trophotometer, and optical densities were monitored at 250 nm. A plot of $a_0b_0/\Delta OD$ vs. $a_0 + b_0$ was linear with the slope and intercept being equal to $1/\Delta\epsilon$ and $k_d/\Delta\epsilon$, respectively. The value of K_d was obtained from these linear plots.

Identification of Cyclodextrin Complexes. Powder Diffraction of Solid Complexes. X-ray powder photographs of β-cyclodextrin, benzoin alkyl ethers, and complexes of cyclodextrin with benzoin alkyl ethers were recorded with a Phillips powder diffractometer employing monochromated Cu Kα radiation. Powder patterns of the complexes were different from those of cyclodextrin and benzoin alkyl ethers and therefore it was concluded that microcrystalline complexes have been formed between β-cyclodextrin and benzoin alkyl ether.

NMR Studies. Sample Preparation. Solutions of the 1:1 complexes were prepared by dissolving 2–3 mg of the complex in about 1 mL of D_2O. Solutions containing different proportions of guest to host were prepared by stirring 0.5, 1, 2, 3, and 4 mg of the benzoin methyl ether with a solution of 5 mg of β-cyclodextrin in 1 mL of D_2O for about an hour.

The NMR spectra of all the β-cyclodextrin complexes and β-cyclodextrin and benzoin methyl ether in D_2O and $CDCl_3$ were recorded with a Bruker WH 270 spectrometer equipment with ASPECT 2000 computing system. The difference NOE measurements were made by collecting two sets of free induction decays sequentially in different parts of the computer memory (8K each) corresponding to low power on-resonance saturation of a peak and off-resonance irradiation, respectively. The free induction decays were recorded by alternating between on-resonance and off-resonance irradiation after each scan, and typically 200 scans were employed. A delay of 3 s between scans and an irradiation period of 3 s were used before acquisition (1.5 s) was started. Identical exponential multiplication was done on both the free induction decays. The difference of their Fourier transforms was then compared with the Fourier transform of the off-resonance irradiated free induction decay to estimate the NOE. No special sample preparation was used for the NOE experiment.

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Registry No. **10a**, 92549-02-5; **10b**, 102979-46-4; **10c**, 102979-47-5; β-CD/**3** 1:1 adduct, 102979-42-0; γ-CD/**3** 1:1 adduct, 102979-43-1; β-CD/**2** 1:1 adduct, 102979-44-2; β-CD/**1** 1:1 adduct, 102979-45-3.

Supplementary Material Available: H^1 NMR spectra of β-cyclodextrin and β-cyclodextrin–benzoin methyl ether complex, X-ray powder photographs for (a) β-cyclodextrin, (b) benzoin isopropyl ether, and (c) inclusion complex of β-cyclodextrin with benzoin isopropyl ether, progress of the reaction with respect to time in the case of cyclodextrin–benzoin methyl ether complex, and Benesi–Hilderbrand plots to estimate K_d for all three benzoin ethers are given in Figures 1–4, respectively (5 pages). Ordering information is given in any current masthead page.

Facile Synthesis of 2′-Deoxy-3′-keto- and 2′-Deoxypseudouridine Derivatives and Analogues. Palladium(II)-Mediated Coupling Reactions of Furanoid Glycals

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C-Nucleosides, of either α or β configuration, are formed selectively in a palladium-mediated coupling reaction between furanoid glycals and (1,3-dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl)mercuric acetate. Control of anomeric configuration is accomplished by suitable choice of substituents for glycal 3-*O*- and 5-*O*-hydroxy groups; attack of organopalladium reagent and glycosidic bond formation occurs on the least sterically hindered face of the glycal ring. Removal of substituents from the coupled products yielded 2′-deoxy-3′-keto C-nucleosides, which upon metal hydride reduction produced the corresponding 2′-deoxy C-nucleosides.

In a previous report,[2] we described palladium-mediated coupling of furanoid glycals[3] with (1,3-dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl)mercuric acetate (**1**)[4] which formed regio- and stereospecifically a glycosidic carbon–carbon bond linking C-5 of the pyrimidine moiety and C-1 of a glycal. This study of C-nucleoside[5] synthesis by palladium-mediated coupling of furanoid glycals has now been extended by (a) investigation of the directive effect on organopalladium coupling of various substituents on the glycal oxygens, (b) evaluation of methods for complete or selective removal of C-nucleoside 3′-O and 5′-O directive groups, and (c) preparation of 2′-deoxypseudouridine derivatives by the reduction of corresponding 3′-keto compounds arising as primary products of the coupling reaction or following removal of directive groups of product 3′-enols.

Directive Effect of Oxygen Substituents on Organopalladium Coupling. The stereochemistry of adduct formation in the organopalladium coupling reaction of furanoid glycals leading to C-nucleosides is exquisitely sensitive to steric factors affecting access to the glycal double bond.[2,6,7] The organopalladium reagent (formed by transmetalation of **1**[6,8]) attacks the most accessible face

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(2) Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 2870.
(3) (a) Cheng, J. C. Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.
(4) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1978**, *43*, 4110.
(5) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.
(6) Arai, I.; Lee, T. D.; Hanna, R.; Daves, G. D., Jr. *Organometallics* **1982**, *1*, 742.
(7) Substitution on the double bond does not affect the regiochemistry of the reaction but does depress yields: Lee, T. D.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 399.
(8) Kalinoski, H. T.; Hacksell, U.; Barofsky, D. F.; Barofsky, E.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6476.

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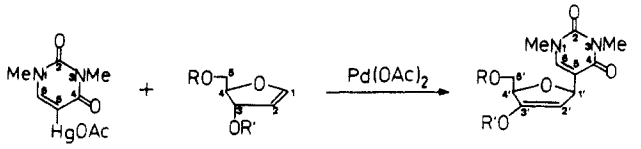
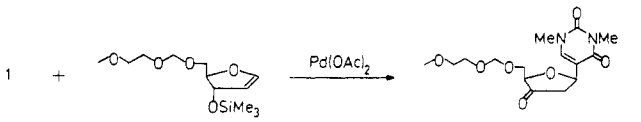
of the glycal double bond (however, vida infra[9]). Thus, each palladium-mediated coupling reaction yields selectively a single palladium adduct of either an α- or a β-C-nucleoside.[2,6] In our initial study of furanoid glycals,[2] we showed that, if both the 3- and 5-hydroxyl groups are substituted with bulky groups, organopalladium reagent attack occurs only from the β face, whereas, if only the 5-hydroxyl is substituted, attack occurs from the α face. In the present study, use of furanoid glycals in which O-3 is substituted and O-5 is free (**2e** and **2f**) led only to β-C-nucleosides.



1 2a-f 3a-f

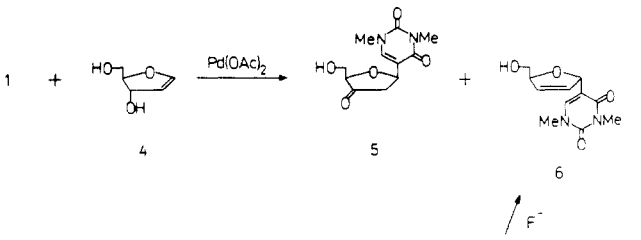
a: R, R'=CH_2OCH_3
b: R=CH_2OCH_3, R'=$Si(i\text{-}Pr)_3$
c: R, R'=$Si(i\text{-}Pr)_3$
d: R=$Si(CH_3)_2t\text{-}Bu$, R'=$Si(i\text{-}Pr)_3$
e: R=H, R'=CH_2OCH_3
f: R=H, R'=$CH_2OCH_2CH_2OCH_3$

The fact that the β-C-nucleosides **3a** and **3c** form selectively when both the 3- and 5-hydroxyls are identically substituted indicates that the reaction is more sensitive to the steric bulk of the substituent at the allylic (3) position than to that at position 5 of the furanoid glycal.[10] Use of a very bulky group at O-3 to direct reaction stereochemistry (e.g., triisopropylsilyl) does not depress the yield of coupled product (**3b**, Table I). Not surprisingly, the presence of such a bulky substituent on the face of the glycal experiencing attack does result in lower, but still quite acceptable, product yields (**3c**, **3d**, Table I). It is noteworthy that, despite its relative lability, the trimethylsilyloxy substituent effectively directs organopalladium adduct formation even though trimethylsilyl is lost during reaction, yielding a 3'-keto C-nucleoside directly (e.g., **2h** → **8c**).

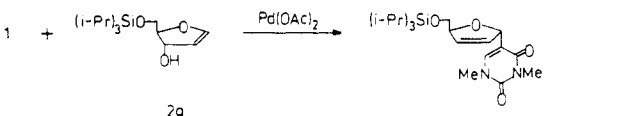


2h 8c

The results obtained upon coupling of the 3,5-O-unsubstituted glycal, 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol[3a] (**4**), are particularly informative. This reaction produced a mixture of the α- and β-C-nucleosides **5** and **6**[11] in yields of 45% and 29%, respectively (Table I). To date, this is the only instance in which products resulting from organopalladium attack on both faces of a glycal have been isolated.[9] This result is indicative that (a) neither the hydroxy nor the hydroxymethyl substituent is sufficiently bulky to effectively direct the coupling reaction and (b) the allylic (3) substituent, which is nearer the glycal double bond, has the greater effect.[10] The α-C-nucleoside **6** was the sole product of a two-step sequence involving



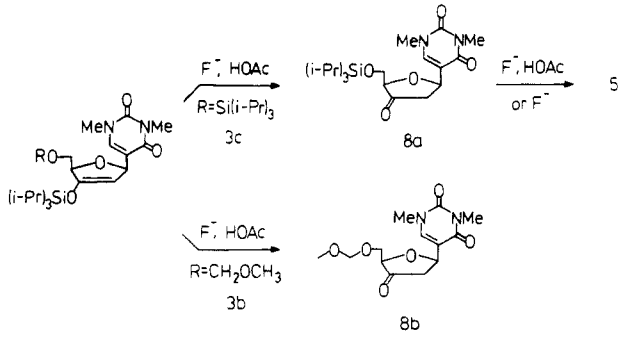
4 5 6



2g 7

coupling of 5-O-substituted glycal **2g** to form **7** followed by desilylation. It is noteworthy that the intermediate adducts leading to **6** and **7**, which possess no syn β-hydrogen or anti β-acetoxy, decompose by syn palladium oxide elimination.[11]

Removal of Substituents from Carbohydrate Hydroxyls of Product C-Nucleosides. C-Nucleoside products resulting from palladium-mediated coupling of furanoid glycals in which *O*-trialkylsilyl groups were used to direct the stereochemistry of adduct formation (i.e., **3c**, **3d**, **7**) react readily with fluoride ion to yield the corresponding O-unsubstituted analogues.[2,12,13] In **3b** where one triisopropylsilyl and one methoxymethyl group were used to differentiate the two carbohydrate hydroxyls, fluoride ion[2,12,13] selectively removed the silyl group to yield the 5'-O-substituted 3'-keto C-nucleoside **8b**. It was

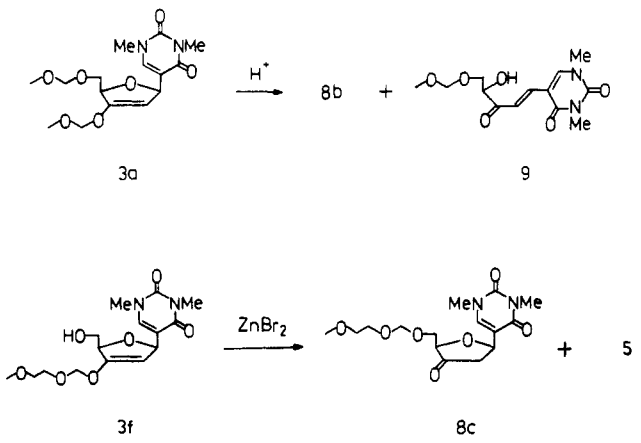


possible to selectively remove the silyl group from the more labile 3'-*O*-trialkylsilyl enol ether moieties in the presence of an 5'-*O*-trialkylsilyl function (**3c** → **8a**) by control of the reaction temperature and time. The hope that a *tert*-butyldimethylsilyl group could be removed selectively in the presence of a triisopropylsilyl group (see **3d**) was not realized.

Efforts to remove methoxymethyl[3] and (β-methoxyethoxy)methyl[14] substituents were much less successful owing to the lability of the C-nucleosides to acid. Attempts to remove methoxymethyl groups of C-nucleosides possessing unsaturated carbohydrate moieties under acidic conditions[3b] (e.g., **3a** → **8b** and/or **5**) always produced a side product (e.g., **9**) in which the carbohydrate ring had opened. Attempts to remove the (β-methoxyethoxy)methyl group of **3f** using zinc bromide[14] resulted in migration of the (β-methoxyethoxy)methyl group from the 3'-O to the 5'-O, forming **8c**.

Reduction of 3'-Keto C-Nucleosides. A number of 1,3-dimethyl-2'-deoxypseudouridines and corresponding 3'-β-hydroxy isomers were prepared by borohydride re-

(9) In a related reaction stereochemical mixtures have been observed: Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533.
(10) We have noted[6] that in coupling reactions of pyranoid glycals the organopalladium attack occurs from the face opposite the allylic substituent.
(11) Hacksell, U.; Daves, G. D., Jr. *Organometallics* **1983**, *2*, 772.
(12) Kraihanzel, C. S.; Poist, J. E. *J. Organomet. Chem.* **1967**, *8*, 239.
(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(14) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.



duction of 3′-keto analogues (**8a–c, 5**); the results of these reductions are summarized in Table II. In all cases, the major product possessed a β-3′-hydroxyl; no conditions were found for selective delivery of a hydride to the more hindered side of the 3′-carbonyl.

It seemed plausible that a metal hydride reagent might chelate to the 5′-oxygen (or other functional group on the carbohydrate β-face) and deliver a hydride to C-3′.[15] This result was not realized, presumably because reaction of the hydride reagent with carbonyl is faster than bonding interaction with hydroxyl or other available functionality.

C-Nucleoside Structural Assignments. Product structures were assigned by chemical and spectrometric data contained in Tables I and III. Particularly important in assignment of C-nucleosides to the α or β series are the homoallylic coupling constants $^4J_{1',4'}$ (Table I)[2,16] observed in ^{1}H nuclear magnetic resonance (NMR) spectra. When H-1′ and H-4′ are trans, $^4J_{1',4'}$ is >5.0 Hz (**6** and **7**, Table I);[2] whereas, when these hydrogens are cis the coupling constant is <4.0 Hz (**3a–f**, Table I). A detailed study[17] of ^{1}H and ^{13}C NMR spectra of 2′-deoxy C-nucleosides (including those prepared here) has demonstrated correlations, using a combination of H,H coupling constant and chemical shift criteria, with carbohydrate stereochemistry which permits secure structure assignments to be made for this relatively little studied compound class.

Experimental Section

General Comments. Chemicals were used as received except for tetrahydrofuran, which was distilled from lithium aluminum hydride under nitrogen. Thin-layer chromatography (TLC) was carried out with prescored silica gel GF plates (Analtech). Preparative TLC was carried out on 1 mm thick, 20 × 20 cm^2, silica gel GF plates. For flash chromatography, silica gel 60 (230–400 mesh ASTM, E. Merck) was used. Columns were eluted with a positive nitrogen pressure. A Varian 5000 liquid chromatograph equipped with an IBM LC/9522 UV detector (254 nm) was used for high-pressure liquid chromatographic (HPLC) analyses (Whatman Partisil PXS 5/25 ODS column). NMR spectra were obtained on a JEOL FX 90Q spectrometer and are referenced to tetramethylsilane. Mass spectra (EI, tight ion source) were obtained with a Finnegan 4023 GC/MS/DS system operating at 70 eV using a direct insertion probe. Elemental analyses were performed by Dr. G. Robertson, Florham Park, NJ. High-resolution mass spectrometry was performed by Dr. T. Wachs, Department of Chemistry, Cornell University.

Palladium-Mediated Reactions of Furanoid Glycals. Furanoid glycals[3a] **2** and **4** were converted to C-nucleosides by using a general procedure illustrated by the synthesis of **3c**. Products were purified by flash chromatography or by preparative TLC, depending on the reaction scale. In either instance the TLC solvent system noted in Table I was used for elution.

(2′*R*)-*cis*-5-[2′,5′-Dihydro-4′-((tris(1-methylethyl)silyl)oxy)-5′-(((tris(1-methylethyl)silyl)oxy)methyl)-2′-furanyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (3c). To a 50-mL vial equipped with a screw lid and a stirring bar was added palladium acetate (404 mg, 1.80 mmol), (1,3-dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl)mercuric acetate[4] (**1**) (718 mg, 1.80 mmol) and acetonitrile (40 mL) at room temperature. The mixture was stirred for 5 min, and then a solution of 1,4-anhydro-2-deoxy-3,5-bis-*O*-[tris(1-methylethyl)silyl]-D-*erythro*-pent-1-enitol[3a] (**2c**) (1.00 g, 2.34 mmol) in acetonitrile (5 mL) was added. After 2 h, sodium bicarbonate (605 mg, 7.20 mmol) was added to the dark solution, and stirring was continued for 21 h. The reaction mixture was filtered through Celite, and volatiles were evaporated. Flash chromatography of the residue using ether/petroleum ether (1:1) as eluant yielded 517 mg (51%) of **3c** as a colorless oil. Characterizing data are included in Table I.

Removal of 5′-*O*-Triisopropylsilyl Group. (2′*S*)-*trans*-5-[2′,5′-Dihydro-5′-(hydroxymethyl)-2′-furanyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (6). To a stirred solution of **7** (75 mg, 0.19 mmol) in 15 mL of tetrahydrofuran was added dropwise a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.22 mL, 0.22 mmol) at room temperature. The reaction was complete in 1 min. After evaporation of volatiles in vacuo, 41 mg (90%) of **6** was obtained as a white solid by preparative TLC using ether/acetone (2:1) for development.

Desilylation of 3′-Triisopropylsilyl Enol Ether for Preparation of 2′-Deoxy-3′-keto C-Nucleosides. 1,3-Dimethyl-5-[5′-*O*-(tris(1-methylethyl)silyl)-β-D-glyceropentofuran-3′-ulos-1′-yl]-2,4(1*H*,3*H*)-pyrimidinedione (8a). To a solution of **3c** (80 mg, 0.14 mmol) and acetic acid (17 mg, 0.28 mmol) in 25 mL of tetrahydrofuran at −78 °C was added a 1 M solution of tetrabutylammonium fluoride (0.28 mL, 0.28 mmol). After 30 min, one drop of acetic acid was added to the reaction mixture, and cooling was discontinued. Filtration through glass wool followed by evaporation of volatiles in vacuo gave a light yellow oil, which was purified by preparative TLC using ether for development to give 48 mg (86%) of **8a**.

1,3-Dimethyl-5-[5′-*O*-(methoxymethyl)-β-D-glyceropentofuran-3′-ulos-1′-yl]-2,4(1*H*,3*H*)-pyrimidinedione (8b). Desilylation of **3b**[2] (653 mg, 1 mmol) was accomplished by using the procedure described above for preparation of **8a**. Flash chromatography on a silica gel column (2 × 15 cm) using ethyl acetate for elution afforded 423 mg (97%) of pure **8b**: UV λ_{max} ($CHCl_3$) 270 nm.

1,3-Dimethyl-5-[5′-*O*-((methoxyethoxy)methyl)-β-D-glyceropentofuran-3′-ulos-1′-yl]-2,4(1*H*,3*H*)-pyrimidinedione (8c). The method of Corey[14] was used: A mixture of **3f** (80 mg, 0.23 mmol) and zinc bromide (anhydrous, 527 mg, 2.34 mmol) in 15 mL of dichloromethane was stirred at room temperature for 1.5 h. The reaction mixture was then washed with saturated aqueous sodium bicarbonate and brine and then dried over magnesium sulfate. After concentration of the dried solution, the residue was subjected to preparative TLC using ethyl acetate/methanol (19:1) for development to afford three components: 25 mg (31%, top band) of **8c**, 16 mg (27%, middle band) of **5** and 11 mg (14%) of recovered **3f**. Characterizing data for the products are in Table I.

1′-(1,3-Dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl)-(4′*R*)-4′-hydroxy-5′-(methoxymethoxy)-1′-penten-3′-one (9). A solution of **3a**[2] (80 mg, 0.23 mmol) and sulfuric acid (catalytic amount, about 5 mol %) in 5 mL of ethanol/acetone (1:1) was heated under reflux for 1 h, then cooled to room temperature, and neutralized with sodium bicarbonate. The volatiles were removed in vacuo, and the residue was partitioned between dichloromethane and water. The aqueous layer was extracted twice with dichloromethane, and the organic extracts were combined

(15) For reported reductions involving use of similar concepts, see: (a) Cazaux, L.; Maroni, P. *Bull. Chim. Soc. Fr.* **1972**, 780. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233. (c) Lansbury, P. T.; Vacca, J. P. *Tetrahedron Lett.* **1982**, *23*, 2623. (d) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. (e) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (f) Thompson, H. W.; McPherson, E. *J. Org. Chem.* **1977**, 3350. (g) Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2212.

(16) Barfield, M.; Spear, R. J.; Sternhell, S. *J. Am. Soc.* **1971**, *93*, 5322. Barfield, M.; Sternhell, S. *Ibid.* **1972**, *94*, 1905. Barfield, M.; Spear, R. J.; Sternhell, S. *Ibid.* **1975**, *97*, 5160.

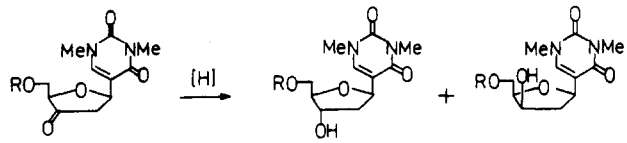
(17) Hacksell, U.; Cheng, J. C. Y.; Daves, G. D., Jr. *J. Carbohydr. Chem.* **1986**, *5*, 287.

Table I. Formation and Analysis of 1,3-Dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl C-Nucleosides[a]

				chromatographic, analytic, and spectrometric properties of the products												
						anal. (HRMS)[c]			^{1}H NMR spectra[d]							
entry	reactant	product	yield, %	R_f (solvent)[b]	MS, m/z of $M^{\cdot+}$ (rel intensity)	calcd	found	solv	H_6	$H_{1'}$	$H_{2'}$ or ($H_{2''}$)	$H_{3'}$	$H_{4'}$	$H_{5'}$,$H_{5''}$	NMe, OMe	$J_{1',4'}$, Hz
1[e]	**2a**	**3a**	71	0.33 (E)		C, 52.6; H, 6.48; N, 8.18	C, 52.4; H, 6.53;, N, 7.92	C_6D_6	7.21	6.02	5.38		4.88–4.70	4.03–3.52	3.20, 3.12 3.04, 2.71	3.0
2[e]	**2b**	**3b**	92	0.37 (1:1 E/P)		C, 58.1; H, 8.42; N, 6.16	C, 58.0; H, 8.69; N, 6.03	C_6D_6	7.32	6.02	5.28		4.95–4.55	3.95–3.55	3.20, 3.16, 2.73	3.4
3	**2c**	**3c**	51	0.50 (1:1 E/PE)	566 (0.5)	C, 59.6; H, 9.65; N, 4.79	C, 59.6; H, 9.74; N, 4.61	C_6D_6	7.15	5.96	5.87		4.72	4.10, 3.85	3.19, 2.83	3.7
4	**2d**	**3d**	45	0.63 (1:1 E/PE)		C, 59.5; H, 9.22; N, 5.34	C, 59.3; H, 9.45; N, 5.29	$CDCl_3$	7.45	5.68	4.94		4.54	3.82	3.36, 3.33	3.7
5[f]	**2e**	**3e**	65	0.55 (2:1 E/A)		C, 52.3; H, 6.08; N, 9.39	C, 52.1; H, 6.26; N, 9.22	$CDCl_3$	7.34	5.63	4.98		4.73	3.78	3.43, 3.37, 3.30	3.9
6	**2f**	**3f**	77	0.38 (2:1 E/A)		C, 52.6; H, 6.48; N, 8.18	C, 52.3; H, 6.67; N, 8.25	$CDCl_3$	7.42	5.65	5.02		4.70	3.82–3.48	3.37, 3.33, 3.30	3.9
7[f]	**4**	**5**	45	0.24 (EA)	254 (0.2)	(254.0903)	(254.0897)	$CDCl_3$	7.42	4.95	2.74 (2.64)		3.95	3.80	3.38, 3.27	
		6	29	0.24 (EA)	238 (0.8)	(238.0953)	(238.0971)	CD_3CO-CD_3	7.44	5.68	6.01	5.95	4.96	3.58	3.39, 3.22	5.9
8[f]	**2g**	**7**	33	0.62 (2:1 E/PE)				C_6D_6	6.62	5.93	6.24	5.69	5.00	3.75	3.38, 3.33	5.8
9[g]	**3c**	**8a**	86	0.47 (E)	411 (MH^+, 1)	(411.2315)	(411.2315)	$CDCl_3$	7.51	5.12	3.05 (2.14)		4.12–3.91		3.39, 3.35	
10[g]	**3b**	**8b**	97	0.39 (EA)	298 (0.5)	(298.1165)	(298.1158)	$CDCl_3$	7.48	5.14	3.07 (2.30)		4.16–4.09	3.88–3.84	3.44, 3.35	
11	**2h**	**8c**	59	0.51 (19:1 EA/M)	342 (0.06)	(342.1427)	(342.1390)	$CDCl_3$	7.45	5.11	3.03 (2.26)		4.09	3.86	3.41, 3.37, 3.33	

[a] All reactions are coupling reactions except entries 9 and 10 (see *g*). The general procedure for the coupling reaction can be found in Experimental Section. For entries 5, 7, and 8, see also *f*. [b] Thin-layer chromatography (TLC). The same solvent system was used for purification of the product(s) either by preparative TLC or flash chromatography: E, diethyl ether; PE, petroleum ether; A, acetone; EA, ethyl acetate; M, methanol. [c] HRMS, high-resolution mass spectrometry. [d] Chemical shifts (δ) in ppm downfield from tetramethylsilane. Chemical shifts for the substituents on carbohydrate oxygen not listed in the table are (δ): CH_2OCH_3, CH_2O, 4.58–4.98. $CH_2OCH_2CH_2OCH_3$, CH_2O, 4.71–5.06; OCH_2CH_2O, 3.82–3.48. Si(*i*-Pr)$_3$, 1.04–111. $SiMe_2$-*t*-Bu, Me's, 0.03, 0.05; *t*-Bu, 0.87. [e] See ref 2. [f] Entry 5, stirred for 1 day at room temperature and 1.5 h at 55 °C; entry 7, stirred for 42 h at room temperature and 1 h at 65 °C; entry 8, stirred for 2 days at room temperature and 2 h at 75 °C. [g] Tetrabutylammonium fluoride and acetic acid were used for the desilylation, see Experimental Section.

Table II. Reduction of 2′-Deoxy-3′-keto C-Nucleosides



5, 8 10 11

3′-keto C-nucleoside	R	reducing agent	temp, °C	yield,[a] %	3′-OH_α/3′-OH_β[b]	products
8a	$Si(i\text{-}Pr)_3$	$NaBH_4$	0	88	1:2	**10a/11a**
8b	CH_2OCH_3	$NaBH_4$	0	73	1:3	**10b/11b**
8c	$CH_2OCH_2CH_2OCH_3$	$NaBH_4$	−78	55	1:2	**10c/11c**
5	H	$LiBH_4$	−78	60	1:2	**10d/11d**

[a] Isolated yield. [b] Determined by high-pressure liquid chromatography.

Table III. ^{13}C Nuclear Magnetic Resonance Spectra of C-Nucleosides (δ)[a]

cmpd	N_1CH_3	C_2	N_3CH_3	C_4	C_5	C_6	C_1'	C_2'	C_3'	C_4'	C_5'	other
3c[b]	36.18	151.40	27.40	162.29	115.27	138.83	84.39	102.00	150.70	78.86	65.32	$SiCH(CH_3)_2$'s, 18.24, 18.03, 12.50, 12.34
3d	36.97	151.60	27.54	162.49	115.30	139.79	83.61	100.73	150.14	77.65	63.46	$SiCH(CH_3)_2$, 17.73, 11.45; $SiC(CH_3)_3$, 25.86, 18.38; $Si(CH_3)_2$, −5.34, −5.45
3e	35.61	150.08	27.76	162.60	112.11	139.79	81.33	96.12	150.57	79.82	60.97	OCH_3, 55.06; OCH_2O, 94.28
3f	36.86	151.44	27.59	162.60	113.57	141.36	82.69	97.64	151.65	79.49	62.16	OCH_3, 58.69; OCH_2O, 94.34; OCH_2CH_2O, 71.37, 68.06
5	37.01	151.20	27.77	162.32	111.08	141.51	81.88	42.21	213.44	73.29	61.72	
6[c]	36.41	151.10	27.26	161.77	112.42	140.70	80.56	129.21	128.62	86.90	63.93	
7	37.02	151.75	27.70	162.32	114.33	139.14	81.44	129.71	128.19	87.08	66.27	$SiCH(CH_3)_2$, 17.90, 11.94
8a	37.02	151.50	27.84	162.20	114.02	138.98	82.16	44.76	213.10	71.08	62.74	$SiCH(CH_3)_2$, 17.90, 11.83
8b	37.13	151.46	27.77	162.12	113.23	139.41	80.73	43.12	212.13	71.37	66.25	OCH_3, 55.33; OCH_2O, 96.50
8c	37.19	151.46	27.77	162.12	113.23	139.41	80.73	43.72	212.13	71.37	66.25	OCH_3, 58.97; OCH_2O, 95.55; OCH_2CH_2O, 71.63, 66.95

[a] Chemical shifts in ppm; spectra were recorded in $CDCl_3$ unless otherwise noted. [b] Benzene-d_6. [c] Dimethyl sulfoxide-d_6.

and dried (magnesium sulfate). The solvent was evaporated, and the resulting oil was separated by preparative TLC using ethyl acetate for development to yield two bands: 15 mg (22%) of **8b** (upper band) and 33 mg (47%) of **9** (lower band). The α,β-unsaturated ketone structure **9** was assigned on the basis of the ultraviolet absorption, λ_{max} ($CHCl_3$) 320 nm, and ^1H NMR coupling constant for the olefinic resonances: ^1H NMR ($CDCl_3$) δ 7.63 (d, H-1′), 7.52 (s, H-6), 7.32 (d, H-2′), 4.56 (s, OCH_2O), 4.45 (m, H-4′), 4.02–3.71 (m, H-5′, H-5″), 3.46, 3.34, 3.26 (3 s, 2 NMe, OMe); $J_{1',2'}$ = 15.5 Hz.

Reduction of 2′-Deoxy-3′-keto C-Nucleosides. 1,3-Dimethyl-5-[2′-deoxy-5′-*O*-(tris(1-methylethyl)silyl)-β-D-*threo*-pentofuranosyl]-2,4(1*H*,3*H*)-pyrimidinedione (11a) and 1,3-Dimethyl-5-[2′-deoxy-5′-*O*-(tris(1-methylethyl)silyl)-β-D-*erythro*-pentofuranosyl]-2,4(1*H*,3*H*)-pyrimidinedione (10a). To a cooled (ice bath) solution of **8a** (423 mg, 1.03 mmol) in 40 mL of methanol was added a freshly prepared solution of sodium borohydride (80 mg, 2.12 mmol) in 1 mL of water. TLC analysis indicated that the reaction was complete after 30 min. A large excess of ammonium chloride was added to the reaction mixture, and the volatiles were removed in vacuo. The residue was partitioned between water and dichloromethane, the layers were separated, and the water layer was extracted twice with dichloromethane. The combined organic extract was dried (magnesium sulfate), and the solvent was removed. The resulting oil was separated by preparative TLC using two stages of development, first with chloroform and then with chloroform/ether (3:2). From the upper band was obtained 262 mg (61%) of **11a**; the lower band yielded 114 mg (27%) of **10a**. TLC (3:2 chloroform/ether) exhibited R_f 0.32 for **11a** and R_f 0.21 for **10a**.

11a: MS, *m/z* (relative intensity) 412 (0.5, $M^{\bullet+}$), 369 (2, $M^{\bullet+} - C_3H_7$), 351 (10, $M^{\bullet+} - C_3H_7 - H_2O$). Anal. Calcd for $C_{20}H_{36}N_2O_5Si \cdot 0.5H_2O$: C, 57.0; H, 9.08; N, 6.64. Found: C, 56.9; H, 8.74; N, 6.52.

10a: HRMS, calcd for $C_{20}H_{36}N_2O_5Si$ + H 413.2472, found 413.2469.

5-[2′-Deoxy-5′-*O*-(methoxymethyl)-β-D-*threo*-pentofuranosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (11b) and 5-[2′-Deoxy-5′-*O*-(methoxymethyl)-β-D-*erythro*-pentofuranosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (10b). Reduction of **8b** (460 mg, 1.54 mmol) was performed according to the procedure described for **8a** (above). Preparative TLC using ethyl acetate afforded three fractions: A, 35 mg of **10b**; B, 195 mg of a 3:1 mixture of **10b** and **11b**; C, 105 mg of **11b** (total yield 335 mg, 73%). Fraction B was rechromatographed to give 27 mg of **10b**, 75 mg of **11b**, and 80 mg of a mixed fraction. On TLC (ethyl acetate) **10b** exhibited R_f 0.29 and **11b** exhibited R_f 0.22.

10b: MS, *m/z* (relative intensity) 300 (1.5, $M^{\bullet+}$). Anal. Calcd for $C_{13}H_{20}N_2O_6$: C, 52.0; H, 6.71; N, 9.33. Found: C, 51.8; H, 6.80; N, 9.16.

11b: HRMS, calcd for $C_{13}H_{20}N_2O_6$ 300.1321, found 300.1305.

5-[2′-Deoxy-5′-*O*-[(methoxyethoxy)methyl]-β-D-*threo*-pentofuranosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (10c) and 5-[2′-Deoxy-5′-*O*-[(methoxyethoxy)methyl]-β-D-*erythro*-pentofuranosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (11c). To a solution of **8c** (100 mg, 0.29 mmol) in 3 mL of tetrahydrofuran at −78 °C under nitrogen was added a solution of sodium borohydride in 3 mL of tetrahydrofuran. After being stirred for 3 h, the reaction was quenched by addition of 0.1 mL of acetic acid, cooling was discontinued, and the volatiles were evaporated. HPLC analysis (1:4 acetone/water) of the resulting residue indicated a 95% yield of a 1.9:1 mixture of **11c** and **10c**. The residue was partitioned between water and dichloromethane, the layers were separated, and the water layer was extracted twice with ethyl acetate. The combined organic extract was dried (magnesium sulfate) and separated by preparative TLC using ethyl acetate/methanol (19:1) for six sequential developments to give 37 mg of **11c** and 18 mg of **10c** in a total yield of 55%. On TLC (19:1 ethyl acetate/methanol), **11c** exhibited R_f 0.24 and **10c** showed R_f 0.32.

11c: HRMS, calcd for $C_{15}H_{24}N_2O_7$ 344.1583, found 344.1589.

10c: HRMS, calcd for $C_{15}H_{24}N_2O_7$ 344.1583, found 344.1589.

5-(2′-Deoxy-β-D-*threo*-pentofuranosyl)-1,3-dimethyl-2,4-(1*H*,3*H*)-pyrimidinedione (11d) and 5-(2′-Deoxy-β-D-*erythro*-pentofuranosyl)-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione[18] (10d). (a) Reduction of 5. A solution of **5** (100 mg,

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0.39 mmol) and lithium borohydride (0.2 mL of a 2 M solution in tetrahydrofuran, 0.4 mmol) in 1.8 mL of tetrahydrofuran was stirred for 1.5 h at −78 °C. The reaction was quenched with acetic acid and methanol; the mixture was then allowed to warm to room temperature. The volatiles were removed in vacuo, and the residue was separated by two successive stages of TLC: the first plate was developed with acetone/chloroform (3:2) to remove unreacted **5**; the second plate was developed with chloroform/methanol (9:1) to yield 40 mg (40%) of **11d** and 21 mg (21%) of **10d**, which exhibited spectrometric properties indistinguishable from those previously reported.[18]

(b) 10d by Desilylation of 10a. To a cooled (ice bath) solution of **10a** (114 mg, 0.28 mmol) in 25 mL of tetrahydrofuran was added 0.28 mL of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran. The reaction was complete (TLC) in 30 min. The volatiles were removed, and the resulting residue was purified by preparative TLC using acetone/chloroform (3:2) (R_f 0.26) for development to yield 67 mg (94%) of **10d**.

(c) 11d by Desilylation of 11a. Desilylation of **11a** (125 mg, 0.30 mmol) was accomplished according to the procedure described above for desilylation of **10a** to afford 66 mg (86%) of **11d**: R_f 0.49 (9:1 chloroform/methanol); MS, m/z (relative intensity) 257 (6, M + H^+).

Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 49.8; H, 6.49; N, 10.6. Found: C, 49.5; H, 6.62; N, 10.3.

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Registry No. 1, 65904-27-0; **2a**, 86436-80-8; **2b**, 86436-81-9; **2c**, 96760-97-3; **2d**, 96760-96-2; **2e**, 96761-01-2; **2f**, 103003-61-8; **2g**, 96760-93-9; **2h**, 96760-95-1; **3a**, 86455-85-8; **3b**, 86436-84-2; **3c**, 98839-18-0; **3d**, 103003-62-9; **3e**, 103003-63-0; **3f**, 103003-50-5; **4**, 96761-00-1; **5**, 103003-52-7; **6**, 103003-47-0; **7**, 103003-46-9; **8a**, 103003-48-1; **8b**, 103003-49-2; **8c**, 103003-51-6; **9**, 103003-53-8; **10a**, 103003-55-0; **10b**, 103003-56-1; **10c**, 103003-59-4; **10d**, 65358-16-9; **11a**, 103003-54-9; **11b**, 103003-57-2; **11c**, 103003-58-3; **11d**, 103003-60-7.

Stereocontrolled Total Synthesis of 1α,25-Dihydroxycholecalciferol[1] and 1α,25-Dihydroxyergocalciferol

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1α,25-Dihydroxycholecalciferol (**4**) and 1α,25-dihydroxyergocalciferol (**7**), the hormonally active forms of vitamin D_3 (**1**) and vitamin D_2 (**5**), were synthesized by a Horner–Wittig reaction of the phosphine oxide **11** with the ketones **10** and **12**, respectively. The synthon **11** was obtained by a sequence that involves the stereospecific opening of epoxide **15**, with sodium acetate in acetic acid, followed by oxidative degradation of the isopropenyl side chain and dehydration of the intermediate **22**. Photoisomerization of the resulting **23** gave **24**, which was finally converted to **11**. The hydroxylated ketone **10** was obtained from the known intermediate **28**. The introduction of the 25-hydroxy side chain was achieved by reaction of the lithium derivative of **30** with the tosylate **29** to give **31**, which was catalytically hydrogenated to **32** and then converted to **10**. The ketone **12** was prepared by a stereocontrolled route that involves as the key step, the [3 + 2] dipolar cycloaddition of nitrone **35** with methyl 3,3-dimethylacrylate (**36**) to give a 1:1 mixture of isoxazolidines **37** and **38**. Stereochemical control was achieved by taking advantage of the thermal reversibility of the cycloaddition, which allows the reequilibration of undesired **37**. Isoxazolidine **38** was readily transformed to **43** by reduction, followed by elimination of the nitrogen function, and finally oxidation to **12**.

In the past two decades, extensive investigations of the vitamin D_3 (cholecalciferol, **1**) metabolism have led to the discovery of a number of transformations which this essential vitamin undergoes in biological systems.[2] The most fundamental of these transformations is the sequence of hydroxylations of **1**, which starts in the liver to give 25-hydroxycholecalciferol (**2**) and then continues in the kidney to give 24(*R*),25-dihydroxycholecalciferol (**3**) and 1α,25-dihydroxycholecalciferol (**4**). The latter is believed to be the hormonally active form of the vitamin and plays a central role in the maintenance of the calcium and phosphorus homeostasis in the blood plasma and in the induction of mineralization and calcium mobilization of the bones. In addition, the widespread distribution of receptors for **4** in many tissues not regarded to participate directly in mineral metabolism[3] seems to indicate that this hormone plays a much wider biological role than initially suspected. More recently, 1α,25-dihydroxycholecalciferol has also been found to induce differentiation of certain myeloid and leukemic cells,[4] thus suggesting a possible link between the vitamin D system and cancers.

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