Palladium-Catalyzed Rearrangements of 2-Cyclopentenyloxypyrimidines in the Preparation of Pyrimidine Carbonucleosides

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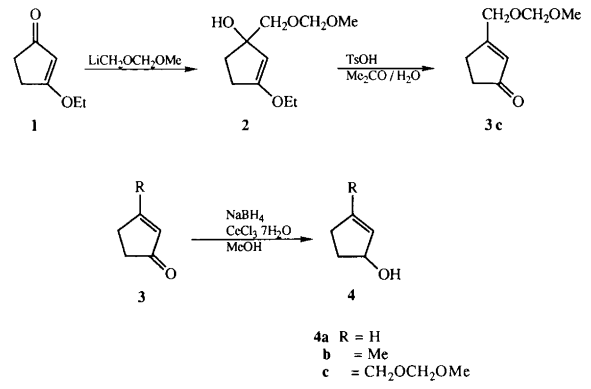
Allylic 2-cyclopentenyloxypyrimidines have been prepared and rearranged by Pd(0)-induced catalysis to pyrimidine carbonucleosides analogues. For acid-sensitive substrates the rearrangement was performed in the presence of a base. Assignment of regio- and stereo-chemistry is based on NMR spectroscopy.

Pd(0)-catalyzed cycloalkenylation of nucleoside bases is becoming a useful method for the preparation of allylic carbonucleosides with the potential for further manipulation of the double bond.[1,2] We have described a method for the preparation of the antiviral agent Carbovir,[3] as well as other allylic carbonucleosides from either pyrimidine or purine nucleoside bases and appropriately substituted cyclopentenyl acetates.[4] In this report we describe methodology which can yield carbonucleosides by an allylic rearrangement of a corresponding 2-cyclopentenyloxypyrimidine (Scheme 2). The work is an extension of our previous studies on allylic (Claisen) rearrangements of acyclic 2-allyloxypyrimidine derivatives.[5] It was found that the Claisen rearrangement can be effected with Pd(II)-catalysis. Pd(0)-catalysis, which involves a π-allylpalladium complex, gives rise to a 1,3- and/or a 3,3-rearrangement depending on the reaction conditions and the substitution pattern in the allyl ligand.

The allylic cyclopentenyloxypyrimidines **9** (Scheme 2), which serve as substrates for the rearrangement studies, were prepared from the allylic cyclopentenyl alcohols **4** (Scheme 1). The latter were available by 1,2-reduction

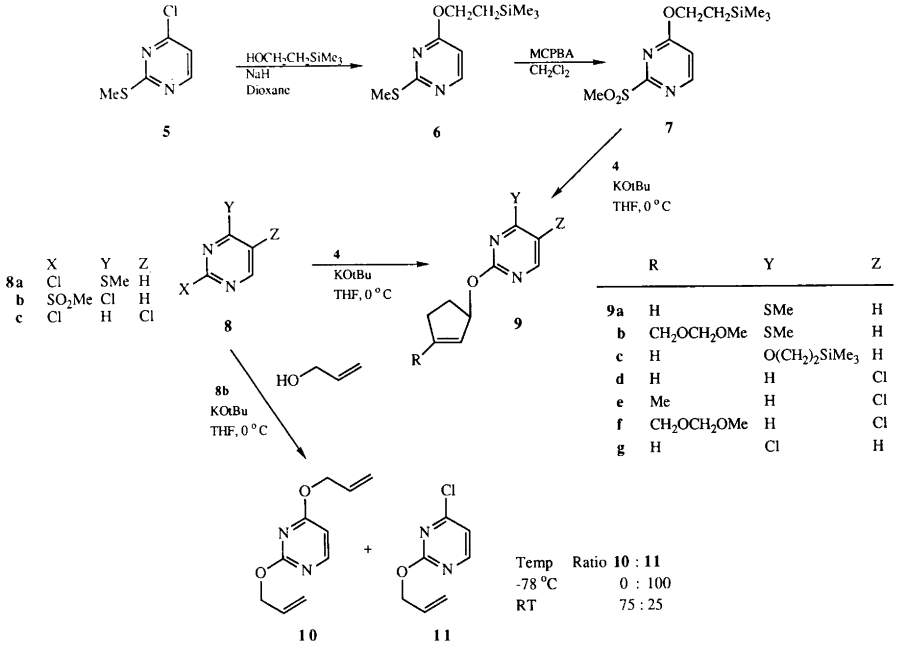


Scheme 1.

of cyclopentenones **3** by using a mixture of sodium borohydride and cerium(III) chloride.[6] The substrate with the methoxymethyl-protected (MOM-) hydroxymethyl substituent on the γ-carbon of the allylic system was prepared from commercially available 3-ethoxycyclopentenone **1**, which was alkylated on the carbonyl carbon using an appropriate alkyllithium reagent.[7]

For the preparation of uridine analogues **15** (Scheme 3) the 4-position in the pyrimidine must carry a substituent which can be converted into a hydroxy group either by substitution or by removal of an *O*-protecting group. In the pyrimidines described the 4-substituent was either a β-trimethylsilylethoxy group (**7**), a methylthio group (**8a**) or a chloro substituent (**8b**). We have found the silylethoxy group to be very useful for the protection of hydroxy groups in purines.[4] The protected hydroxy group was introduced in the form of 2-trimethylsilylethanol by nucleophilic substitution of the chlorine in the 4-position in the pyrimidine **5**. The 2-methylthio group in the product **6** was oxidized to its sulfone **7** by *m*-chloroperbenzoic acid (MCPBA) prior to nucleophilic displacement by the potassium salts of the cyclopentenols **4**. In 2,4-dichloropyrimidine it is the 4-chlorine which is the more reactive in nucleophilic substitutions. For selective nucleophilic substitution in the 2-position a substituent more strongly activating than a chlorine substituent is required. For model studies with 4-chloro-2-methylsulfonylpyrimidine (**8b**) the potassium olate of allyl alcohol was used. A mixture of the diallylated uracil **10** and the monoallylated derivative **11** (ratio 3:1) was obtained at room temperature. However, complete chemoselectivity for displacement of the sulfonyl group was achieved when the reaction was run at −78 °C. Adapting the latter conditions to the reaction between **8b** and the cyclopentenol **4a** furnished the desired 2-cyclopentenyloxy derivative **9g**.

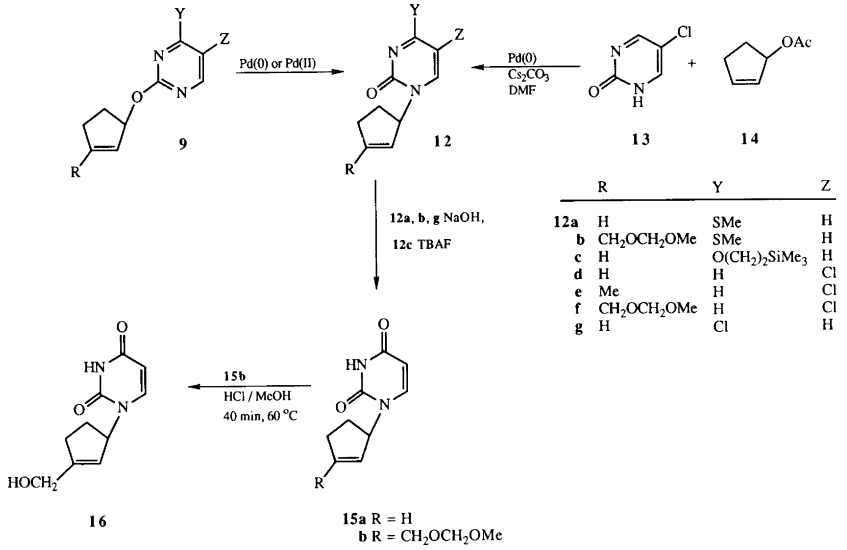
Cyclopentenyloxypyrimidines **9** which are not substituted in the cyclopentenyl ring, can be purified by chromatography. The derivatives which carry a sub-



	X	Y	Z
8a	Cl	SMe	H
b	SO_2Me	Cl	H
c	Cl	H	Cl

	R	Y	Z
9a	H	SMe	H
b	CH_2OCH_2OMe	SMe	H
c	H	$O(CH_2)_2SiMe_3$	H
d	H	H	Cl
e	Me	H	Cl
f	CH_2OCH_2OMe	H	Cl
g	H	Cl	H

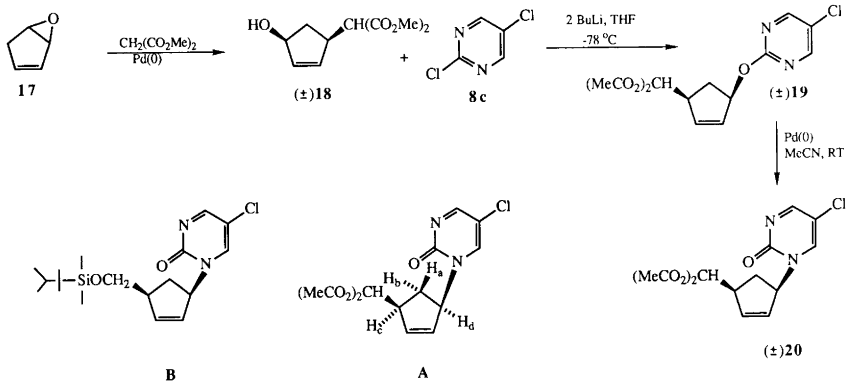
Scheme 2.



	R	Y	Z
12a	H	SMe	H
b	CH_2OCH_2OMe	SMe	H
c	H	$O(CH_2)_2SiMe_3$	H
d	H	H	Cl
e	Me	H	Cl
f	CH_2OCH_2OMe	H	Cl
g	H	Cl	H

15a R = H
b R = CH_2OCH_2OMe

Scheme 3.



Scheme 4.

stituent on the double bond (R = Me, CH_2OMOM) are acid sensitive and more difficult to purify. The products from the alkylation reaction, however, are relatively pure and could be used further in the reaction sequence without additional purification.

For the allylic rearrangement to proceed, catalysis by a Pd(0)- or Pd(II)-complex is required. The rearrangements are best carried out in the presence of a base (Table 1) because of the acid sensitivity of the cyclopentenyl derivatives; triethylamine in THF or cesium carbonate in DMF was used. Direct alkylation with the cyclopentenyl acetate **14** of the anionic form of the pyrimidine **13** resulted in a lower yield (33%) than in the rearrangement reaction (88%).

In principle the rearrangement can take place onto either N-1 or N-3 in unsymmetrical pyrimidines. In the acyclic allylic pyrimidines the allylic groups select N-1, which is also the case for the cyclopentenyl derivatives **12** (*vide infra*).

UV absorptions can be used in regio-assignments of *N*-monoalkylated uracils in that the UV absorption of N-1-alkylated uracils is little affected by the pH of its solution whereas the UV absorption of N-3-alkylated uracils are pH dependent.[8] The uracil hydrolysis product **15a** from the rearranged product was tentatively assigned the 4-methylthio structure **12a** and showed UV absorption maxima at 269 and 210 nm in phosphate buffer at pH 7, and at 267 and 217 nm in 0.1 M NaOH. The wavelengths for the absorption maxima are similar, and the structure of the product is therefore consistent with the N-1-alkylated uracil **15a**. In addition, the structure of its precursor **12a** was ascertained by means of a long-range INEPT experiment; selective pulsing of H-6 gave resonances for C2, C4 and C'1 in accordance with the assigned structure.[9]

For the synthesis of uridine carbonucleosides both the chlorine in **12g** and the methylthio group in **12a** and **12b** were displaced by sodium hydroxide. The trimethylsilylethoxy group was cleaved by tetrabutylammonium fluoride (TBAF) to furnish the uracil derivatives **15a** and **15b**. The MOM group in the latter (**15b**) was removed with hydrogen chloride in methanol. This procedure establishes a route to carbonucleosides which are substituted by a hydroxymethyl group on an olefinic carbon as found in antibiotics such as Neplanocin A.[10]

Table 1. Pd-catalyzed rearrangements of 2-(2-cyclopentenyloxy)pyrimidines **9** in THF.

Entry	Product	Catalyst[a]	Base	Yield (%)
1	**12a**	None	—	0[b]
2	**12a**	A	—	79
3	**12b**	A	—	48
4	**12c**	A	—	0[d]
5	**12c**	A	Cs_2CO_3[c]	95
6	**12c**	A	$N(Et)_3$	93
7	**12d**	C	—	65
8	**12d**	A	—	88
9	**12d**	B	—	62
10	**12e**	A	—	75
11	**12f**	A	—	58
12	**12g**	A	Cs_2CO_3[c]	58

[a] A = $Pd[(OiPr)_3P]_4$, B = $PdCl_2(PhCN)_2$, C = $Pd(PPh_3)_4$. [b] Only starting material left. [c] Solvent was DMF. [d] Only 4-(2-trimethylsilylethoxy)-2(1*H*)-pyrimidinone was formed.

The stereochemistry of the rearrangement was investigated using a cyclopentenol with a malonyl substituent in the 4-position (**19**) (Scheme 4). The substrate for the preparation of **19** was cyclopentadiene monoxide which furnished the *cis*-cyclopentenol **18** in the reaction with a malonate using Pd(0)-catalysis.[11] Compound **18** reacted sequentially with butyllithium (2 equiv.) and 2,5-dichloropyrimidine at −78°C to give the cyclopentenyl pyrimidinyl ether **19**. Pd(0)-catalyzed rearrangement gave **20** in 91% yield.

The stereochemistry in Pd(0)-catalyzed coupling reactions with allylic acetates is controlled by the stereochemistry of the intermediate Pd-template. Soft nucleophiles lead to retention of configuration.[12] The same stereochemical course was expected in the rearrangement of the allylic 2-pyrimidinyl ethers **9** and **19**. The stereostructure assigned to the rearrangement product obtained from **19**, i.e. **20**, is supported by ^1H NMR spectroscopy. The chemical shifts for the cyclopentenyl protons in **20** are close to the values for its 4'-dimethylthexylsilyloxymethyl analogue **B** where the structure was subjected to a close NMR study.[4] The couplings of the cyclopentenyl protons in **20**, with the indexing shown in structure **A**, were J_{ac} 6.7, J_{bc} 8.3, J_{bd} 7.3 and J_{ad} 3.0 Hz. Since $J_{bc} > J_{ac}$ H_b and H_c have a *cis*-relationship, and since $J_{bd} > J_{ad}$ H_b and H_d have a *cis*-relationship in accordance with the *cis*-configuration assigned to the carbonucleoside **20**.[11]

Experimental

The ^1H NMR spectra were recorded at 300 MHz with either a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz on the same instruments. The mass spectra under electron impact conditions were recorded at 70 eV ionizing potential and methane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.).

3-Methoxymethoxymethyl-2-cyclopentenone (**3c**). 3-Ethoxy-2-cyclopentenone (0.57 ml, 4.79 mmol) was added via a syringe to a solution of (methoxy)methoxymethyl lithium[7] (4.60 mmol) in dry THF (15 ml) at −78°C. The mixture was stirred for 15 min at −78°C and the reaction was quenched by the addition of saturated aqueous ammonium chloride (20 ml). The mixture extracted with ethyl acetate and the organic layer was washed with water and brine. The dried ($MgSO_4$) solution was evaporated at reduced pressure. The crude product was dissolved in acetone (5 ml) and water (5 ml), and *p*-toluenesulfonic acid (0.06 g) was added. The mixture was stirred for 2 h, and then extracted with diethyl ether. The dried ($MgSO_4$)

solution was evaporated and the product was purified by flash chromatography on silica gel using first hexane and then hexane–EtOAc 1:1 (v/v) for elution; yield 423 mg (59%), oily substance. ^{1}H NMR ($CDCl_3$): δ 2.38–2.58 (CH_2CH_2, m), 3.36 (OMe, s), 4.35 (CH_2O, s), 4.66 (OCH_2O, s), 6.14 (CH=, t, *J* 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ 28.9 (CH_2), 35.3 (CH_2), 56.0 (OMe), 67.1 (CH_2O), 96.7 (OCH_2O), 129.5 (CH=), 178.0 (C=), 209.5 (C=O). MS: 156 (3, *M*), 127 (11), 96 (12), 95 (10), 94 (13), 67 (12), 45 (100), 41 (12).

2-Cyclopentenol (**4a**) *and 3-methyl-2-cyclopentenol* (**4b**) were prepared as described.[6]

3-Methoxymethoxymethyl-2-cyclopentenol (**4c**). Sodium borohydride (0.056 g, 1.47 mmol) was added to a solution of 3-methoxymethoxymethyl-2-cyclopentenone (0.23 g, 1.47 mmol) and cerium(III) chloride heptahydrate (0.549 g, 1.47 mmol) in methanol (4 ml) at ambient temperature. The mixture was stirred for 20 min, pH adjusted to ca. 7 with dilute aqueous HCl, the mixture extracted with diethyl ether and the dried (Na_2SO_4) solution was evaporated. The product was purified by flash chromatography on silica gel eluting with hexane–EtOAc 1:1 (v/v); yield 146 mg (63%). ^{1}H NMR ($CDCl_3$): δ 1.71–2.40 (CH_2CH_2, m), 3.37 (OMe, s), 4.12 (CH_2O, s), 4.64 (OCH_2O, s), 4.82–4.86 (CHO, m), 5.73–5.75 (CH=, m). ^{13}C NMR ($CDCl_3$): δ 31.7 (CH_2), 34.3 (CH_2), 55.7 (OMe), 66.3 (CH_2O), 77.9 (CHO), 96.4 (OCH_2O), 129.5 (CH=), 146.1 (C=). MS(CI-CH_4): 159 (7, *M* + 1), 157 (34), 143 (17), 141 (90), 111 (17), 97 (32), 79 (37), 45 (100).

2-Methylthio-4-(2-trimethylsilylethoxy)pyrimidine (**6**). 2-Trimethylsilylethanol (2.85 ml, 20 mmol) was added to a 60% oily suspension of sodium hydride (0.8 g, 20 mmol) in dry dioxane (60 ml). The solution was stirred for 20 min under N_2 at ambient temperature, and then cooled to 0°C. 4-Chloro-2-methylthiopyrimidine (3.21 g, 20 mmol) was added at 0°C, and the solution was stirred overnight at ambient temperature. The solvent was evaporated and the residue was dissolved in ether and washed with water (2×). The dried ($MgSO_4$) solution was evaporated and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 12:1 (v/v); yield 3.53 g (73%), oily substance. ^{1}H NMR ($CDCl_3$): δ 0.05 ($SiMe_3$, s), 1.06–1.14 (CH_2Si, m), 2.52 (SMe, s), 4.41–4.49 (CH_2O, m), 6.31 (H-5, d, *J* 5.8 Hz), 8.17 (H-6, d, *J* 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ 0.9 ($SiMe_3$), 14.5 (SMe), 17.9 (CH_2Si), 65.1 (CH_2O), 104.2 (C-5), 157.5 (C-6), 169.0 (C-2), 172.4 (C-4). MS: 242 (19, *M*), 214 (30), 199 (77), 181 (43), 167 (31), 142 (46), 105 (47), 73 (100).

2-Methylsulfonyl-4-(2-trimethylsilylethoxy)pyrimidine (**7**). 2-Methylthio-4-(2-trimethylsilylethoxy)pyrimidine (1.0 g, 4.13 mmol) in CH_2Cl_2 (40 ml) was added to a solution of 55% MCPBA (3.88 g, 12.39 mmol) in CH_2Cl_2 (40 ml) at 0°C. The solution was stirred overnight at ambient temperature, and then washed with sodium sulfite, sodium hydrogen carbonate and water. The dried ($MgSO_4$) solution was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 2:1 (v/v); yield 815 mg (72%), m.p. 38°C. ^{1}H NMR ($CDCl_3$): δ 0.08 ($SiMe_3$, s), 1.11–1.19 (CH_2Si, m), 3.32 (SO_2Me, s), 4.53–4.61 (CH_2O, m), 6.84 (H-5, d, *J* 5.8 Hz), 8.51 (H-6, d, *J* 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ 0.9 ($SiMe_3$), 17.7 (CH_2Si), 39.4 (SO_2Me), 67.1 (CH_2O), 112.1 (C-5), 157.9 (C-6), 165.5 (C-2), 170.8 (C-4).

Synthesis of substituted 2-(2-cyclopentenyloxy)pyrimidines (**9a, b, d–f**). A solution of the allylic alcohol (2.01 mmol) in dry THF (5 ml) was added dropwise with stirring to potassium *tert*-butoxide (0.246 g, 2.19 mmol) in dry THF (5 ml) under N_2 at 0°C. The mixture was stirred at 0°C for 15 min before a solution of the pyrimidine **8** (1.82 mmol) in dry THF (5 ml) was added dropwise at 0°C. The resulting solution was stirred at ambient temperature overnight, diluted with diethyl ether and washed with water (3×). The dried ($MgSO_4$) solution was evaporated and the products were purified by flash chromatography on silica gel eluting with hexane–EtOAc 2:1 (v/v).

2-(2-Cyclopentenyloxy)-4-methylthiopyrimidine (**9a**). Compound **9a** was obtained from 2-cyclopentenol and 2-chloro-4-methylthiopyrimidine;[13] yield 356 mg (94%). ^{1}H NMR ($CDCl_3$): δ 2.01–2.09/2.34–2.63 (CH_2CH_2, m), 2.56 (SMe, s), 5.95–6.03 (CH= and CHO, m), 6.12–6.15 (CH=, m), 6.78 (H-5, d, *J* 5.4 Hz), 8.12 (H-6, d, *J* 5.4 Hz). ^{13}C NMR ($CDCl_3$): δ 12.4 (SMe), 30.0 (CH_2), 31.2 (CH_2), 83.2 (OCH), 112.2 (C-5), 129.7 (C=), 137.5 (C=), 156.2 (C-6), 164.4 (C-2), 172.5 (C-4). MS: 204 (15, *M*), 143 (34), 142 (37), 127 (19), 68 (24), 67 (72), 66 (100), 65 (32).

2-(3-Methoxymethoxymethyl-2-cyclopentenyloxy)-4-methylthiopyrimidine (**9b**). Compound **9b** was obtained from 3-methoxymethoxymethyl-2-cyclopentenol and 2-chloro-4-methylthiopyrimidine;[13] yield 323 mg (63%). ^{1}H NMR ($CDCl_3$): δ 2.01–2.61 (CH_2CH_2, m), 2.52 (SMe, s), 3.35 (OMe, s), 4.07–4.22 (CH_2O, m), 4.62 (OCH_2O, s), 5.90–5.92 (CHO and CH=, m), 6.75 (H-5, d, *J* 5.4 Hz), 8.08 (H-6, d, *J* 5.4 Hz). ^{13}C NMR ($CDCl_3$): δ 12.8 (SMe), 30.9 (CH_2), 31.8 (CH_2), 55.7 (OMe), 66.2 (CH_2O), 83.5 (OCH), 96.4 (OCH_2O), 112.6 (C-5), 125.7 (CH=), 148.8 (C=), 156.7 (C-6), 164.8 (C-2), 173.0 (C-4). MS: 282 (2, *M*), 221 (32), 142 (94), 127 (40), 79 (32), 78 (33), 68 (32), 45 (100).

5-Chloro-2-(2-cyclopentenyloxy)pyrimidine (**9d**). Compound **9d** was obtained from 2-cyclopentenol and 2,5-dichloropyrimidine;[14] yield 243 mg (68%), m.p. 32°C. Anal. $C_9H_9ClN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.92–2.71

(CH_2CH_2, m), 5.85–5.95 (CHO, m), 5.96–6.01 (CH=, m), 6.14–6.17 (CH=, m), 8.44 (H-4, 6, s). ^{13}C NMR ($CDCl_3$): δ 31.2 (CH_2), 32.5 (CH_2), 84.8 (CHO), 124.0 (C-5), 129.5 (CH=), 138.3 (CH=), 157.4 (C-4, 6), 163.3 (C-2). MS: 198/196 (0.7/2.3, *M*), 131 (27), 130 (11), 102 (13), 67 (100), 66 (93), 65 (23), 41 (30).

5-Chloro-2-(3-methyl-2-cyclopentenyloxy)pyrimidine (**9e**). Compound **9e** was obtained from 3-methyl-2-cyclopentenol and 2,5-dichloropyrimidine;[14] yield 245 mg (64%). ^1H NMR ($CDCl_3$): δ 1.80 (Me, s), 2.02–2.47 (CH_2CH_2, m), 5.59–5.60 (CH=, m), 5.79–5.83 (OCH, m), 8.41 (H-4, 6, s). ^{13}C NMR ($CDCl_3$): δ 18.0 (Me), 32.0 (CH_2), 36.4 (CH_2), 85.6 (OCH), 123.8 (C-5), 123.9 (CH=), 149.1 (C=), 157.4 (C-4, 6), 163.5 (C-2). MS: 212/210 (1.1/3.3, *M*), 132 (7), 130 (22), 102 (16), 81 (49), 80 (55), 79 (100), 77 (37).

5-Chloro-2-(3-methoxymethoxymethyl-2-cyclopentenyloxy)pyrimidine (**9f**). Compound **9f** was obtained from 3-methoxymethoxymethyl-2-cyclopentenol and 2,5-dichloropyrimidine;[14] yield 251 mg (51%). ^1H NMR ($CDCl_3$): δ 2.03–2.50 (CH_2CH_2, m), 3.36 (OMe, s), 4.15 (CH_2O, s), 4.64 (OCH_2O, s), 5.83–5.91 (CHO and CH=, m), 8.42 (H-4, 6, s). ^{13}C NMR ($CDCl_3$): δ 30.8 (CH_2), 31.8 (CH_2), 55.8 (OMe), 66.2 (CH_2O), 84.4 (OCH), 96.4 (OCH_2O), 124.1 (C-5), 125.1 (CH=), 149.3 (C=), 157.8 (C-4, 6), 163.8 (C-2). MS(CI-CH_4): 273/271 (7.8/22.4, *M* + 1), 209 (15), 177 (15), 175 (46), 133 (34), 131 (100), 79 (41), 45 (66).

2-(2-Cyclopentenyloxy)-4-(2-trimethylsilylethoxy)pyrimidine (**9c**). A solution of 2-cyclopentenol (0.169 g, 2.01 mmol) in dry THF (5 ml) was added dropwise with stirring to potassium *tert*-butoxide (0.246 g, 2.19 mmol) in dry THF (5 ml) under N_2 at 0°C. The mixture was stirred at 0°C for 15 min before a solution of 2-methylsulfonyl-4-(2-trimethylsilylethoxy)pyrimidine (0.5 g, 1.82 mmol) in dry THF (5 ml) was added dropwise at 0°C. The resulting solution was stirred at ambient temperature for 1.5 h, diluted with diethyl ether and washed with water (3×). The dried ($MgSO_4$) solution was evaporated. The product was unstable on silica gel, but the crude product was pure enough for use in the subsequent reactions. Yield 476 mg (94%), oily substance. ^1H NMR (C_6D_6): δ −0.08 (TMS, s), 0.95–1.04 (CH_2Si, m), 1.93–2.33 (CH_2CH_2, m), 4.39–4.47 (CH_2O, m), 5.82–6.12 (CHO, CH=CH and H-5, m), 7.96 (H-6, d, *J* 5.7 Hz). ^{13}C NMR (C_6D_6): δ −1.1 (TMS), 17.9 (CH_2Si), 30.8 (CH_2), 31.7 (CH_2), 64.8 (CH_2O), 83.5 (OCH), 102.5 (C-5), 131.0 (CH=), 137.3 (CH=), 158.9 (C-6), 166.3 (C-2), 171.9 (C-4).

4-Chloro-2-(2-cyclopentenyloxy)pyrimidine (**9g**). A solution of 2-cyclopentenol (0.22 g, 2.62 mmol) in dry THF (5 ml) was added dropwise with stirring to potassium *tert*-butoxide (0.318 g, 2.83 mmol) in dry THF (5 ml) under N_2 at 0°C. The mixture was stirred at 0°C for 15 min before the solution was cooled to −78°C. A solution of 4-chloro-2-methylsulfonylpyrimidine[15] (0.454 g, 2.36 mmol) in dry THF (5 ml) was added at −78°C. The resulting solution was stirred at −78°C for 85 min, diluted with diethyl ether and washed with water (3×). The dried ($MgSO_4$) solution was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 2:1 (v/v); yield 380 mg (82%), oily substance. ^1H NMR ($CDCl_3$): δ 1.92–2.67 (CH_2CH_2, m), 5.89–6.09 (OCH and CH=, m), 6.11–6.14 (CH=, m), 6.92 (H-5, d, *J* 5.3 Hz), 8.34 (H-6, d, *J* 5.3 Hz). ^{13}C NMR ($CDCl_3$): δ 30.3 (CH_2), 31.6 (CH_2), 84.7 (OCH), 116.1 (C-5), 129.5 (CH=), 138.6 (CH=), 160.4 (C-6), 162.8 (C-2), 165.3 (C-4). MS: 198/196 (1.8/6, *M*), 130 (11), 113 (13), 95 (15), 67 (100), 66 (50), 52 (17), 41 (42).

4-Chloro-2-propenyloxypyrimidine (**11**). A solution of allyl alcohol (0.166 g, 2.86 mmol) in dry THF (5 ml) was added dropwise with stirring to potassium *tert*-butoxide (0.35 g, 3.12 mmol) in dry THF (5 ml) under N_2 at 0°C. The mixture was stirred at 0°C for 15 min. The solution was cooled to −78°C and a solution of 4-chloro-2-methylsulfonylpyrimidine[15] (0.5 g, 2.59 mmol) in dry THF (5 ml) was added dropwise. The resulting solution was stirred at −78°C for 2 h, diluted with diethyl ether and washed with water (2×). The dried ($MgSO_4$) solution was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 4:1 (v/v); yield 428 mg (97%). ^1H NMR ($CDCl_3$): δ 4.86–4.90 (OCH_2, m), 5.23–5.46 (CH_2=, m), 5.95–6.12 (CH=, m), 6.97 (H-5, d, *J* 5.1 Hz), 8.37 (H-6, d, *J* 5.1 Hz). ^{13}C NMR ($CDCl_3$): δ 69.2 (OCH_2), 115.5 (C-5), 118.9 (CH_2=), 132.5 (CH=), 160.5 (C-6), 163.0 (C-2), 165.2 (C-4). MS: 172/170 (3/9, *M*), 169 (29), 135 (49), 116 (15), 114 (39), 95 (16), 41 (100), 39 (75).

When the same reaction was run at ambient temperature, a mixture of 2,4-diallyloxypyrimidine **10** and 4-chloro-2-propenyloxypyrimidine **11** (ratio 3:1) was formed.

2,4-Dipropenyloxypyrimidine (**10**). ^1H NMR ($CDCl_3$): δ 4.77–4.82 (2×OCH_2, m), 5.16–5.38 (2×CH_2=, m), 5.90–6.12 (2×CH=, m), 6.32 (H-5, d, *J* 6 Hz), 8.12 (H-6, d, *J* 6 Hz). ^{13}C NMR ($CDCl_3$): δ 67.7 (OCH_2), 68.8 (OCH_2), 102.7 (C-5), 118.3 (CH_2=), 118.7 (CH_2=), 132.6 (CH=), 133.1 (CH=), 158.7 (C-6), 164.8 (C-2), 170.8 (C-4). MS: 192 (5, *M*), 151 (14), 108 (17), 96 (19), 95 (29), 82 (15), 80 (15), 41 (100).

Pd-catalyzed rearrangements of substituted 2-(2-cyclopentenyloxy)pyrimidines (**9**). A mixture of the pyrimidine **9** (0.8 mmol) and 7% Pd(0) or Pd(II) in dry THF or dry DMF (5 ml) under N_2 was heated to 70°C overnight. The solution was evaporated and the product was purified by flash chromatography on silica gel using first hexane–

EtOAc 6:1 (v/v) and then EtOAc for elution. To some of the reactions was added one equiv. of base (Table 1).

1-(2-Cyclopentenyl)-4-methylthio-2(1H)-pyrimidinone (**12a**). Yield 131 mg (79%), m.p. 89°C. Found: C, 58.31; H, 5.95. Calc. for $C_{10}H_{12}N_2OS$: C, 57.63; H, 5.80. ^{1}H NMR ($CDCl_3$): δ 1.61–1.70/2.45–2.68 (CH_2CH_2, m), 2.56 (SMe, s), 5.67–5.71 (CH=, m), 5.80–5.85 (NCH, m), 6.21 (H-5, d, *J* 7 Hz), 6.26–6.30 (CH=, m), 7.27 (H-6, d, *J* 7 Hz). ^{13}C NMR ($CDCl_3$): δ 12.8 (SMe), 31.3 (CH_2), 31.4 (CH_2), 63.1 (NCH), 103.6 (C-5), 128.8 (CH=), 139.0 (CH=), 140.2 (C-6), 155.0 (C-2), 176.9 (C-4). MS: 208 (39, *M*), 193 (15), 143 (38), 142 (27), 127 (25), 67 (100), 66 (83), 65 (36).

1-(3-Methoxymethoxymethyl-2-cyclopentenyl)-4-methylthio-2(1H)-pyrimidinone (**12b**). Yield 108 mg (48%). Anal. $C_{13}H_{18}N_2O_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.62–1.73/2.36–2.73 (CH_2CH_2, m), 2.52 (SMe, s), 3.36 (OMe, s), 4.17 (CH_2O, s), 4.64 (OCH_2O, s), 5.56–5.58 (CH=, m), 5.74–5.80 (NCH, m), 6.17 (H-5, d, *J* 7 Hz), 7.29 (H-6, d, *J* 7 Hz). ^{13}C NMR ($CDCl_3$): δ 13.2 (SMe), 32.1 (CH_2), 32.2 (CH_2), 55.9 (OMe), 63.4 (NCH), 66.3 (OCH_2), 96.7 (OCH_2O), 104.0 (C-5), 124.1 (CH=), 140.7 (C-6), 150.5 (C=), 155.3 (C-2), 177.4 (C-4).

1-(2-Cyclopentenyl)-4-(2-trimethylsilylethoxy)-2(1H)-pyrimidinone (**12c**). Yield 211 mg (95%). ^{1}H NMR ($CDCl_3$): δ −0.01 (TMS, s), 1.00–1.09 (CH_2Si, m), 1.54–1.66/2.38–2.64 (CH_2CH_2, m), 4.36–4.45 (CH_2O, m), 5.61–5.66 (CH=, m), 5.77–5.84 (H-5 and NCH, m), 6.17–6.22 (CH=, m), 7.32 (H-6, d, *J* 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ −0.9 (TMS), 17.8 (CH_2Si), 31.6 (CH_2), 31.8 (CH_2), 63.2 (NCH), 65.9 (OCH_2), 96.4 (C-5), 129.5 (CH=), 138.9 (CH=), 143.5 (C-6), 157.4 (C-2), 171.4 (C-4). MS: 278 (2, *M*), 185 (14), 169 (46), 100 (16), 73 (100), 67 (75), 66 (38), 45 (25).

5-Chloro-1-(2-cyclopentenyl)-2(1H)-pyrimidinone (**12d**). *Method A: by rearrangement.* Yield 138 mg (88%), m.p. 76°C. Anal. $C_9H_9ClN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.66–1.77/2.44–2.75 (CH_2CH_2, m), 5.71–5.89 (CH= and CHN, m), 6.38–6.41 (CH=, m), 7.68 (H-6, d, *J* 3.3 Hz), 8.50 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 31.2 (CH_2), 31.3 (CH_2), 64.8 (CHN), 111.0 (C-5), 127.7 (CH=), 140.8 (CH=), 141.7 (C-6), 154.7 (C-2), 164.2 (C-4). MS: 198/196 (2/6, *M*), 133 (6), 131 (18), 67 (100), 66 (67), 65 (15), 41 (26), 39 (25).

Method B: by direct allylation. 5-Chloro-2(1*H*)-pyrimidinone (0.207 g, 1.59 mmol) and Cs_2CO_3 (0.517 g, 1.59 mmol) were dissolved in dry DMF (10 ml) and the solution heated to 50°C for 15 min under N_2. The mixture was cooled to ambient temperature, and 2-cyclopentenyl acetate (0.2 g, 1.59 mmol), palladium(II) acetate (0.025 g, 0.11 mmol) and triisopropyl phosphite (0.165 g, 0.79 mmol) were added. The mixture was stirred at 60°C overnight and DMF was removed at reduced pressure. The product was purified by flash chromatography on silica gel using EtOAc for elution: yield 103 mg (33%).

5-Chloro-1-(3-methyl-2-cyclopentenyl)-2(1H)-pyrimidinone (**12e**). Yield 126 mg (75%); m.p. 83°C. Anal. $C_{10}H_{11}ClN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.64–1.78/2.35–2.78 (CH_2CH_2, m), 1.93 (Me, s), 5.28–5.30 (CH=, m), 5.67–5.74 (NCH, m), 7.66 (H-6, d, *J* 3.3 Hz), 8.48 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 18.5 (Me), 33.6 (CH_2), 36.8 (CH_2), 66.5 (NCH), 111.5 (C-5), 121.8 (CH=), 141.9 (C-6), 151.8 (C=), 154.7 (C-2), 163.9 (C-4). MS: 212/210 (1.8/5.6, *M*), 132 (15), 130 (44), 102 (28), 81 (74), 80 (63), 79 (100), 77 (37).

5-Chloro-1-(3-methoxymethoxymethyl-2-cyclopentenyl)-2-(1H)-pyrimidinone (**12f**). Yield 126 mg (58%). Anal. $C_{12}H_{15}ClN_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.65–1.80/2.40–2.80 (CH_2CH_2, m), 3.42 (OMe, s), 4.24 (CH_2O, s), 4.70 (OCH_2O, s), 5.62–5.65 (CH=, m), 5.76–5.81 (NCH, m), 7.70 (H-6, d, *J* 3.3 Hz), 8.50 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 29.6 (CH_2), 30.2 (CH_2), 56.0 (OMe), 65.3 (NCH), 66.2 (CH_2O), 97.0 (OCH_2O), 111.0 (C-5), 122.7 (CH=), 142.3 (C-6), 152.6 (C=), 154.7 (C-2), 164.8 (C-4). MS: 272/270 (0.3/1.0, *M*), 131 (7), 80 (14), 79 (25), 78 (13), 77 (9), 71 (11), 45 (100).

4-Chloro-1-(2-cyclopentenyl)-2-(1H)-pyrimidinone (**12g**). Yield 91 mg (58%), m.p. 110°C. Anal. $C_9H_9ClN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.59–1.75/2.41–2.75 (CH_2CH_2, m), 5.64–5.81 (NCH and CH=, m), 6.31–6.37 (CH= and H-5, m), 7.54 (H-6, d, *J* 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 31.8 (CH_2), 31.9 (CH_2), 64.6 (NCH), 105.7 (C-5), 128.3 (CH=), 140.8 (CH=), 145.1 (C-6), 157.4 (C-2), 165.7 (C-4).

2-Cyclopentenyl acetate (**14**).[16] Acetic anhydride (1.655 g, 16.2 mmol) in dry dichloromethane (25 ml) was added dropwise to a solution of 2-cyclopentenol (1.135 g, 13.51 mmol) and 4-dimethylaminopyridine (2.06 g, 16.89 mmol) in dry dichloromethane (25 ml) under N_2 at 0°C. The mixture was stirred for 1 h at 0°C, diluted with dichloromethane and shaken with aqueous $CuSO_4$ (4×), $NaHCO_3$ (2×) and brine (1×). The dried ($MgSO_4$) solution was evaporated and the residual material was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 10:1 (v/v): yield 1.22 g (72%), oily substance.

Preparation of substituted 1-(2-cyclopentenyl)uracils (**15**). *Method A: cleavage of the 2-trimethylsilylethoxy group in 1-(2-cyclopentenyl)-4-(2-trimethylsilylethoxy)-2(1H)-pyrimidinone* **12c**. A 0.5 M solution of tetrabutylammonium fluoride in dry acetonitrile (1.4 ml) was added to 1-(2-cyclopentenyl)-4-(2-trimethylsilylethoxy)-2(1*H*)-pyrimidinone (0.1 g, 0.359 mmol), and the mixture was stirred at ambient temperature under N_2 for 5 h before water (1 ml) was added, the pH adjusted to 5 with acetic acid and the mixture evaporated. The product was

purified by flash chromatography on silica gel eluting with EtOAc: yield 51 mg (80%).

Method B: hydrolysis of 4-chloro-1-(2-cyclopentenyl)-2(1H)-pyrimidinone **12g**. 4-Chloro-1-(2-cyclopentenyl)-2(1*H*)-pyrimidinone (50 mg, 2.54×10^{-4} mmol) was dissolved in NaOH (5 ml, 2 M), and the mixture was stirred at ambient temperature for 72 h. The pH was adjusted to 4 with diluted H_2SO_4 and the mixture was extracted with chloroform. The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel eluting with EtOAc: yield 40 mg (89%).

Method C: hydrolysis of 1-(2-cyclopentenyl)-4-methylthio-2(1H)-pyrimidinone **12a** *and 1-(3-methoxymethoxymethyl-2-cyclopentenyl)-4-methylthio-2(1H)-pyrimidinone* **12b**. The substituted 1-(2-cyclopentenyl)-4-methylthio-2(1*H*)pyrimidinone (0.213 mmol) was dissolved in NaOH (5 ml, 1.35 M), and the mixture was stirred at ambient temperature for 72 h. The pH was adjusted to 4 with dilute H_2SO_4, and the mixture was extracted with chloroform. The dried ($MgSO_4$) solution was evaporated and the product was purified by spinning the crude product in hexane.

1-(2-Cyclopentenyl)uracil (**15a**). Yield 28 mg (75%), m.p. 136°C. Anal. $C_9H_{10}N_2O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.61–1.72/2.43–2.62 (CH_2CH_2, m), 5.62–5.73 (NCH and CH=, m), 5.70 (H-5, d, *J* 8 Hz), 6.24–6.27 (CH=, m), 7.13 (H-6, d, *J* 8 Hz), 9.08 (NH, s). ^{13}C NMR ($CDCl_3$): δ 31.7 (CH_2), 32.5 (CH_2), 62.6 (NCH), 103.0 (C-5), 128.7 (CH=), 139.1 (CH=), 141.0 (C-6), 151.2 (C-2), 163.5 (C-4). MS: 178 (19, *M*), 113 (27), 68 (6), 67 (100), 66 (40), 65 (9), 41 (24), 39 (19).

1-(3-Methoxymethoxymethyl-2-cyclopentenyl)uracil (**15b**). Yield 43 mg (80%), m.p. 80°C. Anal. $C_{12}H_{16}N_2O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.62–1.79/2.39–2.70 (CH_2CH_2, m), 3.39 (OMe, s), 4.18 (CH_2O, s), 4.67 (OCH_2O, s), 5.56–5.72 (NCH, CH= and H-5, m), 7.18 (H-6, d, *J* 8 Hz), 9.48 (NH, s). ^{13}C NMR ($CDCl_3$): δ 31.5 (CH_2), 32.1 (CH_2), 55.9 (OMe), 62.1 (NCH), 66.2 (CH_2O), 96.8 (OCH_2O), 102.9 (C-5), 123.8 (CH=), 141.3 (C-6), 105.4 (C=), 151.5 (C-2), 163.9 (C-4). MS: 252 (0.2, *M*), 190 (11), 147 (8), 80 (7), 79 (18), 78 (6), 67 (7), 45 (100).

1-(3-Hydroxylmethyl-2-cyclopentenyl)uracil (**16**). 1-(3-Methoxymethoxymethyl-2-cyclopentenyl)uracil (0.05 g, 0.2 mmol) was dissolved in methanol (5 ml) and a trace of concentrated HCl was added. The mixture was stirred for 40 min at 60°C. The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel eluting with EtOAc; yield 34 mg (82%). Anal. $C_{10}H_{12}N_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.67–1.81/2.27–2.69 (CH_2CH_2, m), 4.31 (CH_2O, s), 5.57–5.72 (NCH, CH= and H-5, m), 7.21 (H-6, d, *J* 8 Hz), 9.30 (NH, s). ^{13}C NMR ($CDCl_3$): δ 31.1 (CH_2), 31.3 (CH_2), 59.5 (NCH), 61.7 (CH_2O), 102.3 (C-5), 121.8 (CH=), 141.0 (C-6), 151.0 (C-2), 152.9 (C=), 163.4 (C-4). MS: 208 (3, *M*), 190 (33), 147 (20), 97 (85), 96 (26), 79 (95), 67 (100), 41 (71).

(±)-cis-5-Chloro-2-[4-bis(methoxycarbonyl)methyl-2-cyclopentenyloxy]pyrimidine (**19**). A solution of BuLi (2.92 ml, 1.6 M) in dry THF (5 ml) was added dropwise with stirring to (±)-*cis*-4-bis(methoxycarbonyl)methyl-2-cyclopentenol[11] (0.5 g, 2.34 mmol) in dry THF (10 ml) under Ar at −78°C. The mixture was stirred at −78°C for 30 min, before a solution of 2,5-dichloropyrimidine (0.348 g, 2.34 mmol) in dry THF (10 ml) was added dropwise at −78°C. The resulting solution was stirred at −78°C for 15 min, and then at ambient temperature overnight. 10% NH_4Cl was added, and the solution was diluted with diethyl ether and washed with $NaHCO_3$ and water. The dried ($MgSO_4$) solution was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 4:1 (v/v). Oily substance; yield 214 mg (28%). Anal. $C_{14}H_{15}ClN_2O_5$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.68–1.79 (H-5′β, m), 2.64–2.78 (H-5′α, m), 3.29–3.44 (H-4′ and CH, m), 3.71 (Me, s), 3.72 (Me, s), 5.76–5.82 (H-1′, m), 6.03 (CH=CH, s), 8.40 (H-4, 6, s). ^{13}C NMR ($CDCl_3$): δ 34.9 (C-5′), 43.7 (C-4′), 52.6 (2×Me), 56.8 (CH), 82.5 (C-1′), 124.0 (C-5), 131.5/137.6 (C-2′ and C-3′), 157.4 (C-4, 6), 163.1 (C-2), 168.7 (C=O).

(±)-cis-5-Chloro-1-[4-bis(methoxycarbonyl)methyl-2-cyclopentenyl]-2(1H)-pyrimidinone (**20**). A mixture of (±)-*cis*-5-chloro-2-[4-bis(methoxycarbonyl)methyl-2-cyclopentenyloxy]pyrimidine (59 mg, 1.81×10^{-4} mol), palladium(II) acetate (3 mg, 1.26×10^{-5} mol) and triisopropyl phosphite (19 mg, 9.03×10^{-5} mol) in dry MeCN (5 ml) under argon was stirred at ambient temperature for 5 h. The solution was evaporated and the residual material was subjected to flash chromatography on silica gel eluting with EtOAc; yield 54 mg (91%). ^{1}H NMR ($CDCl_3$): δ 1.46–1.60 (H-5′β, m), 2.98–3.09 (H-5′α, m), 3.38–3.53 (H-4′ and CH, m), 3.74 (2×Me, s), 5.71–5.81 (H-1′ and CH=, m), 6.22–6.27 (CH=, m), 7.76 (H-6, d, *J* 3 Hz), 8.50 (H-4). ^{13}C NMR ($CDCl_3$): δ 35.7 (C-5′), 44.2 (C-4′), 52.7 (2×Me), 54.6 (CH), 64.1 (C-1′), 111.0 (C-5), 129.2/139.9 (C-2′ and C-3′), 142.3 (C-6), 154.7 (C-2), 163.5 (C-4), 167.3 (CO). MS: 328/326 (1.6/4.7, *M*), 197 (65), 195 (87), 165 (33), 164 (17), 137 (100), 131 (23), 105 (56).

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