon atmosphere. The reaction mixture was stirred for 3 h at the same temperature, warmed to rt for 24 h, and then treated with a 1.2 M aqueous solution of Rochelle's salts (potassium sodium tartrate salts) (60 mL). After vigorous stirring for 3 h, the toluene layer was removed, and then water was added to the residue. The aqueous layer was extracted with cyclohexane (3 × 50 mL) and then continuously extracted with EtOAc for 12 h. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give compound **6** (546.00 mg, 1.91 mmol, 57% crude) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.89 (s, 1H, NH), 5.80 (m, 1H, ═CH), 4.16−3.66 (m, 10H, CH_2OH and −C*H*NHBoc), 2.61−2.55 (m, 1H, −C*H*CH_2OH), 2.44−2.31 (m, 1H, $-CH_2-$), 2.28−2.19 (m, 1H, −C*H*CH_2OH), 2.10−1.98 (m, 1H, $-CH_2-$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 156.5 (C═O), 136.2 (═C), 126.7 (═CH), 79.4 ($C(CH_3)_3$), 66.0 (C-7), 60.4 (CH_2OH), 60.2 (CH_2OH), 45.9 (CHNBoc), 42.4 (CH), 41.3 (CH), 30.7 (CH_2), 28.4 ($C(CH_3)_3$).

(+)-*N*-tert-Butoxycarbonyl((1*R*,5*R*,6*S*)-4,5,6-tris(acetyloxymethyl)cyclohex-3-en-1-yl)amine ((+)-7). A solution of crude **6** (546 mg, 1.91 mmol), acetic anhydride (30 mL), and DMAP (100 mg, 0.82 mmol) in pyridine (15 mL) was stirred for 24 h at rt under argon atmosphere. Evaporation of the solvents under reduced pressure followed by column chromatography on silica gel (cyclohexane/EtOAc 8/2) afforded compound (+)-7 (705 mg, 1.70 mmol, 90%, 51% from (+)-**4**) as a colorless oil: $[\alpha]^{20}_{D}$ +22 (*c* 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.89−5,85 (m, 1H, ═CH), 5.50 (d, 1H, NH, *J* = 8.5 Hz), 4.56 (d, 1H, ═CCH_2OAc, *J* = 12.6 Hz), 4.49 (d, 1H, CH_2OAc, *J* = 12.6 Hz), 4.35 (dd, 1H, CH_2OAc, *J* = 6.2, 12.2 Hz), 4.21 (dd, 1H, CH_2OAc, *J* = 6.7, 11. Hz), 4.16−4.06 (m, 2H, CH_2OAc), 4.05−3.95 (m, 1H, C*H*NHBoc), 2.89−2.81 (m, 1H, CH), 2.54−2.37 (m, 2H, CH and CH_2), 2.16−2.03 (m, 1H, CH_2), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.44 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$) δ 170.8 (C═O, OAc), 170.6 (C═O, OAc), 170.2 (C═O, OAc), 155.4 (C═O, Boc), 130.9 (═C), 128.4 (═CH), 79.4 ($C(CH_3)_3$), 66.5 (CH_2OAc), 62.6 (CH_2OAc), 61.8 (CH_2OAc), 45.2 (CHNHBoc), 38.1 (CH), 36.8 (CH), 31.0 (CH_2), 28.4 ($C(CH_3)_3$), 20.9 (3 × CH_3 OAc); HRMS calcd for $C_{20}H_{32}NO_8$ $[M + H]^+$ 414.2128, found 414.2133.

((1*R*,5*R*,6*S*)-4,5,6-Tris(acetyloxymethyl)cyclohex-3-en-1-yl)-amine (8). To a stirred, cooled (0 °C) solution of compound **7** (801 mg, 1.94 mmol) in dry CH_2Cl_2 (10 mL) was added TMSOTf (0.70 mL, 5.53 M, 3.87 mmol) under argon atmosphere. The reaction mixture was stirred at the same temperature for 4 h and then treated with a saturated aqueous solution of $NaHCO_3$ (35 mL). Extraction with CH_2Cl_2, drying of the organic phase ($MgSO_4$), filtration, and then evaporation afforded compound **8** (580 mg, 1.85 mmol, 95% crude) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.81−5.69 (m, 1H, =CH), 4.48 (m, 2H, =CCH_2OAc), 4.31 (dd, 1H, CH_2OAc, *J* = 5.2, 11.4 Hz), 4.22 (d, 2H, CH_2OAc, *J* = 6.5 Hz), 4.05 (dd, 1H, CH_2OAc, *J* = 7.5, 11.4 Hz), 3.27−3.07 (m, 1H, C*H*NHBoc), 2.82−2.64 (m, 1H, CH), 2.41−2.09 (m, 3H, CH and CH_2), 2.01 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.98 (s, 3H, OAc).

(+)-((1*R*,5*R*,6*S*)-4,5,6-Tris(hydroxymethyl)cyclohex-3-en-1-yl)adenine ((+)-12). A solution of amine **8** (0.305 g, 0.974 mmol), *N*-(2,6-dichlorophenyl)formamide **9** (0.380 g, 1.999 mmol), and Et_3N (0.8 mL, 5.730 mmol) in dry dioxane (6 mL) was refluxed for 12 h under argon atmosphere. After evaporation of the solvent, the mixture was dissolved in diethoxymethyl acetate (10 mL), heated at 120 °C for 24 h, and then concentrated. The residue was dissolved in MeOH (6 mL), and then 30% aqueous NH_4OH solution (0.6 mL) was added. After being stirred for 1 h, the mixture was concentrated. The crude product **11** was taken in a saturated methanolic ammonia solution (40 mL), and the mixture was heated at 80 °C for 24 h in steel bomb under 11 bar. Evaporation of the solvent and then column chromatography on silica gel (EtOAc/MeOH: 90/10 to 80/20) afforded compound (+)-**12** (0.060 g, 0.197 mmol, 20%) as a pale yellow solid: $[\alpha]^{20}_{D}$ +60 (*c* 0.64, MeOH); ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H, CH═N), 8.21 (s, 1H, CH═N), 5.95−5.91 (m, 1H, ═CH), 4.94−4.86 (m, 1H, C*H*NHBoc), 4.21 (d, 1H, ═CCH_2OH, *J* = 13.0 Hz), 4.11 (d, 1H, ═CCH_2OH, *J* = 13.0 Hz), 3.79 (dd, 1H, CH_2OH), 3.72 (dd, 1H, CH_2OH), 3.69 (dd, 1H, CH_2OH), 3.58 (dd, 1H, CH_2OH), 3.04−2.89 (m, 2H, CH), 2.71−2.58 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 158.8 (CNH_2), 155.1 (NCH═N), 152.4 (C═*C*N), 142.8 (NCH═N), 140.8 (═CCH_2-OH), 124.9 (*C*H═), 121.7 (*C*═CN), 66.9 (═C*C*H_2OH), 63.4 (CH_2-OH), 60.6 (CH_2OH), 56.0 (CHNH), 44.9 (CH), 44.6 (CH), 29.6 (CH_2); HRMS calcd for $C_{14}H_{20}N_5O_3$ $[M + H]^+$ 306.1566, found 306.1578.

(+)-((1*R*,5*R*,6*S*)-4,5,6-Tris(acetyloxymethyl)cyclohex-3-en-1-yl)-3-((*E*)-3-methoxy-2-methylacryloyl)urea ((+)-14). A solution of 3-methoxy-2-methylacryloyl chloride[12] (0.418 g, 3.1 mmol) and silver cyanate (0.8 g, 5.3 mmol, previously dried in vacuo over P_2O_5 at 100 °C for 3 h in the dark), in dry benzene (3.3 mL), was refluxed for 30 min and then cooled to 0 °C. The supernatant liquor was added dropwise to a solution of amine **8** (0.360 g, 1.100 mmol) in dry DMF (4 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 2 h and then at rt overnight. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 1/1) to afford compound (+)-**14** (0.240 g, 0.539 mmol, 49%) as a colorless oil: $[\alpha]^{20}_{D}$ +9 (*c* 2.7, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 9.08 (d, 1H, NH, *J* = 8.3 Hz), 7.79 (br s, 1H, (CO)N*H*(CO)), 7.31 (d, 1H, MeOCH═, *J* = 1.3 Hz), 5.87−5.83 (m, 1H, ═CH), 4.52 (br s, 2H, ═CCH_2OAc), 4.35−4.08 (m, 5H, CHNH, CH_2OAc), 3.86 (s, 3H, OCH_3), 3.04−2.95 (m, 1H, CH), 2.62−2.56 (m, 1H, CH), 2.55−2.45 (m, 1H, CH_2), 2.18−2.03 (m, 1H, CH_2), 2.12 (m, 3H, OAc), 2.07 (m, 3H, OAc), 2.05 (m, 3H, OAc), 1.77 (d, 3H, $CH_{3thymine}$, *J* = 1.3 Hz); ^{13}C NMR (CD_3OD) δ 171.2 ($OCOCH_3$), 170.7 ($OCOCH_3$), 170.6 ($OCOCH_3$), 169.3 (NCONH), 158.5 (MeO*C*H═), 154.1 (HNCO), 131.5 (═*C*CH_2OAc), 127.9 (*C*H═), 107.3 (CH_3C═), 66.4 (═CCH_2OAc), 63.2 (CH_2OAc), 61.5 (CH_2-OAc, OCH_3), 47.3 (CHNH), 38.9 (CH), 37.5 (CH), 29.3 (CH_2), 20.9 ($OCOCH_3$), 8.8 ($CH_{3thymine}$); HRMS calcd for $C_{21}H_{31}N_2O_9$ $[M + H]^+$ 455.2033, found 455.2030.

(+)-((1*R*,5*R*,6*S*)-4,5,6-Tris(hydroxymethyl)cyclohex-3-en-1-yl)thymine ((+)-15). A solution of urea (+)-**14** (0.170 g, 0.397 mmol) in a 1/1 mixture of 30% aqueous NH_4OH solution and MeOH (30 mL) was heated at 100 °C in a sealed tube for 24 h. Evaporation of the solvents then column chromatography on silica gel (CH_2Cl_2/MeOH 95/5 to 85/15) led to compound (+)-**15** (0.059 g, 0.199 mmol, 50%) as a colorless oil: $[\alpha]^{20}_{D}$ +70 (*c* 0.55, MeOH); ^{1}H NMR

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(CD_3OD) δ 7.51 (d, 1H, NCH=, J = 1.2 Hz), 5.85 (m, 1H, =CH), 4.66 (m, 1H, CHN), 4.15 (d, 1H, =CCH_2OH, J = 12.7 Hz), 4.03 (d, 1H, =CCH_2OH, J = 12.7 Hz), 3.84 (dd, 1H, CH_2OH, J = 11.6, 5.3 Hz), 3.76 (dd, 1H, CH_2OH, J = 11.6, 7.1 Hz), 3.70 (dd, 1H, CH_2OH, J = 11.6, 7.2 Hz), 3.63 (dd, 1H, CH_2OH, J = 11.6, 5.3 Hz), 2.94−2.87 (m, 1H, CH), 2.78−2.67 (m, 1H, CH_2), 2.52−2.46 (m, 1H, CH), 2.32−2.22 (m, 1H, CH_2), 1.89 (d, 3H, $CH_{3thymine}$, J = 1.2 Hz); ^{13}C NMR (CD_3OD) δ 167.9 (NCONH), 154.8 (NHCO), 142.0 (C=CCH_3), 140.4 (=CCH_2OH), 125.2 (HC=), 111.5 (C=CCH_3), 66.9 (=CCH_2OH), 63.6 (CH_2OH), 60.5 (CH_2OH), 57.9 (CHN), 45.4 (CH), 43.4 (CH), 28.3 (CH_2), 13.9 ($CH_{3thymine}$); HRMS calcd for $C_{14}H_{21}N_2O_5$ $[M+H]^+$ 297.1450, found 297.1466.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR data for all compounds and crystallographic data for compound **4**. COSY and HSQC NMR spectra for compounds **4**, **6**, **7**, **12**, **14**, and **15**. HMBC and NOESY NMR spectra for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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