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A synthetic approach to a novel class of enantiopure cyclopentyl carbocyclic nucleosides and related compounds

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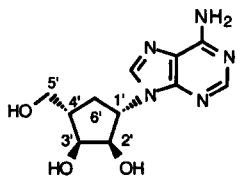
Abstract: A synthetic entry to a novel class of cyclopentyl carbocyclic nucleosides and other functional derivatives, in enantiopure form, is presented. As a structural feature of these compounds, the base-moiety is separated from the carbocyclic ring by a C_2-chain containing a quaternary stereogenic center and additional chemical functions. © 1997 Elsevier Science Ltd

Introduction

Although the first natural carbocyclic nucleoside, (−)-aristeromycin **1**, was discovered as early as 1968 from *Steptomyces citricolor* n.sp.,[1] the interest in the synthesis and study of the biological activities of the carbocyclic nucleosides was greatly renewed several years later, from the discovery in 1981 of the neplanocine family, isolated from *Actinoplacea ampullariella* sp., and the verification of their antineoplasic activity, especially in neplanocine A **2**.[2] During the last fifteen years, an enormous amount of work has been developed on the search of both natural and synthetic novel carbocyclic nucleosides showing properties that make them suitable to be used in therapies against cancer or viruses.[3] The finding that carbocyclic nucleosides such as **3** and **4**, containing cyclobutane[4] or cyclopropane[5] rings, display remarkable activity[6] has stimulated the synthesis of modified analogs with enhanced properties. In addition to the type and further substitutions of the heterocyclic base, the most relevant modifications are related to the nature and number of substituents, as well as the size of the carbocyclic ring and the configuration of the stereogenic centers. Moreover, *homologs* in which the base is not directly attached to *C-1'* have been synthesized, compound **5** showing satisfactory anti-HSV activity.[7]



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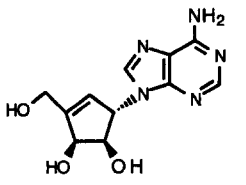

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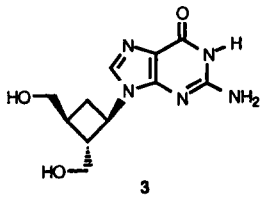

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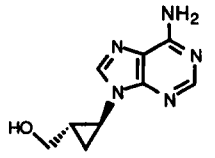

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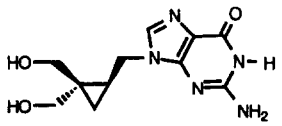

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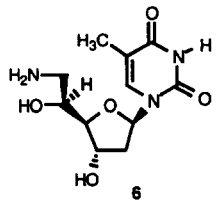

6

In this paper, we describe a synthetic approach to cyclopentane homologs in which the base is separated from the carbocyclic ring by a C_2-chain bearing a quaternary stereogenic center and additional functional groups. It is noteworthy that, although nucleosides such as **6**, with branched (*C-*

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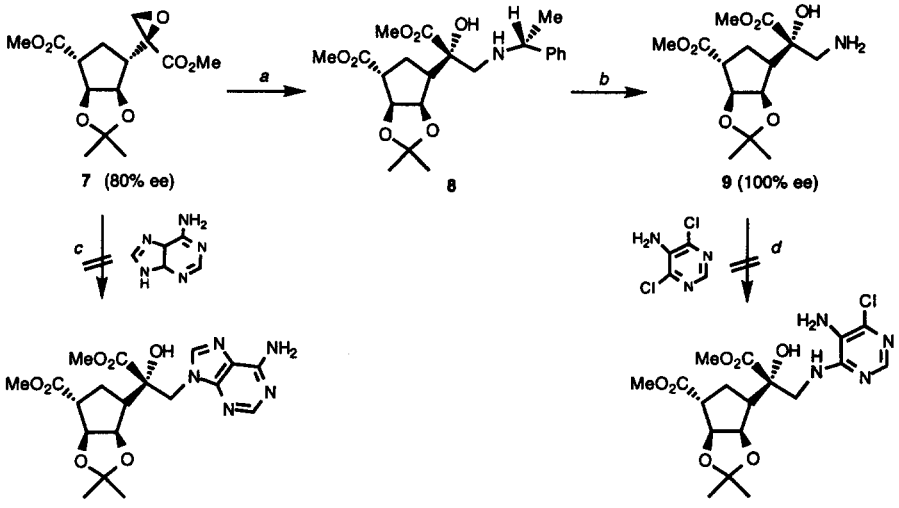
5′)-chain have recently been synthesized and incorporated in oligonucleotide sequences,[8] nucleosides with a similar fragment intercalated between *C-1′* and the base-frame are not described.

The common synthetic precursor to these compounds is epoxide **7** (Scheme 1), obtained in 80% ee in our laboratory by ozonolysis and concomitant decarboxylation of Ohno's hemiester,[9] followed by addition of diazomethane to the carbonyl group of the resultant keto ester.[10] Compound **7** bears the *2′,3′-vic*-diol function (numeration refers to nucleosides) protected as an acetonide, an ester at *C-4′* that will be converted to a hydroxymethyl group, and the epoxyester function, with a stereogenic center directly bonded to *C-1′*, suitable to introduce a purine or pyrimidine-type base by direct nucleophilic ring-opening. As an alternative way, hydroxyamine **9** is convenient to introduce the heterocyclic system by means of one-step methods using reagents containing the pre-formed heterocycle, or through cyclization of an appropriate acryloyl urea. In turn, hydroxy amine **9** had been synthesized by reaction of epoxide **7** with (*R*)-α-methylbenzylamine and subsequent hydrogenation.[10b]



Reagents. a: (R)-α-methylbenzylamine, DMF. (b) 7 atm H_2, 10% Pd/C, AcOH. c: NaH, 18-crown-6, DMF. d: Et_3N, n-BuOH

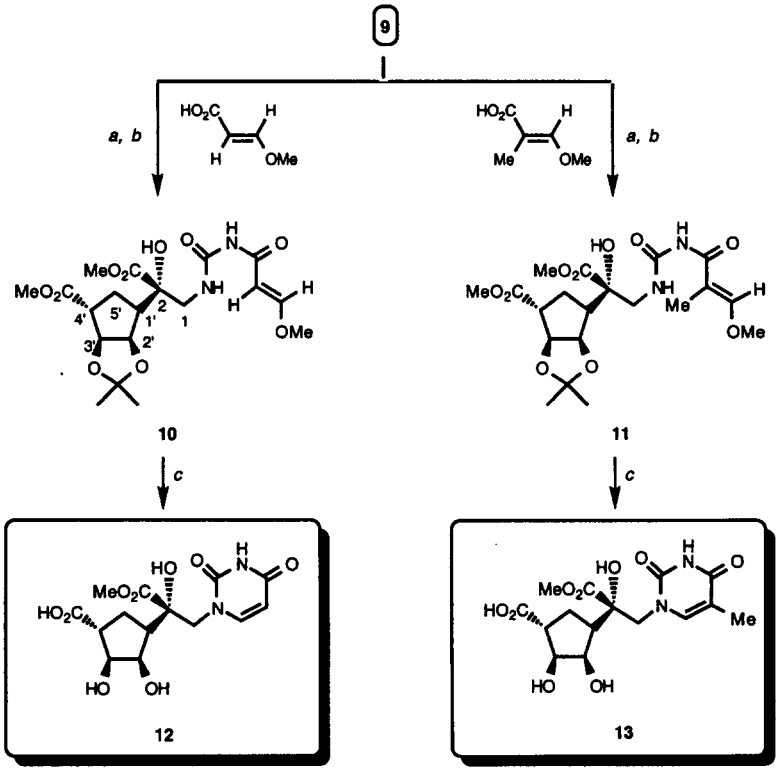
Scheme 1.

Results and discussion

The first synthetic goal was the introduction of the pre-formed heterocyclic moiety onto precursors such as **7** or **9** (Scheme 1) by utilizing well established methods.[3] Nucleophilic oxirane-ring opening by adenine sodium salt was attempted using adenine and NaH/18-crown-6 in DMF, without satisfactory results. Moreover, reaction of amine **9** with 5-amino-4,6-dichloropyrimidine and Et_3N in *n*-BuOH at several temperatures did not afford the expected product either.

Next, we proceeded to create the heterocyclic thymine and uracil moieties from amine **9** according to the protocol formerely developed by Shaw and Warrener, that involves the hydrolysis of an acyl urea resultant from the reaction of an amine with an acryloyl isocyanate (Scheme 2).[11] This last reagent is generated in situ from an acryloyl chloride and silver cyanate. Thus, the synthesis of the uracil derivative **12** was accomplished by initial reaction with 3-methoxyacryloyl isocyanate in anhydrous dichloromethane at −78°C for 30 minutes, then 1.5 h at 0°C, giving compound **10** in 31% yield.[12] Subsequent hydrolysis of **10** in boiling (10:1) 0.2 N HCl–ethanol for 16 hours, afforded quantitatively **12**. In this step, cyclization was accompanied by deprotection of the diol and by chemoselective hydrolysis of the ester directly bonded to the cyclopentane ring. Compound **12** is a solid, m.p. 131–134°C, $[\alpha]_D$+19.4 (c 0.70, methanol). A significantly better yield (50%) was obtained from the

reaction of **9** with 3-methoxy-2-methylacryloyl isocyanate leading to compound **11** which, under hydrolysis, gave quantitatively the thymine derivative **13** as a solid, m.p. 78°C, $[\alpha]_D$+11.4 (c 0.7, methanol).

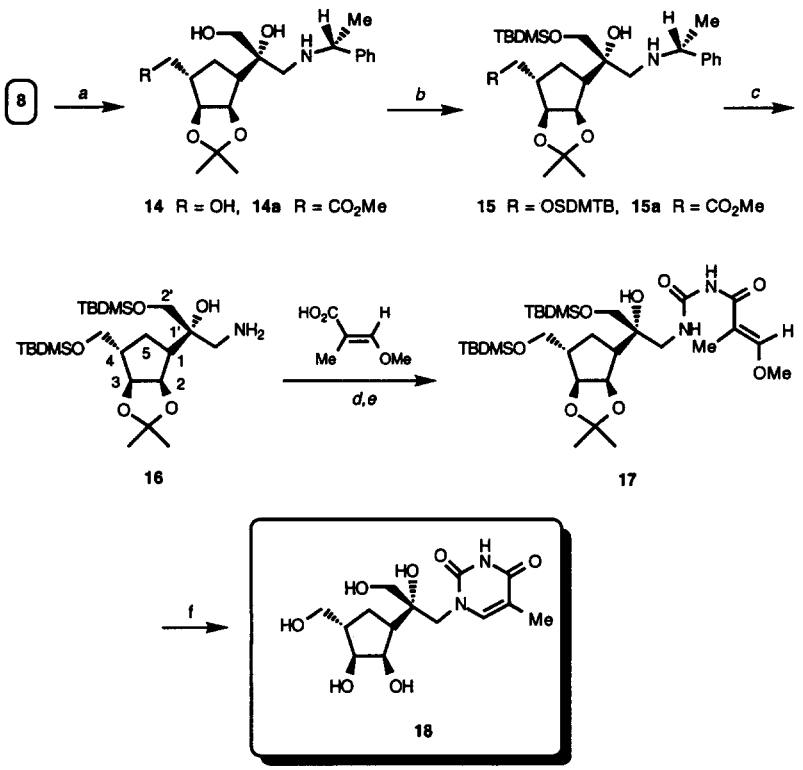


Reagents. a: $(COCl)_2$. b: AgOCN. c: (10:1) 0.2N HCl-EtOH

Scheme 2.

The low solubility of compounds **12** and **13** in the solvents usually required in the reduction with hydrides made them unsuitable to transform the carboxyl group in the (*C-4'*)-hydroxymethyl chain commonly present in the cyclopentyl nucleosides. For this reason, the synthetic strategy was modified as shown in Scheme 3. Actually, the starting material was compound **8** in which the amino group remained conveniently protected to allow the reduction of the two ester groups prior to introduction of the heterocycle precursor-chain.

Reduction was performed with 3 equivalents of lithium borohydride in tetrahydrofuran at room temperature for 24 hours affording triol **14** which was protected as bis(silyl ether) by reaction with *t*-butyldimethylsilyl chloride and 4-(*N,N*,-dimethylamino)pyridine giving **15** in 90% overall yield for the two steps. The tertiary hydroxyl group did not interfere in this last reaction, as expected. The efficiency of the reduction depends on the number of equivalents of hydride and the reaction time. The ester group attached to the side-chain quaternary carbon was shown to be more reactive that the other group as deduced from comparison of entries 3 and 4 in Table 1, and by the fact that that hydroxy ester **15a** was obtained when few equivalents of hydride were employed (entries 2 and 3 in Table 1). The ratio of mono and bis-reduction products was determined on the silyl ethers which were oils easily isolated by column chromatography on neutral silica, allowing their identification and characterization. In contrast, alcohols **14** and **14a** were not susceptible to be isolated and purified.



Reagents. a: $LiBH_4$, THF. b: TBDMSiCl, DMAP, CH_2Cl_2. c· 3 atm H_2, 10% Pd/C, MeOH. d: $(COCl)_2$. e: AgOCN. f: (10:1) 0.2N HCl-EtOH

Scheme 3.

The identity of compound **15a** was assigned using NMR techniques including [^{1}H–^{13}C] heteronuclear correlations in 2D-HMQC and 2D-HMBC experiments.

This relative reactivity of the two methoxycarbonyl groups is in contrast to that observed under acid hydrolysis conditions, as described above. In this case, chemoselectivity could be explained by considering the assistance of the tertiary hydroxyl group to promote the nucleophilic displacement of methoxide ion from the neighbouring ester, giving rise to a highly reactive α-lactone which would be preferably reduced in the reaction conditions.

In the following step of the synthetic sequence depicted in Scheme 3, benzyl amine **15** was hydrogenated at 3 atmospheres pressure with 10% Pd/C as a catalyst and methanol as a solvent, affording quantitatively amine **16** as a solid, m.p. 26–28°C and $[\alpha]_D$+12.7 (c 2.51, chloroform). Unexpectedly, treatment of **16** with 3-methoxyacryloyl isocyanate, under several conditions, only provided unidentified substances, thus avoiding the synthesis of uracil derivatives. On the contrary, reaction of **16** with 3-methoxy-2-methylacryloyl isocyanate furnished compound **17** in 20% yield. This product was treated with boiling (10:1) 0.2 N HCl–ethanol to deprotect the primary and secondary hydroxyl groups and to promote cyclization of the acryloyl urea, affording the thymine derivative **18** (100% yield) as a hygroscopic white solid that showed m.p. 28–30°C and $[\alpha]_D$+8.3 (c 0.60, methanol).

In conclusion, we have synthesized some new and enantiopure cyclopentyl carbocyclic nucleoside homologs and related compounds, all of them showing as a structural feature the presence, between the cyclopentane ring and the base (thymine or uracil), of a C_2-chain bearing a quaternary stereogenic

Table 1. Reduction[a] and subsequent silylation[b] of compound **8** to afford **15** and **15a**

Entry	eq $LiBH_4$[c]	Time (h)	(%) Yield[d]		**15/15a** Ratio
			15	**15a**	
1	1.5	3	---	---	---
2	1.5	24	66	10	7 : 1
3	2.2	16	63	14	5 : 1
4	2.2	24	68	0	---
5	3.0	16	75	0	---
6	3.0	24	90	0	---

[a] All reactions were performed at r.t. [b] TBDMSCl (4 eq) and DMAP (5 eq) in dichloromethane, at r.t. for 2 h. [c] A titrated commercial 2.0M solution of $LiBH_4$ in THF was used. [d] Isolated yield.

center and a *vic*-diol or an α-hydroxyester function. Biological evaluations of the obtained products are under investigation.

Experimental section

Flash column chromatography was carried out on 'Baker analyzed'® silica gel (240–400 mesh, pH 6.7–7.3). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures o.t. being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale). Carbon and proton assignments were made through the performance of DEPT (Distortionless Enhancement by Polarization Transfer), 2D-HMQC (Heteronuclear Multiple-Quantum Coherence) and 2D-HMBC (Heteronuclear Multiple-Bond Connectivity) experiments.

General procedure for coupling of amines with acryloyl isocyanates and subsequent acid hydrolysis

Typical experiments were run as follows for obtaining products **11** and **13**. Oxalyl chloride (95 μL, 0.9 mmol) was added dropwise to an ice-cooled and stirred solution of 3-methoxy-2-methylacrylic acid (93 mg, 0.8 mmol) in anhydrous benzene (10 mL). After stirring at r.t. for 1 h, dry silver cyanate (240 mg, 1.6 mmol) was added and the mixture was heated to reflux for 30 min. Then the mixture was cooled to r.t. and added dropwise to a solution of amine **9** (115 mg, 0.4 mmol) in anhydrous dichloromethane (5 mL), cooled at −78°C, under nitrogen atmosphere. The resultant mixture was stirred at −78°C for 30 min and at 0°C for 1.5 h. The solvents were removed and the residue was chromatographed (mixtures of hexane–ethyl acetate as eluents) to afford 92 mg (55% yield) of compound **11** as a white solid.

Product **11** (83 mg, 0.2 mmol) in (10:1) 0.2 N HCl–EtOH (10 mL) was heated to reflux overnight. The solution was evaporated to dryness affording 65 mg (96% yield) of thimine derivative **13** which was purified by elution (water) through a C_{18}-reverse phase cartridge.

Similarly, compounds **10**, **12**, **17** and **18** were synthesized, and characterized as follows.

(2S,1′S,2′R,3′S,4′R)-(−)-1-[2-(2′,3′-Isopropylidenedioxy-4′-methoxycarbonylcyclopent-1′-yl)-2-hydroxy-2-methoxycarbonylethyl]-3-(3-methoxyacryloyl)urea ***10***

Yield: 47 mg (31%). Solid, m.p. 70°C–73°C; $[\alpha]_D$ −18.5 (c=0.76, in $CHCl_3$); IR (KBr) 3700–3100, 2988, 2952, 1736, 1680, 1553, 1455, 1441, 1384, 1258, 1195, 1159, 1117, 1068, 864 cm^{-1}; MS, ***m/e*** 445 (M+15, 3), 328 (15), 158 (11), 157 (87, -CH_2NHR), 105 (19), 85 (100), 59 (19), 55 (16), 43 (21); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.26 (s, 3H, CH_3 acetonide),1.47 (s, 3H, CH_3 acetonide), 1.86 (complex

abs, 2H, 2×H_5), 2.43 (ddd, J=J′=9.6 Hz, J″=5.7 Hz, 1H, $H_{1'}$/$H_{4'}$), 2.85 (ddd, J=J′=9.6 Hz, J″=5.7 Hz, 1H, $H_{4'}$/$H_{1'}$), 3.61 (dd, J=14.1 Hz, J′=6.0 Hz, 1H, H_1), 3.63 (s, 3H, CH_3 ester), 3.65 (s, 3H, CH_3 ester), 3.71 (s, 3H, OCH_3 urea), 3.72 (m, 1H, H_1), 4.06 (s, 1H), 4.64 (dd, J=7.5 Hz, J′=5.7 Hz, 1H, $H_{2'}$/$H_{3'}$), 4.72 (dd, J=7.5 Hz, J′=5.7 Hz, 1H, $H_{3'}$/$H_{2'}$), 5.30 (d, J=12.3 Hz, 1H, -*H*C=), 7.64 (d, J=12.3 Hz, 1H, MeOC*H*=), 8.92 (dd, J=J′=6.0 Hz, 1H, -CH_2N*H*R), 9.72 (s, 1H, -N*H*CO-); 62.5 MHz ^{13}C NMR ($CDCl_3$) 24.9 (*C*H_3, acetonide), 27.3 (*C*H_3, acetonide), 29.5 (*C*H_2, C-5′), 46.5 (*C*H_2, C-1), 49.4 (*C*H, C-1′/C-4′), 50.1 (*C*H, C-4′/C-1′), 52.0 (O*C*H_3, ester), 53.1 (O*C*H_3, ester), 57.8 (O*C*H_3, urea), 76.6 (*C*$_q$, C-2), 79.7 (*C*H, C-2′/C-3′), 82.3 (*C*H, C-3′/C-2′), 97.3 (*C*H, urea), 113.6 (*C*$_q$, acetonide), 156.2 (*C*=O, -NH*C*ONH-), 163.7 (*C*H, urea), 167.7 (*C*=O, -NH*C*OR), 173.5 (*C*=O, ester), 174.5 (*C*=O, ester). Anal. Calcd. for $C_{19}H_{28}N_2O_{10}$: C, 51.35; H, 6.35; N, 6.30. Found: C, 51.13; H, 6.36; N, 6.33.

(2S,1′S,2′R,3′S,4′R)-(−)-1-[2-(2′,3′-Isopropylidenedioxy-4′-methoxycarbonylcyclopent-1′-yl)-2-hydroxy-2-methoxycarbonylethyl]-3-(3-methoxy-2-methylacryloyl)urea ***11***

Yield: 92 mg (55%). Solid, m.p. 40°C–42°C; $[\alpha]_D$ −17.3 (c=1.10, in $CHCl_3$); IR (KBr) 3700–3100, 2987, 2952, 1736, 1686, 1666, 1553, 1462, 1441, 1293, 1244, 1209, 1152, 1060, 864, 759 cm^{-1}; MS, *m/e* 443 (M-15, -*CH*$_3$, 2), 328 (21), 230 (15), 171 (69, -*CH*$_2$*NHR*), 142 (29), 99 (100), 83 (28), 59 (20), 43 (17); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.26 (s, 3H, CH_3 acetonide), 1.46 (s, 3H, CH_3 acetonide), 1.71 (s, 3H, CH_3 urea), 1.85 (complex abs, 2H, 2×H_5), 2.40 (ddd, J=10.4 Hz, J′=8.3 Hz, J″=5.6 Hz, 1H, $H_{1'}$/$H_{4'}$), 2.85 (ddd, J=10.4 Hz, J′=8.6 Hz, J″=5.6 Hz, 1H, $H_{4'}$/$H_{1'}$), 3.57 (dd, J=14.0 Hz, J′=4.9 Hz, 1H, H_1), 3.65 (s, 3H, OCH_3 ester), 3.73 (s, 3H, OCH_3 ester), 3.75 (dd, J=14.0 Hz, J′=4.9 Hz, 1H, H_1), 3.82 (s, 3H, OCH_3 urea), 3.94 (broad s, 1H), 4.66 (dd, J=7.5 Hz, J′=5.6 Hz, 1H, $H_{2'}$/$H_{3'}$), 4.73 (dd, J=7.5 Hz, J′=5.6 Hz, 1H, $H_{3'}$/$H_{2'}$), 7.32 (s, 1H, -*H*C=), 8.37 (broad s, 1H, -N*H*COR), 9.00 (dd, J=J′=4.9 Hz, 1H, -CH_2N*H*R); 62.5 MHz ^{13}C NMR ($CDCl_3$) 8.7 (*C*H_3, urea), 24.9 (*C*H_3, acetonide), 27.3 (*C*H_3, acetonide), 29.6 (*C*H_2, C-5′), 46.4 (*C*H_2, C-1), 49.4 (*C*H, C-1′/C-4′), 50.2 (*C*H, C-4′/C-1′), 52.0 (O*C*H_3, ester), 53.2 (O*C*H_3, ester), 61.4 (*C*H_3, O*C*H_3 urea), 76.6 (*C*$_q$, C-2), 79.7 (*C*H, C-2′/C-3′), 82.3 (*C*H, C-3′/C-2′), 107.0 (*C*$_q$, double bond), 113.6 (*C*$_q$, acetonide), 155.0 (*C*=O, -NH*C*ONH-), 158.6 (*C*H, double bond), 169.1 (*C*=O, -NH*C*OR), 173.4 (*C*=O, ester), 174.6 (*C*=O, ester). Anal. Calcd. for $C_{20}H_{30}N_2O_{10}$: C, 52.20; H, 6.60; N, 6.11. Found: C, 52.19; H, 6.79; N, 5.99.

*(2S,1′S,2′R,3′S,4′R)-(−)-1-[2-(4′-*tert*-Butyldimethylsilyloxymethyl-2′,3′-isopropylidene-dioxycyclopent-1′-yl)-2-*tert*-butyldimethylsilyloxymethyl-2-hydroxyethyl]-3-(3-methoxy-2-methylacryloyl)urea* ***17***

Yield: 28 mg (20%). Colorless oil; $[\alpha]_D$ −3.1° (c=1.30, in $CHCl_3$); IR (film) 3650–3050, 2931, 2061, 1681, 1666, 1553, 1469, 1455, 1377, 1363, 1251, 1209, 1145, 1096, 1061, 836, 780 cm^{-1}; MS, *m/e* 631 (M+1, 1), 516 (1), 268 (9), 225 (10), 195 (19), 172 (15), 169 (41), 115 (14), 105 (11), 99 (100), 89 (21), 75 (59), 73 (79), 59 (20), 57 (18), 43 (12), 41 (24); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.00 (s, 6H, 2×SiCH_3), 0.03 (s, 6H, 2×SiCH_3), 0.85 (s, 12H, 4×CH_3 of ^{t}Bu), 0.87 (s, 6H, 2×CH_3 of ^{t}Bu), 1.26 (s, 3H, CH_3 acetonide), 1.34–1.60 (complex abs, 2H), 1.46 (s, 3H, CH_3 acetonide), 1.74 (s, 3H, CH_3 urea), 1.87 (ddd, J=12.6 Hz, J′=J″=6.4 Hz, 1H), 2.13 (ddd, J=12.6 Hz, J′=J″=6.2 Hz, 1H), 3.31–3.83 (complex abs, 6H), 3.86 (s, 1H), 4.22 (dd, J=6.8 Hz, J′=6.2 Hz, 1H, $H_{2'}$/$H_{3'}$), 4.62 (dd, J=J′=6.8 Hz, 1H, $H_{3'}$/$H_{2'}$), 7.25 (s, 1H, -*H*C=). 7.97 (s, 1H, -N*H*COR), 8.95 (dd, J=J′=5.7 Hz, 1H, -CH_2N*H*R); 62.5 MHz ^{13}C NMR ($CDCl_3$) −1.6 (Si*C*H_3), −1.4 (Si*C*H_3), −1.3 (Si*C*H_3), 8.8 (*C*H_3, urea), 18.1 (*C*$_q$ of ^{t}Bu), 18.3 (*C*$_q$ of ^{t}Bu), 25.2 (*C*H_3, acetonide), 25.8 (*C*H_3 of ^{t}Bu), 25.9 (*C*H_3 of ^{t}Bu), 27.7 (*C*H_3, acetonide), 29.0 (*C*H_2, C-5′), 45.5 (*C*H_2, C-1), 47.1 (*C*H, C-1′/C-4′), 49.6 (*C*H, C-4′/C-1′), 61.5 (O*C*H_3), 64.3 (*C*H_2OSi), 65.1 (*C*H_2OSi), 74.0 (*C*$_q$, C-2), 80.5 (*C*H, C-2′/C-3′), 81.9 (*C*H, C-3′/C-2′), 107.0 (*C*$_q$, double bond), 112.6 (*C*$_q$, acetonide), 156.0 (*C*=O, -NH*C*ONH-), 158.5 (*C*H, double bond), 168.7 (*C*=O, -NH*C*OR). Anal. Calcd. for $C_{30}H_{58}N_2Si_2O_8$: C, 57.11; H, 9.27; N, 4.44. Found: C, 57.40; H, 9.08; N, 4.35.

(2S,1′S,2′R,3′S,4′R)-(+)-1-[2-Hydroxy-2-(2′,3′-dihydroxy-4′-hydroxycarbonylcyclopent-1′-yl)-2-methoxycarbonylethyl]-1H-pyrimidine-2,4-dione ***12***

Yield: 36 mg (97%). Solid, m.p. 131°C–134°C.; $[\alpha]_D$+19.4 (c=0.70, in MeOH); IR (KBr) 3700–2500, 1715, 1685, 1462, 1441, 1384, 1279, 1251, 1209, 1173, 1145, 1082 cm^{-1}; MS, *m/e* 342 (M-16, 1), 247 (M-111, *-Uracil*), 229 (31), 197 (18), 155 (10), 127 (12), 126 (100), 125 (18), 113 (20), 82 (42), 71 (14), 55 (34), 43 (13); 250 MHz ^{1}H-NMR (D_2O) 1.39 (ddd, J=12.9 Hz, J′=J″=10.3 Hz, 1H, $H_{5'}$), 1.88 (ddd, J=12.9 Hz, J′=J″=8.1 Hz, 1H, $H_{5'}$), 2.34 (ddd, J=J′=10.3 Hz, J″=5.2 Hz, 1H, $H_{1'}/H_{4'}$), 2.70 (ddd, J=10.3 Hz, J′=J″=8.1 Hz, 1H, $H_{4'}/H_{1'}$), 3.61 (s, 3H, O*C*H_3 ester), 3.91 (dd, J=8.1 Hz, J′=5.2 Hz, 1H, $H_{2'}/H_{3'}$), 3.97 (d, J=14.3 Hz, 1H, H_1), 4.04 (dd, J=10.3 Hz, J′=5.2 Hz, 1H, $H_{3'}/H_{2'}$), 4.22 (d, J=14.3 Hz, 1H, H_1), 5.56 (d, J=7.7 Hz, 1H, *-HC*=), 7.45 (d, J=7.7 Hz, 1H, *-HC*=); 62.5 MHz ^{13}C NMR (D_2O) 26.0 (*C*H_2, C-5), 48.6 (*C*H, C-1′/C-4′), 50.0 (*C*H, C-4′/C-1′), 54.4 (*C*H_2, C-1), 54.4 (O*C*H_3, ester), 72.4 (*C*H, C-2′/C-3′), 76.2 (*C*H, C-3′/C-2′), 78.1 (C_q, C-2), 102.2 (*C*H, uracil), 149.1 (*C*H, uracil), 153.2 (*C*=O, -NH*C*ONR-), 167.6 (*C*=O, -NH*C*OR), 175.5 (*C*=O, ester), 178.7 (*C*=O, acid).

(2S,1′S,2′R,3′S,4′R)-(+)-1-[2-Hydroxy-2-(2′,3′-dihydroxy-4′-hydroxycarbonylcyclopent-1′-yl)-2-methoxycarbonylethyl]-5-methyl-1H-pyrimidine-2,4-dione ***13***

Yield: 65 mg (96%). Solid, m.p. 78°C–dec.; $[\alpha]_D$+11.4 (c=0.70, in MeOH); IR (KBr) 3700–2200, 1729, 1687, 1469, 1441, 1384, 1413, 1353, 1251, 1195, 1096, 1061 cm^{-1}; MS, *m/e* 355 (M-17, 3), 243 (9), 229 (9), 197 (11), 140 (100), 127 (15), 121 (17), 106 (14), 96 (46), 69 (11), 55 (26), 41 (13); 250 MHz ^{1}H-NMR (D_2O) 1.34 (ddd, J=14.2 Hz, J′=12.2 Hz, J″=8.1 Hz, 1H, $H_{5'}$), 1.62 (s, 3H, C*H*$_3$ Thy), 1.79 (ddd, J=12.2 Hz, J′=J″=8.1 Hz, 1H, $H_{1'}/H_{4'}$), 2.24 (ddd, J=14.2 Hz, J′=9.6 Hz, J″=5.1 Hz, 1H, $H_{5'}$), 2.61 (ddd, J=9.6 Hz, J′=8.1 Hz, J″=5.1 Hz, 1H, $H_{4'}/H_{1'}$), 3.52 (s, 3H, O*C*H_3 ester), 3.83 (d, J=14.2 Hz, 1H, H_1), 3.84 (dd, J=8.1 Hz, J′=5.1 Hz, 1H, $H_{2'}/H_{3'}$), 3.94 (dd, J=J′=5.1 Hz, 1H, $H_{3'}/H_{2'}$), 4.09 (d, J=14.2 Hz, 1H, H_1), 7.20 (s, 1H, *-HC*=); 62.5 MHz ^{13}C NMR (D_2O) 12.3 (*C*H_3, Thy), 26.0 (*C*H_2, C-5′), 48.6 (*C*H, C-1′/C-4′), 50.0 (*C*H, C-4′/C-1′), 54.2 (*C*H_2, C-1), 54.3 (O*C*H_3, ester), 72.4 (*C*H, C-2′/C-3′), 76.2 (*C*H, C-3′/C-2′), 78.1 (C_q, C-2), 111.2 (C_q, double bond Thy), 144.8 (*C*H, double bond Thy), 153.2 (*C*=O, -NH*C*ONR-), 167.7 (*C*=O, -NH*C*OR), 175.5 (*C*=O, ester), 177.3 (*C*=O, acid).

(2S,1′S,2′R,3′S,4′R)-(+)-1-[2-Hydroxy-2-hydroxymethyl-2-(2′,3′-dihydroxy-4′-hydroxymethyl-cyclopent-1′-yl)ethyl]-5-methyl-1H-pyrimidine-2,4-dione ***18***

Yield: 13 mg (96%). Hygroscopic white solid. m.p. 28–30°C; $[\alpha]_D$+8.3 (c=0.60, in MeOH); IR (KBr) 3700–2400, 1695, 1684, 1476, 1455, 1406, 1384, 1370, 1258, 1216, 1159, 1054, 864 cm^{-1}; MS, *m/e* 323 (M-7, 1), 321 (5), 231 (18), 213 (27), 155 (100),140 (57), 137 (28), 127 (53), 121 (29), 109 (33), 96 (61), 79 (42), 69 (41), 55 (45), 43 (47), 41 (54); 250 MHz ^{1}H-NMR (D_2O) 0.85 (m, 1H), 1.48 (s, 3H, C*H*$_3$ Thy), 1.56 (m, 1H), 1.60–1.85 (complex abs, 2H), 2.80–3.37 (complex abs, 6H), 3.62–3.78 (complex abs, 2H), 7.13 (s, 1H, double bond Thy); 62.5 MHz ^{13}C NMR ($CDCl_3$) 12.3 (*C*H_3, Thy), 25.0 (*C*H_2, C-5), 45.6 (*C*H, C-1′/C-4′), 48.8 (*C*H, C-4′/C-1′), 52.5 (*C*H_2, C-1), 63.4 (*C*H_2OH), 64.2 (*C*H_2OH), 72.8 (*C*H, C-2′/C-3′), 75.2 (*C*H, C-3′/C-2′), 76.2 (C_q, C-2), 111.3 (C_q, double bond Thy), 145.4 (*C*H, double bond Thy), 154.4 (*C*=O, -NH*C*ONR-), 167.8 (*C*=O, -NH*C*OR-).

Silyl ethers ***15*** *and* ***15a*** *through alcohols* ***14*** *and* ***14a***

To an ice-cooled and stirred solution of diester **8** (100 mg, 0.2 mmol) in anhydrous THF (6 mL) 540 μL of 2.0M $LiBH_4$ in THF (1.1 mmol) was added dropwise under nitrogen atmosphere. The mixture was stirred at 0°C for 15 min and at r.t. overnight. The solvent was removed and the residue was poured into MeOH–H_2O (4 mL). The resultant solution was extracted with ethyl acetate (5×4 mL), the organic extracts were dried and solvents were removed to afford 86 mg of triol **14** as a white solid which was unable to be purified by crystallization or chromatography and identified by its spectroscopic data as follows. MS, *m/e* 366 (M+1, 2), 134 (57), 105 (100, *-NHCHMePh*); 250 MHz

^{1}H NMR ($CDCl_3$) 1.25 (s, 3H, CH_3 acetonide), 1.37 (d, J=6.6 Hz, 3H, CH_3-CHPh-NHR), 1.44 (ddd, J=J′=J″=6.0 Hz, 1H, H_5), 1.47 (s, 3H, CH_3 acetonide), 1.87 (ddd, J=12.1 Hz, J′=J″=6.0 Hz, 1H, H_5), 2.08 (ddd, J=12.1 Hz, J′=7.1 Hz, J″=5.5 Hz, 1H, H_1/H_4), 2.17 (ddd, J=12.1 Hz, J′=6.0 Hz, J″=5.9 Hz, 1H, H_4/H_1), 2.65 (d, J=12.2 Hz, 1H, $H_{2'}$), 2.82 (d, J=12.2 Hz, 1H, $H_{2'}$), 3.31 (broad s, 1H), 3.47 (s, 1H), 3.48 (dd, J=J′=7.1 Hz, 2H, CH_2OH), 3.62 (d, J=5.9 Hz, 2H, CH_2OH), 3.75 (q, J=6.6 Hz, 1H), 4.28 (dd, J=7.1 Hz, J′=5.5 Hz, 1H, H_2/H_3), 4.48 (dd, J=J′=7.1 Hz, 1H, H_3/H_2), 7.21–7.36 (complex abs, 5H, Ph); 62.5 MHz ^{13}C NMR ($CDCl_3$) 23.7 (*C*H_3, acetonide), 25.0 (*C*H_3, acetonide), 27.5 (*C*H_3-CHPh-NHR), 28.2 (*C*H_2, C-5), 46.8 (*C*H, C-1/C-4), 49.3 (*C*H, C-4/C-1), 53.7 (*C*H_2, C-2′), 58.4 (*C*H, *C*HMePh-NHR), 64.2 (*C*H_2OH), 68.8 (*C*H_2OH), 71.8 (*C*q, C-1′), 80.4 (*C*H, C-2/C-3), 82.6 (*C*H, C-3/C-2), 112.5 (*C*q, acetonide), 126.5 (*C*H, Ph), 127.2 (*C*H, Ph), 128.5 (*C*H, Ph), 144.5 (*C*q, Ph).

To an ice-cooled solution of crude **14** (86 mg) in dichloromethane (10 mL) DMAP (231 mg, 1.9 mmol) and *tert*-butyldimethylsilyl chloride (215 mg, 1.5 mmol) were successively added and the resultant mixture was stirred at 0°C for 10 min and then at r.t. for 24 h. Solvent was removed and the residue was chromatographed (mixtures of hexane–ethyl acetate as eluents) to give 130 mg (90% yield for the two steps) of bis(silyl) ether **15**.

Working in a similar manner but using 2.2 eq of $LiBH_4$ in the reduction of **8**, at r.t. for 16 h, a mixture of **14** and **14a** was obtained which, by silylation, afforded a 5:1 mixture of ethers **15** and **15a** in 77% overall yield. These compounds were isolated by column chromatography and characterized as follows.

*(1S,2R,3S,4S,1′S)-(+)-4-*tert*-Butyldimethylsilyloxymethyl-1-(1′-*tert*-butyldimethylsilyloxymethyl-1′-hydroxy-1′-hydroxymethyl-1′-[(R)-α-methylbenzylaminomethyl])-2,3-isopropylidene-dioxycyclopentane **15***

Colorless oil, o.t. 140–145°C (0.1 Torr); $[\alpha]_D$+18.0 (c=1.28, in $CHCl_3$); IR (film) 3700–3200, 2959, 2931, 2861, 1469, 1455, 1377, 1370, 1258, 1209, 1096, 1061, 1005, 836, 780, 702 cm^{-1}; MS, *m/e* 595 (M+1, 3), 594 (M, 6), 390 (25), 169 (9), 134 (23), 120 (8), 106 (10), 105 (100), 89 (6), 79 (8), 75 (20), 73 (30), 57 (8); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.00 (s, 6H, 2×SiCH_3), 0.03 (s, 6H, 2×SiCH_3), 0.85 (s, 18H, 6×CH_3 of ^{t}Bu), 1.14 (s, 3H, CH_3 acetonide), 1.33 (d, J=6.6 Hz, CH_3-CHPh-NHR), 1.41 (s, 3H, CH_3 acetonide), 1.45 (ddd, J=J′=J″=12.4 Hz, 1H, H_5), 1.81 (ddd, J=12.4 Hz, J′=J″=6.6 Hz, 1H, H_5), 1.94–2.10 (complex abs, 2H), 2.45 (d, J=12.2 Hz, 1H, H_2′), 2.74 (d, J=12.2 Hz, 1H, H_2′), 3.42 (s, 1H), 3.48 (d, J=7.0 Hz, 1H, -CH_2OTBDMS), 3.52 (d, J=7.0 Hz, 1H, -CH_2OTBDMS), 3.68 (d, J=4.6 Hz, 1H, -CH_2OTBDMS), 3.72 (d, J=4.6 Hz, 1H, -CH_2OTBDMS), 3.76 (q, J=J′=J″=6.6 Hz, 1H, C*H*MePh-NHR), 4.11 (dd, J=7.0 Hz, J′=6.6 Hz, 1H, H_4/H_5), 4.34 (dd, J=7.0 Hz, J′=6.0 Hz, 1H, H_5/H_4), 7.14–7.29 (complex abs, 5H, Ph); 62.5 MHz ^{13}C NMR ($CDCl_3$) −5.6 (Si*C*H_3), −5.5 (Si*C*H_3), −5.4 (Si*C*H_3), 18.1 (C_q of ^{t}Bu), 18.2(C_q of ^{t}Bu), 24.4 (*C*H_3, acetonide), 25.0 (*C*H_3, acetonide), 25.7 (*C*H_3 of ^{t}Bu), 25.8 (*C*H_3 of ^{t}Bu), 27.6 (*C*H_3-CHPh-NHR), 29.1 (*C*H_2, C-5), 47.5 (*C*H, C-1/C-4), 49.0 (*C*H, C-4/C-1), 51.7 (*C*H_2, C-2′), 58.3 (*C*H, *C*HMePh-NHR), 64.4 (*C*H_2OTBDMS), 67.8 (*C*H_2OTBDMS), 71.7 (C_q, C-1′), 80.6 (*C*H, C-2/C-3), 81.6 (*C*H, C-3/C-2), 112.1 (C_q, acetonide), 126.6 (*C*H, Ph), 126.8 (*C*H, Ph), 128.3 (*C*H, Ph), 145.3 (C_q, Ph). Anal. Calcd. for $C_{32}H_{59}NSi_2O_5$: C, 64.71; H, 10.01; N, 2.36. Found: C, 64.76; H, 9.97; N, 2.37.

*(1R,2S,3R,4S,1′S)-(+)-1-(1′-*tert*-Butyldimethylsilyloxymethyl-1′-hydroxy-1′-hydroxymethyl-1′-[(R)-α-methylbenzylaminomethyl])-2,3-isopropylidenedioxycyclopentane-1-carboxylic acid methyl ester **15a***

Colorless oil, $[\alpha]_D$+14.2 (c=1.55, in $CHCl_3$); IR (film) 3600–3200, 2959, 2931, 2861, 1736, 1471, 1462, 1455, 1380, 1257, 1209, 1173, 1096, 1068, 836, 780, 702 cm^{-1}; MS, *m/e* 508 (M+1, 1), 492 (M-15, -CH_3,1), 390 (11), 134 (36), 120 (10), 106 (11), 105 (100), 89 (6), 75 (15), 73 (19), 59 (6), 43 (5); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.01 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3), 0.86 (s, 9H, 3×CH_3 of ^{t}Bu), 1.13 (s, 3H, CH_3 acetonide), 1.33 (d, J=6.6 Hz, CH_3-CHPh-NHR), 1.42 (s, 3H, CH_3 acetonide), 1.86–2.03 (complex abs, 3H, H_7 and H_6), 2.42 (d, J=12.2 Hz, 1H, H_2′), 2.75 (m, 1H, H_3), 2.76 (d,

J=12.2 Hz, 1H, H_2'), 3.40 (s, 2H, -CH_2OTBDMS), 3.67 (s, 3H, OCH_3), 3.77 (q, J=J'=J''=6.6 Hz, 1H, C*H*MePh-NHR), 4.36 (dd, J=7.5 Hz, J'=4.4 Hz, 1H, H_4), 4.60 (dd, J=J'=7.5 Hz, 1H, H_5), 7.17–7.29 (complex abs, 5H, Ph); 62.5 MHz ^{13}C NMR ($CDCl_3$) −1.6 (SiCH_3), −1.5 (SiCH_3), 18.1 (C_q of ^{t}Bu), 24.2 (CH_3 acetonide), 24.9 (CH_3 acetonide), 25.9 (CH_3 of ^{t}Bu), 27.4 (CH_3-CHPh-NHR), 29.6 (CH_2, C-5), 49.2 (*C*H C-1/C-4), 50.2 (*C*H C-4/C-1), 51.3 (CH_2, C-2'), 51.9 (OCH_3), 58.2 (*C*H, *C*HMePh-NHR), 67.6 (CH_2-OTBDMS), 71.5 (C_q, C-1'), 80.3 (*C*H, C-2/C-3), 82.1 (*C*H, C-3/C-2), 112.8 (C_q, acetonide), 126.7 (*C*H, Ph), 126.9 (*C*H, Ph), 128.3 (*C*H, Ph), 145.1 (C_q, Ph), 173.9 (*C*=O, ester). Anal. Calcd. for $C_{27}H_{45}NSiO_6$: C, 63.87; H, 8.93; N, 2.76. Found: C, 63.90; H, 8.90; N, 2.78.

*(1S,2R,3S,4S,1'S)-(+)-1-(1'-Aminomethyl-1'-*tert*-butyldimethylsilyloxymethyl-1'-hydroxy)-4-*tert*-butyldimethylsilyloxymethyl-2,3-isopropylidenedioxycyclopentane* **16**

Benzylamine **15** (235 mg, 0.4 mmol) in methanol (10 mL) was hydrogenated at 3 atmospheres pressure in the presence of 10% Pd/C (106 mg) at r.t. for 3 h. The mixture was filtered through Celite and the catalyst was washed with methanol (10 mL). The combined filtrates were evaporated to dryness yielding quantitatively 190 mg of amine **16** as a solid, m.p: 26–28°C; $[\alpha]_D$+12.7 (c=2.51, en $CHCl_3$); IR (KBr) 3700–3100, 2959, 2931, 2861, 1609, 1476, 1462, 1377, 1370, 1258, 1209, 1103, 1061, 836, 780 cm^{-1}; MS, *m/e* 491 (M+1, 1), 490 (M, 3), 374 (21), 288 (14), 213 (17), 195 (20), 171 (21), 169 (48), 137 (12), 105 (12), 89 (33), 75 (86), 73 (100), 59 (22), 57 (13), 43 (19); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.00 (s, 6H, 2×SiCH_3), 0.04 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.84 (s, 9H, 3×CH_3 of ^{t}Bu), 0.85 (s, 9H, 3×CH_3 of ^{t}Bu), 1.26 (s, 3H, CH_3 acetonide), 1.44 (s, 3H, CH_3 acetonide), 1.51 (ddd, J=J'=J''=12.6 Hz, 1H, H_5), 1.85 (ddd, J=12.6 Hz, J'=J''=6.3 Hz, 1H, H_1/H_4), 2.06 (ddd, J=12.6 Hz, J'=J''=6.3 Hz, 1H, H_4/H_1), 2.12 (m, 1H), 3.15 (d, J=13.5 Hz, 1H, H_2'), 3.22 (d, J=13.5 Hz, 1H, H_2'), 3.53 (m, 2H, CH_2OTBDMS), 3.63 (d, J=5.3 Hz, 1H, -CH_2OTBDMS), 3.72 (d, J=5.3 Hz, 1H, -CH_2OTBDMS), 4.25 (dd, J=7.1 Hz, J'=5.1 Hz, 1H, H_4/H_5), 4.62 (dd, J=J'=7.1 Hz, 1H, H_5/H_4); 62.5 MHz ^{13}C NMR ($CDCl_3$) −1.8 (SiCH_3), −1.7 (SiCH_3), −1.5 (SiCH_3), 18.0 (C_q of ^{t}Bu), 18.1(C_q of ^{t}Bu), 25.1 (CH_3, acetonide), 25.7 (CH_3 of ^{t}Bu), 27.6 (CH_3, acetonide), 28.7 (CH_2, C-5), 45.9 (CH_2, C-2'), 46.4 (*C*H, C-1/C-4), 49.5 (*C*H, C-4/C-1), 64.2 (CH_2OTBDMS), 66.6 (CH_2OTBDMS), 71.4 (C_q, C-1'), 79.2 (*C*H, C-2/C-3), 81.9 (*C*H, C-3/C-2), 113.0 (C_q, acetonide). Anal. Calcd. for $C_{24}H_{51}NSi_2O_5$: C, 58.85; H, 10.49; N, 2.86. Found: C, 58.76; H, 10.46; N, 2.78.

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12. Yields of these reactions are usually in the range 15–45%. See, for instance Ref. 6(b).

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