62. Synthesis of Carbocyclic *C*-Nucleosides Containing Nonnatural Pyrimidine Bases

by **Stefan Hildbrand**[1]), **Christian Leumann***, and **Rolf Scheffold**†[2])

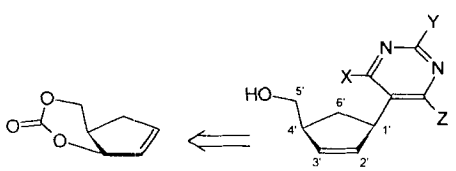
Institut für organische Chemie der Universität Bern, Freiestrasse 3, CH-3012 Bern

(6.II.96)

A series of new carbocyclic *C*-nucleosides with a *cis*-4′-(hydroxymethyl)cyclopent-2′-enyl sugar moiety and unnatural pyrimidine bases (**2**–**6**) were synthesized in racemic form in two steps starting from the easily accessible cyclic carbonate **1**.

Introduction. – In the last few years, carbocyclic analogs of purine and pyrimidine nucleosides have become prime candidates in the search for new antiviral and chemotherapeutic agents [1]. Within this context, we recently developed a short and efficient synthesis of the carbocyclic 2′,3′-didehydro-2′,3′-dideoxyguanosine analog (−)-carbovir [2]. The key step in this synthesis was the stereoselective Pd^0-catalyzed allylic substitution of the optically pure cyclic carbonate **1** with 2-amino-6-chloro-1*H*-purine. This substitution reaction has now been extended from N- to C-nucleophiles, and thus opens a new and efficient route to carbocyclic nucleosides with unnatural *C*-pyrimidine bases.

Relatively little attention has been paid so far to the synthesis of such carbocyclic *C*-nucleosides – compounds in which the heterocyclic base is linked to the carbocycle *via* a C–C bond. To date, the preferred strategy for the synthesis of these nucleoside analogs proceeds *via* the construction of functionalized carbafuranoses by *Diels-Alder* reactions. On this route, *Katagiri, Kaneko*, and coworkers developed a method for the synthesis of carbocyclic pyrimidine *C*-nucleosides [3] and carbocyclic oxazinomycins [4], while *Cookson et al.* [5] described a synthesis of carbocyclic ribo-*C*-nucleosides and their corresponding 2′-deoxy derivatives. *Koizumi* and coworkers [6] reported the first enantioselective synthesis of the carbocyclic analog of showdomycin and *Stoodley* and coworkers [7] that of carbocyclic tiazofurin.



1

2[3]) X = Y = Z = OH
3[3]) X = Z = OH, Y = NH_2
4[3]) X = Z = Me, Y = NH_2
5[3]) X = Y = Z = NH_2
6[3]) X = Z = NH_2, Y = SH

[1]) Part of the planned Ph. D. thesis of *S. H.*, University of Bern.

[2]) Deceased, November 28, 1994.

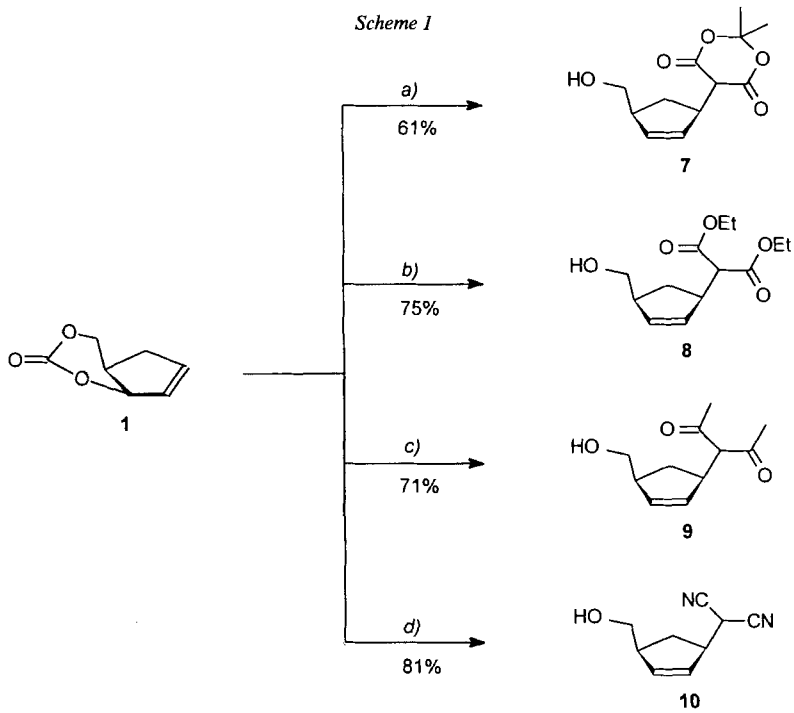
[3]) Numbering according to [1a]. For convenience, only one tautomeric form is drawn.

Here we report on the synthesis of the new nucleoside analogs **2–6** containing a *cis*-4′-(hydroxymethyl)cyclopent-2′-enyl sugar moiety and unnatural pyrimidine bases in two steps starting from the cyclic allylic carbonate **1** [2].

Results and Discussion. – As starting material, the racemic cyclic allylic carbonate **1** was used. Compound **1** is in principle also accessible in enantiomerically pure form [2]. The introduction of the pyrimidine bases into this carbocyclic core system was achieved in the two-step sequence: regio- and stereoselective introduction of activated C-nucleophiles by way of a Pd^0-catalyzed substitution, followed by completion of the base portion by condensation with urea or guanidine or derivatives thereof.

The allylic substitution reactions with the nucleophiles 2,2-dimethyl-1,3-dioxane-4,6-dione (*Meldrum*'s acid), diethyl malonate, acetylacetone, and malonodinitrile were typically conducted in THF in the presence of 1.25% Pd^0 catalyst, prepared *in situ* from tris(dibenzylideneacetone)dipalladium(0)–chloroform ($[Pd_2(dba)_3]\cdot CHCl_3$) and PPh_3 [8] (*Scheme 1*). The reactions were generally complete after 1–2 h, and the formation of only one stereoisomer in each case (see **7–10**) was observed. Compounds **7–10** could be isolated by column chromatography in 61–81% yield[4]). No traces of regioisomers (attack

Scheme 1



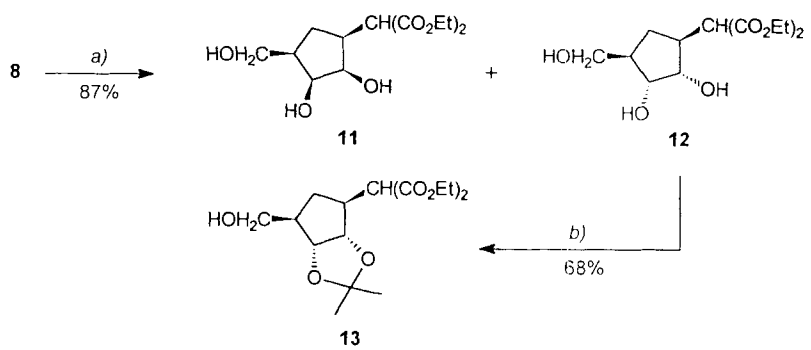
a) *Meldrum*'s acid, Pd^0/PPh_3, THF. *b*) $CH_2(CO_2Et)_2$, Pd^0/PPh_3, THF. *c*) $CH_2(COMe)_2$, Pd^0/PPh_3, THF. *d*) $CH_2(CN)_2$, Pd^0/PPh_3, THF.

[4]) The catalyst in these substitution reactions could also be replaced by Pd/C (10%) [9]. In this way, **7–10** were obtained in 50–70% yield.

of the nucleophile at C(3′)) or diastereoisomers could be detected by anal. GC and NMR[5]). The assignment of the relative configuration at C(1′) in **7**–**10** is based on the large difference in the ^{1}H-NMR chemical shift of the two diastereotopic protons at C(6′) (0.5–1.5 ppm), which is typical for *cis*-1,4-disubstituted cyclopent-2-enes [10].

In the case of **8**, the configuration was additionally assigned using its conformationally restricted derivative **13** (*Scheme 2*) by NOE studies. To this end, **8** was *cis*-dihydroxylated with OsO_4 and 4-methylmorpholine 4-oxide monohydrate (NMO · H_2O) to afford a 2:1 mixture of the two triols **11** and **12** which were easily separated by column chromatography. Treatment of **12** with 2,2-dimethoxypropane and catalytic amounts of *p*-toluenesulfonic acid (TsOH) in acetone afforded the acetonide **13** in 68% yield, the relative configuration of which was determined by NOE measurements (see *Exper. Part*). These (not optimized) transformations formally open also the access to the corresponding carboribonucleoside analogs.

Scheme 2



a) Cat. OsO_4/NMO · H_2O, acetone/H_2O 8:1. *b*) $Me_2C(OMe)_2$, cat. TsOH, acetone.

The products **8**–**10** were expected to be good candidates for the build-up of pyrimidine bases [11]. Treatment of the diethyl malonate adduct **8** with urea in refluxing EtOH under basic conditions followed by acidification gave the crystalline barbituric-acid derivative **2** in 51% yield (*Scheme 3*). Derivative **3** was accessible by refluxing **8** with guanidine in 58% yield after recrystallization[6]).

Also the β-diketone **9** could be converted to carbocyclic *C*-nucleosides, as exemplified by the formation of 4,6-dimethylpyrimidine nucleoside **4** on refluxing **9** with excess guanidine carbonate in EtOH (55% yield after chromatography). While neither malonodinitrile nor its α-monoalkyl derivatives have been condensed successfully with urea, the cyclizations with guanidines and thioureas are well known[7]). Thus, guanidine and the malonodinitrile derivative **10** reacted in EtOH to give the pyrimidine-2,4,6-triamine **5** in

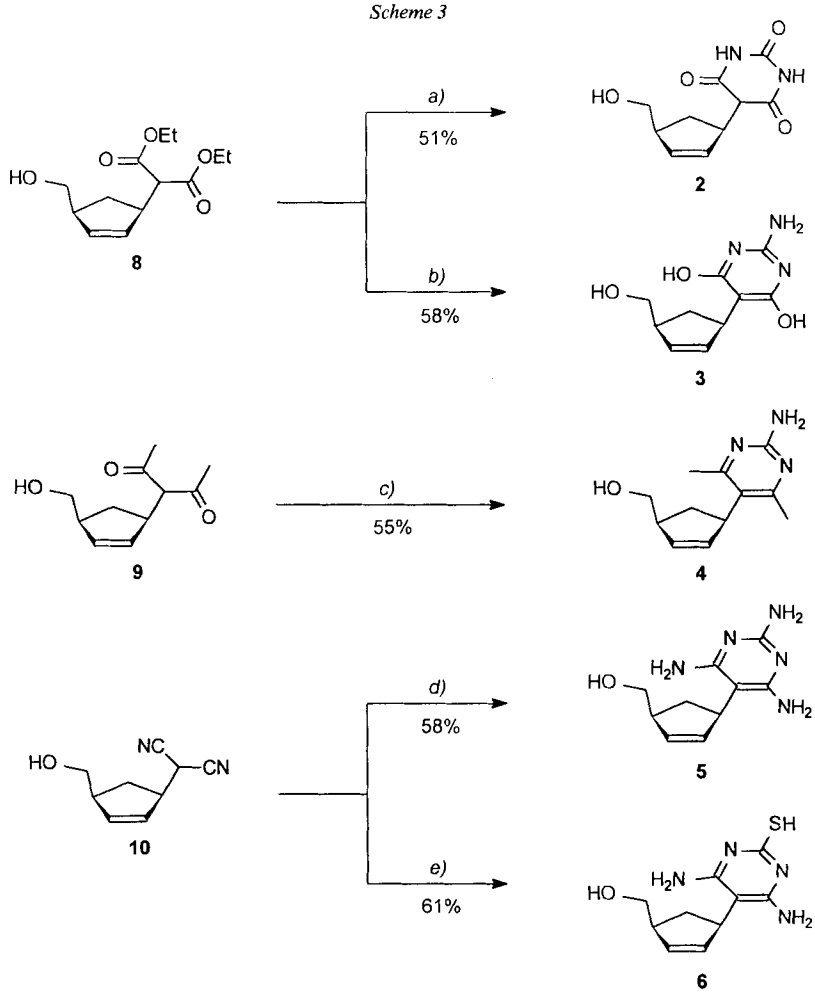
---

[5]) The only exception with respect to stereoselectivity was encountered when diethyl methylmalonate was used as the nucleophile. An inseparable mixture of several unidentified products resulted in this case.

[6]) Reaction of **8** with thiourea under similar conditions (NaOEt/EtOH, reflux) gave the corresponding thiobarbiturate (MS evidence), however, in disappointingly low yield (< 10%).

[7]) To date, the corresponding 4,6 diaminopyrimidin-2(1*H*)-ones have been prepared only by indirect methods (*e.g.* by *S*-alkylation and hydrolysis of the 4,6 diaminopyrimidine-2(1*H*)-thiones [11b]).

Scheme 3



a) $(H_2N)_2CO$, NaOEt/EtOH, then 25% HCl. *b*) $(H_2N)_2CNH \cdot HCl$, NaOEt/EtOH, then 1M HCl. *c*) $[(H_2N)_2CNH]_2 \cdot H_2CO_3$, EtOH. *d*) $(H_2N)_2CNH \cdot HCl$, NaOEt/EtOH. *e*) $(H_2N)_2CS$, NaOEt/EtOH, then H_2O/AcOH.

58% yield after recrystallization. Refluxing of **10** and thiourea in NaOEt/EtOH followed by acidification afforded the 4,6-diaminopyrimidine-2(1*H*)-thione **6** in 61% yield after recrystallization.

In summary, we have shown that the cyclic allylic carbonate **1** is a versatile intermediate in the synthesis of carbocyclic *C*-nucleosides, since it allows the regio- and stereoselective introduction of C-nucleophiles *via* Pd^0-catalysis. The newly prepared carbocyclic pyrimidine *C*-nucleosides **2**, **3**, **5**, and **6** are currently tested for biological activity.

The authors are grateful to Mr. *A. Saxer* for anal. GC and Dr. *C. Müller* for NOE measurements. This work was financially supported by the *Swiss National Science Foundation*.

Experimental Part

General. All reactions were carried out under Ar starting from racemic **1** [2]. Chemicals and solvents: Tris(dibenzylideneacetone)dipalladium(0)–chloroform ($[Pd_2(dba)_3]\cdot CHCl_3$), *Aldrich*; *Florisil* for chromatography (16–13 mesh), *Fluka*, THF, distilled over K/benzophenone; all other reagents and solvents. *Fluka purum* or *puriss.* TLC: pre-coated sheets (*Alugram® Sil G/UV$_{254}$*), *Macherey-Nagel*; visualization with 0.7% aq. $KMnO_4$ soln. Flash column chromatography (FC): silica gel (30–60 μm), *Baker*. Anal. GC (t_R in min): *Hewlett-Packard-5794* gas chromatograph, 20-m *Duran*-glass cap. column coated with *SE-54* (*df* 0.15 μm); temp.-program from 40 to 250°, 3°/min; FID. M.p. (uncorrected): *Büchi 510*. IR: *Perkin-Elmer-782*; $\tilde{\nu}$ [cm^{-1}]. ^{1}H- and ^{13}C-NMR: *Bruker-AC-300* (300 and 75 MHz, resp.); δ [ppm] (Me_4Si = 0 or (D_6)DMSO = 2.49 and 39.70, resp.), J [Hz]; ^{13}C multiplicities from DEPT spectra. 1D-NOE: *DRX500 Bruker* (500 MHz); δ (irradiated)→δ (obersved). MS (m/z (%)): *Varian-MAT-CH-7A*, ionization energy 70 eV; only fragments with intensities ≥ 10% of the base peak.

(1′RS,4′SR)-2,2-Dimethyl-5-[4′-(hydroxymethyl)cyclopent-2′-enyl]-1,3-dioxane-4,6-dione (**7**). A soln. of $[Pd_2(dba)_3]\cdot CHCl_3$ (9.2 mg, 0.009 mmol) and PPh_3 (18.5 mg, 0.071 mmol) in THF (0.75 ml) was stirred for 15 min at r.t. A soln. of **1** (50 mg, 0.36 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (*Meldrum*'s acid; 103 mg, 0.71 mmol) in THF (0.4 ml) was added dropwise within 5 min and the mixture stirred for 90 min at r.t. The mixture was filtered over *Florisil* and the solvent distilled off. Purification of the residue by FC (AcOEt) yielded **7** (52 mg, 61%). Colorless solid. M.p. 106–108°. TLC (AcOEt): R_f 0.54. IR (KBr): 3400 (br.), 2860*m*, 1780*s*, 1745*s*, 1440*w*, 1390*s*, 1300*s*, 1240*m*, 1205*s*, 1160*w*, 1135*w*, 1095*w*, 1050*s*, 990*s*, 920*w*, 875*m*, 830*w*, 735*m*, 635*w*. ^{1}H-NMR ($CDCl_3$)^3): 1.59 (*dt*, J = 13.3, 6.9, 1 H–C(6′)); 2.45 (*dt*, J = 13.3, 8.8, 1 H–C(6′)); 1.76 (*s*, Me); 1.81 (*s*, Me); 2.12 (br. *s*, OH); 2.92–3.06 (*m*, H–C(4′)); 3.55–3.72 (*m*, H–C(1′), 2 H–C(5′)); 3.82 (*d*, J = 6.0, H–C(5)); 5.78 (*dt*, J = 5.5, 2.2, H–C=C); 5.91 (*dt*, J = 5.5, 2.2, H–C=C). ^{13}C-NMR ($CDCl_3$): 164.93 (*s*); 164.87 (*s*); 133.43 (*d*); 133.05 (*d*); 105.06 (*s*); 65.29 (*t*); 50.10 (*d*); 48.09 (*d*); 44.30 (*d*); 30.56 (*t*); 28.55 (*q*); 26.89 (*q*). MS: 240 (< 1, M^+), 184 (12), 183 (19), 153 (14), 146 (10), 79 (35), 77 (13), 67 (12), *66* (100), 59 (12), 43 (10).

Diethyl (1′RS,4′SR)-2-[4′-(Hydroxymethyl)cyclopent-2′-enyl]propanedioate (**8**). As described for **7**, with $[Pd_2(dba)_3]\cdot CHCl_3$ (110 mg, 0.106 mmol), PPh_3 (220 mg, 0.84 mmol), THF (8 ml), and **1** (0.58 g, 4.14 mmol) and diethyl propanedioate (1.32 g, 8.24 mmol) in THF (4 ml; within 10 min, then 70 min). FC (Et_2O/pentane 5:2) of the residual dark oil afforded **8** (0.80 g, 75%). Slightly-yellowish oil. TLC (Et_2O/pentane 5:2): R_f 0.35. GC: single isomer (t_R 34.77). IR (film): 3440*m*, 2980*s*, 2940*m*, 2880*m*, 1750*s*, 1730*s*, 1470*m*, 1450*m*, 1370*s*, 1305*s*, 1265*s*, 1175*s*, 1150*s*, 1095*m*, 1035*s*, 855*w*, 750*w*, 650*w*. ^{1}H-NMR ($CDCl_3$)^3): 1.27 (*t*, J = 7.2, 2 Me); 1.37 (*dt*, J = 13.6, 6.8, 1 H–C(6′)); 1.70 (br. *d*, OH); 2.32 (*dt*, J = 13.6, 8.5, 1 H–C(6′)); 2.86–3.00 (*m*, H–C(4′)); 3.31 (*d*, J = 9.6, H–C(2)); 3.34–3.46 (*m*, H–C(1′)); 3.50–3.66 (*m*, 2 H–C(5′)); 4.13–4.26 (*m*, 2 CO_2CH_2); 5.70–5.80 (*m*, H–C(2′), H–C(3′)). ^{13}C-NMR ($CDCl_3$): 168.72 (*s*); 168.66 (*s*); 133.6 (*d*); 133.4 (*d*); 66.02 (*t*); 61.35 (2*t*); 57.31 (*d*); 48.26 (*d*); 45.16 (*d*); 30.89 (*t*); 14.1 (2*q*). MS: 256 (< 1, M^+), 226 (23), 165 (15), 164 (15), 161 (14), *160* (100), 152 (35), 151 (27), 137 (11), 133 (40), 123 (19), 115 (15), 105 (17), 91 (10), 88 (10), 86 (16), 84 (14), 79 (33), 77 (10), 67 (10), 66 (13), 18 (26).

(1′RS,4′SR)-3-[4′-(Hydroxymethyl)cyclopent-2′-enyl]pentane-2,4-dione (**9**). As described for **7**, with $[Pd_2(dba)_3]\cdot CHCl_3$ (9.2 mg, 0.009 mmol), PPh_3 (18.5 mg, 0.071 mmol), THF (0.75 ml), and **1** (50 mg, 0.36 mmol) and pentane-2,4-dione (81 mg, 0.81 mmol) in THF (0.4 ml; within 5 min, then 90 min). FC (Et_2O) of the residual dark oil afforded **9** (50 mg, 71%). Colorless oil. TLC (Et_2O): R_f 0.32. GC: single isomer (t_R 22.83). IR (film): 3440*s* (br.), 2960*s*, 1695*s*, 1420*m*, 1360*s*, 1250*w*, 1185*m*, 1150*s*, 1090*m*, 1040*s*, 740*w*, 620*w*, 585*w*. ^{1}H-NMR ($CDCl_3$)^3): 1.14 (*dt*, J = 13.2, 6.6, 1 H–C(6′)); 2.08 (br. *d*, OH); 2.198 (*s*, Me); 2.204 (*s*, Me); 2.26 (*dt*, J = 13.2, 8.6, 1 H–C(6′)); 2.86–2.99 (*m*, H–C(4′)); 3.43–3.61 (*m*, H–C(1′), 2 H–C(5′)); 3.63 (*d*, J = 10.7, H–C(3)); 5.61 (*dt*, J = 5.9, 2.2, H–C=C); 5.77 (*dt*, J = 5.9, 2.2, H–C=C). ^{13}C-NMR ($CDCl_3$): 203.62 (2*s*); 133.78 (*d*); 133.02 (*d*); 75.67 (*d*); 65.83 (*t*); 48.20 (*d*); 45.19 (*d*); 30.94 (*t*); 29.95 (*q*); 29.51 (*q*). MS: 196 (2, M^+), 154 (16), *153* (100), 135 (15), 123 (56), 117 (45), 107 (11), 101 (80), 93 (10), 81 (13), 79 (21), 77 (13), 67 (12), 66 (34), 43 (61), 18 (14).

(1′RS,4′SR)-2-[4-(Hydroxymethyl)cyclopent-2′-enyl]propanedinitrile (**10**). As described for **7**, with $[Pd_2(dba)_3]\cdot CHCl_3$ (92 mg, 0.089 mmol), PPh_3 (185 mg, 0.71 mmol), THF (7.0 ml), and **1** (0.50 g, 3.57 mmol) and propanedinitrile (0.47 g, 7.11 mmol) in THF (4 ml; within 10 min, then 2 h). FC (Et_2O) of the residue (1.4 g) yielded **10** (0.47 g, 81%). Colorless oil. TLC (Et_2O): R_f 0.33. GC: single isomer (t_R 25.29). IR (film): 3400*s* (br.), 2900*m*, 2260*w*, 1630*w*, 1085*m*, 1035*m*, 755*m*, 625*w*. ^{1}H-NMR ($CDCl_3$)^3): 1.62 (*dt*, J = 14.0, 5.0, 1 H–C(6′)); 1.80 (br. *d*, OH); 2.50 (*dt*, J = 14.0, 8.8, 1 H–C(6′)); 3.00–3.12 (*m*, H–C(4′)); 3.33–3.45 (*m*, H–C(1′)); 3.60–3.75 (*m*, 2 H–C(5′)); 4.00 (*d*, J = 8.0, H–C(2)); 5.82–5.88 (*m*, H–C=C); 5.96–6.02 (*m*, H–C=C). ^{13}C-NMR ($CDCl_3$): 137.71 (*d*); 129.55 (*d*); 112.68 (*s*); 112.47 (*s*); 64.44 (*t*); 48.05 (*d*); 47.17 (*d*); 30.57 (*t*); 27.89 (*d*). MS: 162 (< 1, M^+), 132 (31), 86 (33), 84 (52), 80 (15), 79 (35), 7 (10), 67 (44), *66* (100), 65 (12), 18 (44).

Diethyl (1'RS,2'SR,3'RS,4'SR)-2-[2',3'-Dihydroxy-4'-(hydroxymethyl)cyclopentyl]propanedioate (**11**) *and Diethyl (1'RS,2'RS,3'SR,4'SR)-2-[2',3'-Dihydroxy-4'-(hydroxymethyl)cyclopentyl]propanedioate* (**12**). To a soln. of **8** (0.20 g, 0.78 mmol) and 4-methylmorpholine 4-oxide monohydrate (NMO·H_2O; 0.21 g, 1.55 mmol) in acetone/H_2O 8.1 (2 ml) was added at r.t. a crystal (*ca.* 5 mg) of OsO_4. After stirring the dark soln. for 30 min at r.t., 38–40% aq. $NaHSO_3$ soln. (1 ml) was added and the mixture extracted with CH_2Cl_2 (5 × 50 ml). The org. phase was dried ($MgSO_4$) and the solvent removed. FC (AcOEt→AcOEt/MeOH 20:1) afforded **11** (134 mg, 59%) and **12** (63 mg, 28%) as clear colorless oil.

Data of **11**: TLC (AcOEt/MeOH 20:1): R_f 0.39. IR (film): 3400*s* (br.), 2965*s*, 2870*s*, 1730*s*, 1415*w*, 1370*w*, 1280*m*, 1145*m*, 1110*m*, 1020*m*, 535*w*. ^{1}H-NMR ($CDCl_3$)[3]: 1.27 (*t*-like, J = 7.1, 2 Me); 1.46–1.60 (*m*, 1 H–C(6')); 1.76–1.89 (*m*, 1 H–C(6')); 2.24–2.37 (*m*, 1 H); 2.45–2.58 (*m*, 1 H); 3.27 (br. *s*, OH); 3.60 (*d*, J = 11.0, H–C(2)); 3.65 (*dd*, J = 10.8, 5.9, 1 H–C(5')); 3.80 (*dd*, J = 10.8, 3.5, 1 H–C(5')); 4.10–4.33 (*m*, H–C(2'), H–C(3'), 2 CO_2CH_2). ^{13}C-NMR ($CDCl_3$): 169.22 (*s*); 169.21 (*s*); 74.68 (*d*); 73.26 (*d*); 62.05 (*t*); 61.58 (*t*); 61.49 (*t*); 52.44 (*d*); 41.18 (*d*); 40.44 (*d*); 28.49 (*t*); 14.10 (*q*); 14.03 (*q*). MS: 290 (< 1, M^+), 261 (14), 245 (17), 241 (42), 226 (12), 215 (21), 199 (24), 198 (13), 195 (14), 181 (11), 180 (10), 169 (12), 167 (11), 162 (16), *161* (100), 160 (84), 157 (11), 156 (12), 153 (10), 152 (13), 151 (17), 139 (10), 133 (33), 132 (12), 129 (12), 123 (16), 115 (17), 114 (15), 113 (29), 112 (14), 111 (11), 101 (14), 95 (28), 83 (13), 45 (11), 31 (12).

Data of **12**: TLC (AcOEt/MeOH 20:1): R_f 0.30. IR (film): 3400*s* (br.), 2930*s*, 1730*s*, 1458*m*, 1370*m*, 1250*s*, 1180*s*, 1110*s*, 1025*s*, 865*w*, 605*w*. ^{1}H-NMR ($CDCl_3$)[3]: 1.12 (*dt*, J = 12.8, 10.5, 1 H–C(6')); 1.28 (*t*-like, J = 7.4, 2 Me); 1.96 (*dt*, J = 12.9, 7.7, 1 H–C(6')); 2.11–2.27 (*m*, 1 H); 2.53–2.67 (*m*, 1 H); 2.91 (br. *s*, OH); 3.42 (*d*, J = 8.8, H–C(2)); 3.64 (*dd*, J = 10.6, 7.0, 1 H–C(5')); 3.74 (*dd*, J = 10.6, 5.2, 1 H–C(5')); 3.85–3.94 (*m*, H–C(2'), H–C(3')); 4.15–4.29 (*m*, 2 CO_2CH_2). ^{13}C-NMR ($CDCl_3$): 169.49 (*s*); 168.84 (*s*); 75.19 (*d*); 74.84 (*d*); 64.43 (*t*); 61.82 (*t*); 61.62 (*t*); 54.80 (*d*); 45.91 (*d*); 43.72 (*d*); 27.71 (*t*); 14.06 (*q*); 14.00 (*q*). MS: 290 (< 1, M^+), 241 (19), 215 (14), 195 (11), 162 (10), *161* (100), 160 (55), 133 (35), 115 (16), 113 (12), 105 (10), 101 (11), 95 (15), 18 (11).

Diethyl (1'RS,2'RS,3'SR,4'SR)-2-[4'-(Hydroxymethyl)-2',3'-(isopropylidenedioxy)cyclopentyl]propanedioate (**13**). To a soln. of **12** (44 mg, 0.15 mmol) and 2,2-dimethoxypropane (0.1 ml, *ca.* 0.8 mmol) in acetone (1 ml) was added a catalytic amount of *p*-toluenesulfonic acid (*ca.* 5 mg), and the soln. was stirred for 17 h at r.t. Silica gel (*ca.* 0.3 g) was added, the solvent distilled off, and the residue purified by FC (Et_2O): **13** (34 mg, 68%). Clear colorless oil. TLC (Et_2O): R_f 0.34. IR (film): 3450*m* (br.), 2980*m*, 2940*m*, 1730*s*, 1465*w*, 1403*w*, 1370*m*, 1300*m*, 1258*m*, 1210*m*, 1160*m*, 1065*m*, 1030*m*, 862*m*, 802*w*, 517*w*. ^{1}H-NMR ($CDCl_3$)[3]: 1.27 (*t*, J = 7.2, 3 H); 1.28 (*t*, J = 7.2, 3 H); 1.29 (*s*, 3 H); 1.30–1.47 (*m*, 1 H–C(6')); 1.49 (*s*, 3 H); 1.97 (br. *s*, OH); 2.10–2.33 (*m*, 1 H–C(6'), H–C(4')); 2.60–2.72 (*m*, H–C(1')); 3.43 (*d*, J = 8.1, H–C(2)); 3.63 (*dd*, J = 10.6, 6.3, 1 H–C(5')); 3.70 (*dd*, J = 10.6, 5.5, 1 H–C(5')); 4.15–4.26 (*m*, 2 CO_2CH_2); 4.40 (*dd*, J = 7.0, 5.15, H–C(3')); 4.46 (*dd*, J = 7.0, 5.5, H–C(2')). NOE (500 MHz)[3]: 2.15 (H_α–C(6'))→2.66 (H–C(1')); 2.25 (H–C(4'))→3.65 (2 H–C(5')); 2.66 (H–C(1'))→2.15 (H_α–C(6')), 3.43 (H–C(2)); 3.43 (H–C(2))→2.66 (H–C(1')), 4.66 (H–C(2')); 3.65 (2 H–C(5'))→2.25 (H–C(4')), 4.40 (H–C(3')). ^{13}C-NMR ($CDCl_3$): 168.45 (2*s*); 112.88 (*s*); 83.43 (*d*); 83.03 (*d*); 64.33 (*t*); 61.52 (*t*); 61.45 (*t*); 54.3 (*d*); 47.07 (*d*); 44.66 (*d*); 32.05 (*t*); 27.68 (*q*); 25.34 (*q*); 14.08 (*q*); 14.04 (*q*). MS: 330 (< 1, M^+), 316 (47), *315* (100), 285 (15), 269 (26), 241 (52), 237 (12), 227 (44), 226 (18), 225 (68), 209 (23), 195 (27), 182 (10), 181 (57), 179 (20), 170 (13), 167 (24), 163 (40), 162 (17), 161 (69), 160 (11), 153 (22), 152 (11), 151 (48), 149 (10), 137 (13), 135 (22), 133 (11), 123 (13), 115 (10), 113 (26), 107 (11), 95 (40), 82 (10), 79 (11), 59 (10), 43 (14).

(1'RS,4'SR)-5-[4'-(Hydroxymethyl)cyclopent-2'-enyl]pyrimidine-2,4,6(1H,3H,5H)-trione (**2**). A soln. of **8** (0.49 g, 1.91 mmol) in EtOH (1 ml) was added dropwise at r.t. to a soln. of Na (0.1 g, 4.3 mmol) in EtOH (5 ml). Urea (0.13 g, 2.16 mmol) was added in one portion, and the mixture was refluxed for 4 h. The mixture was brought to pH *ca.* 2 with 25% HCl soln. and allowed to cool to r.t. Insoluble residues were filtered off and washed with a small amount of Et_2O (*ca.* 1 ml). From the filtrate precipitated at 4° slowly a slightly yellow solid, which was filtered off after 4 weeks and dried: **2** (0.22 g, 51%). A sample was recrystallized from H_2O/MeOH. Colorless solid. M.p. 186–188°. IR (KBr): 3470*m*, 3200*m*, 3050*m*, 2810*m*, 1695*s*, 1440*s*, 1360*s*, 1295*m*, 1253*m*, 1225*m*, 1185*m*, 1161*m*, 1073*w*, 1050*s*, 980*w*, 900*m*, 880*w*, 840*m*, 785*m*, 765*w*, 668*w*, 630*w*, 550*w*, 500*s*, 460*w*, 420*m*. ^{1}H-NMR ((D_6)DMSO)[3]: 1.30 (*dt*, J = 13.3, 7.4, 1 H–C(6')); 2.04 (*dt*, J = 13.3, 8.2 1 H–C(6')); 2.62–2.77 (*m*, H–C(4')); 3.14–3.33 (*m*, 2 H–C(5'), H–C(5)); 3.33–3.63 (*m*, H–C(1')); 4.60 (br. *s*, OH); 5.61–5.66 (*m*, H–C=C); 5.69–5.75 (*m*, H–C=C); 11.17 (*s*, NH); 11.19 (*s*, NH). ^{13}C-NMR ((D_6)DMSO): 170.39 (*s*); 169.94 (*s*); 151.41 (*s*); 134.36 (*d*); 131.73 (*d*); 65.57 (*t*); 52.49 (*d*); 48.59 (*d*); 48.42 (*d*); 30.07 (*t*). MS: 224 (< 1, M^+), 194 (38), 193 (52), 150 (13), 130 (34), *129* (100), 128 (27), 122 (14), 108 (17), 107 (51), 106 (10), 105 (17), 94 (11), 86 (14), 79 (32), 78 (33), 77 (33), 67 (31), 66 (57), 65 (21), 44 (20), 28 (13), 18 (27). Anal. calc. for $C_{10}H_{14}N_2O_4$: C 53.57, H 5.39, N 12.49; found: C 53.10, H 5.45, N 12.33.

(1'RS,4'SR)-2-Amino-5-[4'-(hydroxymethyl)cyclopent-2'-enyl]pyrimidine-4,6(1H,5H)-dione (**3**). To a suspension of NaOEt (106 mg, 1.6 mmol) and guanidine hydrochloride (95 mg, 1.0 mmol) in EtOH (2.5 ml) was added **8** (0.20 g, 0.78 mmol). The suspension was refluxed for 52 h and then neutralized (pH *ca.* 6.5) with 1M HCl. From the resulting clear soln., a white solid precipitated upon cooling to 4°, which was filtered off and dried: **3** (90 mg, 52%). The mother liquor was evaporated and the residue adsorbed onto silical gel. FC (CH_2Cl_2→CH_2Cl_2/MeOH 8:1) yielded another 35 mg (20%) of **3**. Recrystallization of the combined product from EtOH/H_2O yielded **3** (101 mg, 58%). Colorless solid. M.p. > 220° (dec.). IR (KBr): 3100*s* (br.), 1600*s* (br.), 1400*s* (br.), 1275*m*, 1170*m*, 1090*m*, 1025*m*, 995*w*, 940*m*, 770*m*, 540*s*. ^{1}H-NMR ((D$_6$)DMSO)[3]): 1.54 (*dt*, *J* = 12.1, 8.2, 1 H–C(6')); 2.03 (*dt*, *J* = 12.1, 8.8, 1 H–C(6')); 2.61–2.82 (*m*, H–C(4')); 3.39 (br. *d*, *J* = 5.5, 2 H–C(5'), OH); 3.88 (*t*, *J* = 8.1, H–C(1')); 5.42–5.54 (*m*, H–C(2'), H–C(3')); 6.85 (br., NH_2). ^{13}C-NMR ((D$_6$)DMSO): 164.03 (2*s*); 152.38 (*s*); 136.75 (*d*); 129.68 (*d*); 91.50 (*s*); 65.38 (*t*); 48.67 (*d*); 39.62 (*d*); 31.96 (*t*). MS: 223 (19, M^+), 205 (12), 204 (26), 193 (48), *192* (100), 128 (56), 108 (10), 107 (59), 105 (12), 86 (16), 79 (19), 77 (15), 67 (10), 66 (11), 44 (18), 28 (11), 18 (11).

(1'RS,4'SR)-4,6-Dimethyl-5-[4'-(hydroxymethyl)cyclopent-2'-enyl]pyrimidin-2-amine (**4**). A soln. of **9** (47 mg, 0.24 mmol) and guanidine carbonate (0.18 g, 1.0 mmol) in EtOH (1.5 ml) was refluxed for 48 h. The solvent was distilled off and the residue suspended in MeOH, adsorbed onto silica gel, and purified by FC (AcOEt→AcOEt/EtOH 6:1): **4** (29 mg, 55%). Colorless solid. IR (KBr): 3340*s*, 3170*s*, 2985*m*, 2900*m*, 1660*s*, 1550*s*, 1480*s*, 1380*m*, 1340*m*, 1215*w*, 1105*w*, 1035*s*, 998*w*, 945*w*, 815*w*, 795*w*, 733*w*, 615*w*, 565*w*. ^{1}H-NMR ((D$_6$)DMSO)[3]): 1.29 (*dt*, *J* = 12.5, 9.9, 1 H–C(6')); 2.23 (*s*, 2 Me); 2.33 (*dt*, *J* = 12.5, 8.1, 1 H–C(6')); 2.75–2.89 (*m*, H–C(4')); 3.39–3.47 (*m*, 2 H–C(5')); 3.95–4.08 (*m*, H–C(1')); 4.63 (*t*, *J* = 5.2, OH); 5.72–5.78 (*m*, H–C=C); 5.78–5.83 (*m*, H–C=C); 6.13 (*s*, NH_2). ^{13}C-NMR ((D$_6$)DMSO): 165.21 (2*s*); 161.06 (*s*); 136.11 (*d*); 131.76 (*d*); 120.96 (*s*); 64.56 (*t*); 48.86 (*d*); 44.27 (*d*); 34.23 (*t*); 23.07 (2*q*). MS: 220 (14), *219* (100. M^+), 189 (15), 188 (92), 186 (29), 173 (18), 160 (16), 149 (14), 148 (10), 147 (40), 146 (35), 136 (11), 131 (15), 130 (12), 124 (21), 120 (17), 119 (12), 115 (14), 106 (10), 105 (14), 103 (11), 97 (16), 79 (11), 77 (14), 18 (13).

(1'RS,4'SR)-5-[4'-(Hydroxymethyl)cyclopent-2'-enyl]pyrimidine-2,4,6-triamine (**5**). To a suspension of NaOEt (0.33 g, 4.8 mmol) and guanidine hydrochloride (0.27 g, 2.8 mmol) in EtOH (5 ml) was added a soln. of **10** (0.41 g, 2.53 mmol) in EtOH (1 ml). The mixture was refluxed for 8 h and filtered hot. On allowing to cool to r.t., a white solid precipitated. After 15 h at 4°, the solid was filtered off and recrystallized from EtOH: **5** (0.33 g, 58%). Colorless solid. M.p. 194–196°. IR (KBr): 3500–2500*s* (br.), 1580*s*, 1445*s*, 1365*m*, 1340*m*, 1232*w*, 1150*w*, 1090*m*, 1060*w*, 1010*m*, 990*w*, 935*s*, 788*s*, 745*m*. ^{1}H-NMR ((D$_6$)DMSO)[3]): 1.47 (*dt*, *J* = 12.5, 9.3, 1 H–C(6')); 2.21 (*dt*, *J* = 12.5, 8.6, 1 H–C(6')); 2.71–2.89 (*m*, H–C(4')); 3.32–3.47 (*m*, 1 H–C(5')); 3.47–3.59 (*m*, 1 H–C(5')); 3.81–3.96 (*m*, H–C(1')); 4.74 (*t*, *J* = 4.8, OH); 5.23 (*s*, NH_2); 5.38 (*s*, 2 NH_2); 5.66–5.86 (*m*, H–C(2'), H–C(3')). ^{13}C-NMR ((D$_6$)DMSO): 162.12 (2*s*); 160.96 (*s*); 136.65 (*d*); 133.33 (*d*); 87.21 (*s*); 63.99 (*t*); 48.62 (*d*); 40.96 (*d*); 31.14 (*t*). MS: 222 (11), 221 (80, M^+), 191 (18), *190* (100), 164 (19), 163 (9), 162 (23), 150 (11), 148 (12), 131 (14), 126 (35), 125 (22), 104 (11), 18 (15). Anal. for calc. $C_{10}H_{15}N_5O$: C 54.28, H 6.83, N 31.65; found: C 54.25, H 6.89, N 31.45.

(1'RS,4'SR)-4,6-Diamino-5-[4'-(hydroxymethyl)cyclopent-2'-enyl]pyrimidine-2(1H)-thione (**6**). To a soln. of NaOEt (0.14 g, 2.1 mmol) and thiourea (0.17 g, 2.2 mmol) in EtOH (3 ml) was added at r.t. a soln. of **10** (0.36 g, 2.2 mmol) in EtOH (1 ml), and the mixture was refluxed for 57 h. To the hot soln., H_2O (*ca.* 6 ml) was added and the mixture acidified by dropwise addition of conc. AcOH. A slighly brown solid precipitated immediately. After 24 h at 4°, the solid was filtered off and recrystallized from H_2O/MeOH: **6** (0.32 g, 61%). Colorless solid. M.p. > 250° (dec.). IR (KBr): 3480*s*, 3320*s*, 3140*s*, 2900*m*, 1668*s*, 1632*s*, 1575*s*, 1521*s*, 1410*w*, 1362*w*, 1340*w*, 1308*m*, 1256*m*, 1250*m*, 1190*m*, 1040*m*, 970*w*, 780*w*, 750*w*, 670*w*, 612*w*, 475*w*, 450*w*. ^{1}H-NMR ((D$_6$)DMSO)[3]): 1.52 (*dt*, *J* = 12.9, 8.7, 1 H–C(6')); 2.24 (*dt*, *J* = 12.9, 9.0, 1 H–C(6')); 2.75–2.90 (*m*, H–C(4')); 3.35–3.46 (*m*, 1 H–C(5')); 3.52–3.65 (*m*, 1 H–C(5')); 3.80–3.95 (*m*, H–C(1')); 4.93 (*s*, OH); 5.57–5.67 (*m*, H–C=C); 5.73–5.81 (*m*, H–C=C); 6.22 (br., 2 NH_2); 10.97 (*s*, SH). ^{13}C-NMR ((D$_6$)DMSO): 175.03 (2*s*); 175.00 (*s*); 134.78 (*d*); 134.38 (*d*); 86.94 (*s*); 63.21 (*t*); 48.33 (*d*); 40.07 (*d*); 29.91 (*t*). MS: 239 (12), *238* (100, M^+), 208 (13), 207 (90), 190 (19), 148 (20), 143 (19), 44 (12), 32 (27), 31 (24), 29 (12), 28 (36), 18 (73), 17 (11).

REFERENCES

[1] For recent reviews, see A. D. Borthwick, K. Biggadike, *Tetrahedron* **1992,** *48,* 571; L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl, R. Guedj, *ibid.* **1994,** *50,* 10611.

[2] S. Hildebrand, T. Troxler, R. Scheffold, *Helv. Chim. Acta* **1994,** *77,* 1236.

[3] N. Katagiri, T. Haneda, C. Kaneko, *Chem. Pharm. Bull.* **1986,** *34,* 4875; N. Katagiri, T. Haneda, S. Tomizawa, C. Kaneko, *Nucleic Acids Symp. Ser.* **1986,** *17,* 1; N. Katagiri, T. Haneda, E. Hayasaka, N. Watanabe, C. Kaneko, *J. Org. Chem.* **1988,** *53,* 226; N. Katagiri, *J. Synth. Org. Chem.* **1989,** *47,* 707; N. Katagiri, M. Nomura, C. Kaneko, *Heterocycles* **1990,** *30,* 211.

[4] N. Katagiri, M. Tomura, T. Haneda, C. Kaneko, *J. Chem. Soc., Chem. Commun.* **1987,** 1422.

[5] R. C. Cookson, P. J. Dudfield, D. I. C. Scopes, *J. Chem. Soc., Perkin Trans. 1* **1986,** 393.

[6] T. Takahashi, H. Kotsubo, T. Koizumi, *Tetrahedron: Asymmetry* **1991,** *2,* 1035.

[7] A. P. Dishington, D. C. Humber, R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1* **1993,** 57.

[8] J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985,** *50,* 1523.

[9] D. E. Bergbreiter, B. Chen, *J. Chem. Soc., Chem. Commun.* **1983,** 1238.

[10] For examples, see J. J. S. Bajorek, R. Battaglia, G. Pratt, J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1* **1974,** 1243; D. R. Deardorff, M. J. Shulman, J. E. Sheppeck, *Tetrahedron Lett.* **1989,** *30,* 6625.

[11] a) For a recent review about the chemistry of pyrimidines, see D. J. Brown, in 'The Chemistry of Heterocyclic Compounds', 'The Pyrimidines', Ed. E. C. Taylor, John Wiley & Sons, Chichester–Brisbane–Toronto–Singapore, 1994, Vol. 52; b) *ibid.* p. 236.