Table IV. ^{1}H-NMR Spectral Data for Compounds 3,[a] δ (ppm)

product	base ring NH	base ring Me	base ring H5	base ring H6	sugar moiety H1′	sugar moiety (H2′, H2″)	sugar moiety H3′	sugar moiety H4′	sugar moiety (H5′, H5″)	carbonate moiety
3a	9.02 (s)	1.95 (s)	-	7.48 (s)	6.20 (dd)	2.49 (m)	5.30 (m)	4.20 (m)	3.95 (m)	3.84 (3 H, s)
3b	8.05 (s)	-	5.75 (d)	7.68 (d)	6.21 (dd)	2.49 (m)	5.29 (m)	4.20 (m)	3.94 (m)	3.82 (3 H, s)
3d	-	1.79 (s)	-	7.72 (s)	6.18 (t)	2.33 (m)	5.15[b]	4.05 (m)	3.62 (m)	5.15,[b] 7.42 (5 H, m)
3e	8.55 (s)	-	5.73 (d)	7.70 (d)	6.21 (t)	2.50 (m)	5.31 (m)	4.20 (m)	3.94 (m)	5.18 (2 H, s), 7.39 (5 H, m)
3g	8.50 (s)	1.94 (s)	-	7.42 (s)	6.19 (dd)	2.51 (m)	5.38 (m)	4.25 (m)	3.97 (m)	4.65 (1 H, dd), 4.98 (1 H, dd), 7.39 (1 H, dd)
3h	8.21 (s)	-	5.78 (d)	7.44 (d)	6.22 (t)	2.51 (m)	5.35 (m)	4.24 (m)	3.95 (m)	4.67 (1 H, dd), 4.99 (1 H, dd), 7.08 (1 H, dd)
3i	8.32 (s)	1.95 (s)	-	7.44 (s)	6.19 (dd)	2.50 (m)	5.30[b]	4.20 (m)	3.94 (m)	4.67 (2 H, m), 5.30,[b] 5.40 (1 H, dd), 5.93 (1 H, m)

product	base ring NH_2	base ring H2	base ring H8	sugar moiety H1′	sugar moiety (H2′, H2″)	sugar moiety H3′	sugar moiety H4′	sugar moiety (H5′, H5″)	carbonate moiety
3c	5.75 (s)	7.80 (s)	8.36 (s)	6.28 (dd)	2.49 (dd), 3.22 (m)	5.51 (m)	4.35 (m)	3.95 (m)	3.85 (3 H, s)
3f	5.98 (s)	7.80 (s)	8.32 (s)	6.27 (dd)	2.50 (dd), 3.21 (m)	5.52 (m)	4.36 (m)	3.91 (m)	5.20 (2 H, s), 7.40 (5 H, m)

[a] All samples measured in $CDCl_3$, except **3d** (DMSO-d_6). [b] Superimposed signals.

group is acetone oxime and *not* acetaldehyde, allowing, therefore, the 3′-*O*-vinyloxycarbonyl derivative of the nucleoside.

Conclusions

In conclusion, we have described a general, new and simple procedure for the synthesis of 3′-carbonates of pyrimidine and purine 2′-deoxynucleosides. In this method, no previous protection of the primary hydroxyl group is necessary, as has been traditionally described for preparation of these compounds.

Experimental Section

General. Amano PS lipase was purchased from Amano Pharmaceutical Co. Deoxynucleosides, **1**, were purchased from Aldrich Chemie. THF was distilled over $LiAlH_4$ in order to avoid moisture. Precoated TLC alumina sheets silica gel 60 F_{254} from Merck were used, and for column chromatography, Merck silica gel 60/230–400 mesh was used. Mp's were taken on samples in open capillary tubes using a Büchi melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1720-X FT spectrometer. NMR spectra were recorded using a Bruker AC300 spectrometer with $CDCl_3$, D_2O, or DMSO-d_6 as solvents. Mass spectra were obtained on a Hewlett-Packard 5897 A spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240 and a Carlo Erba Model 1108 instruments. Acetone *O*-[(alkyloxy)carbonyl]oximes **2** were prepared in almost quantitative yields by treating acetone oxime with the corresponding chloroformate and distilling under vacuum.

General Procedure for the Synthesis of Compounds 3a–i. **1a–c** (2 mmol), 2.1 mmol of **2a–d**, and 1 g of lipase Amano PS was suspended in 15 mL of THF (in the case of **1b**, 0.5 g of molecular sieve activated powder was added to remove hydrated water from starting nucleoside) under nitrogen atmosphere. The mixture was allowed to react at 60 °C and 250 rpm during the time indicated in footnote *a* of Table I. Then, the enzyme was filtered off and washed with MeOH, the residue was evaporated under vacuum, and the product was subjected to flash chromatography (AcOEt–MeOH, 100:1, or in the case of **3c** and **3f**, AcOEt–MeOH–H_2O, 100:10:1). Crystallization takes place from AcOEt or diethyl ether.

Characterization of Products 3a–g. Table I shows reaction time (footnote *a*), yield, mp, IR data, and optical rotations. Tables II and III present the ^{1}H- and ^{13}C-NMR spectral data and solvents used in their measurement.

3a: mass spectra (70 eV), *m/z* (relative intensity) 300 (M^+, 1), 175 (5), 126 (15), 99 (86), 69 (100), 59 (25). Anal. Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.33; N, 9.33. Found: C, 48.13, H, 5.50; N, 9.31.

3b: mass spectra (70 eV), *m/z* (relative intensity) 286 (M^+, 3), 175 (24), 99 (100), 69 (90), 59 (21). Anal. Calcd for $C_{11}H_{14}N_2O_7$: C, 46.15; H, 4.89; N, 9.79. Found: C, 45.88; H, 4.75; N, 9.91.

3c: mass spectra (70 eV), *m/z* (relative intensity) 309 (M^+, 2), 234 (5), 135 (100), 99 (12), 69 (25), 59 (9). Anal. Calcd for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.85; N, 22.65. Found: C, 46.82; H, 4.97; N, 22.48.

3d: mass spectra (70 eV), *m/z* (relative intensity) 376 (M^+, 1), 251 (6), 126 (11), 99 (41), 91 (100), 69 (27). Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.45. Found: C, 57.68; H, 5.54; N, 7.56.

3e: mass spectra (70 eV), *m/z* (relative intensity) 362 (M^+, 1), 251 (6), 112 (6), 99 (38), 91 (100), 69 (26). Anal. Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 4.97; N, 7.73. Found: C, 56.11; H, 4.65; N, 7.58.

3f: mass spectra (70 eV), *m/z* (relative intensity) 385 (M^+, 2), 234 (7), 135 (100), 99 (16), 91 (73), 69 (24). Anal. Calcd for $C_{18}H_{19}N_5O_5$: C, 56.10; H, 4.93; N, 18.18. Found: C, 55.86; H, 4.79; N, 18.32.

3g: mass spectra (70 eV), *m/z* (relative intensity) 312 (M^+, 3), 187 (8), 99 (100), 69 (87), 43 (20). Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.13; N, 8.97. Found: C, 50.28; H, 4.86; N, 9.21.

3h: mass spectra (70 eV), *m/z* (relative intensity) 298 (M^+, 2), 187 (19), 99 (100), 69 (75), 41 (11). Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.70; N, 9.40. Found: C, 48.40; H, 4.63; N, 9.51.

3i: mass spectra (70 eV), *m/z* (relative intensity) 326 (M^+, 1), 201 (9), 99 (100), 69 (70), 41 (32). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.52; N, 8.59. Found: C, 51.50; H, 5.45; N, 8.70.

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Selective Deprotection of Trialkylsilyl Ethers Using Fluorosilicic Acid

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Silyl ethers have become the protecting group of choice for the hydroxyl function. Their popularity is due in part to their ease of formation and removal and their stability to a wide range of reagents and reaction conditions. A variety of methods have been developed for the cleavage of the silicon–oxygen bond,[1] but few of these methods allow

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Table I. Competitive Cleavage Reactions between Bn-O-TBDMS (1) and Bn-O-TIPS (2)

expt	acid[a]	acid (mmol)	amine	amine (mmol)	solvent	temp (°C)	% ether (±2%)[b] TIPS	% ether (±2%)[b] TBDMS	time (h)	selectivity[c]
1	HF	0.500			CH_3CN	0	100	100	3.0	0
2	H_2SiF_6	0.083			CH_3CN	0	71	3	4.5	68
3	H_2SiF_6	0.104			CH_3CN	0	72	2	0.8	70
4	H_2SiF_6	0.104			CH_3CN	rt	61	1	0.3	60
5	H_2SiF_6	0.115	Et_3N	0.083	CH_3CN	0	87	20	21.5	67
6	H_2SiF_6	0.157	Et_3N	0.083	CH_3CN	0	86	4	6.5	82
7	H_2SiF_6	0.208	Et_3N	0.083	CH_3CN	0	82	1	1.3	81
8	H_2SiF_6	0.104			1% aq CH_3CN	0	81	1	4.8	80
9	H_2SiF_6	0.104			5% aq CH_3CN	0	83	1	7.5	82
10	H_2SiF_6	0.104			10% aq CH_3CN	0	85	0.5	8.0	84.5
11	H_2SiF_6	0.208	Et_3N	0.083	5% aq CH_3CN	0	82	0.5	6.0	81.5

[a] The reagents were added to 0.50 mmol of Bn-O-TBDMS and 0.50 mmol of Bn-O-TIPS as described in the Experimental Section. [b] Determined by capillary GC against an internal standard, see Experimental Section. [c] Selectivity = % 2 - % 1.

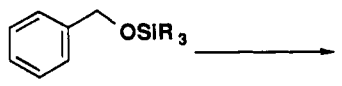
Table II. Stability of Hydroxyl Protecting Groups to Silyl Ether Cleaving Conditions

expt.	compd[a]	H_2SiF_6 (mmol)	Et_3N (mmol)	solvent (5.0 mL)	temp (°C)	% protected compound (±2%) Bn-O-TBDMS	% protected compound (±2%) prot. alcohol	time (h)
12	**9**	0.104		CH_3CN	0	0.5	81	0.8
13	**9**	0.208	0.083	CH_3CN	0	0	81	0.8
14	**9**	0.104		10% aq CH_3CN	0	0	80	6.0
15	**10**	0.104		CH_3CN	0	0.5	86	2.0
16	**10**	0.208	0.083	CH_3CN	0	0.1	66	0.8
17	**10**	0.104		10% aq CH_3CN	0	1	87	5.0
18	**11**	0.104		CH_3CN	0	0.5	21	0.8
19	**11**	0.083		CH_3CN	0	1	15	3.5
20	**11**	0.208	0.083	CH_3CN	0	0.1	11	0.8
21	**11**	0.104		10% aq CH_3CN	0	1	10	5.0
22	**12**	0.104		CH_3CN	0	0.1	100	0.8
23	**13**	0.104		CH_3CN	0	0.1	100	0.8

[a] For each experiment, the reagents were added to 0.50 mmol of Bn-O-TBDMS and 0.50 mmol of the protected alcohol as described in the Experimental Section.

for effective differentiation between two different trialkylsilyl moieties.[2] Selective deprotecting agents could be applied to advantage in complex synthetic sequences in which two protected hydroxyl groups must be unmasked at different stages of the synthesis. A pair of trialkylsilyl ethers of particular interest in synthetic chemistry are *tert*-butyldimethylsilyl (TBDMS) and triisopropylsilyl (TIPS) ethers. They are among the most popular of the many silyl ethers available for the reasons outlined above, and it has been demonstrated that both of these groups can be attached in a regioselective manner.[3] During the course of recent investigations, we demonstrated that aqueous fluorosilicic acid in acetonitrile would selectively cleave a TBDMS ether in the presence of a TIPS ether.[4] As discussed below, we have subsequently demonstrated the generality of this reagent for the selective removal of TBDMS ethers in the presence of TIPS and *tert*-butyldiphenylsilyl (TBDPS) ethers. The reagent also appears to be a general purpose cleaving agent for trialkylsilyl ethers in the presence of certain acid-labile protecting groups and has advantages over other deprotection methods.[5]

The optimum reaction conditions for the selective removal of the TBDMS group in the presence of the TIPS moiety were developed using a mixture of benzyl alcohol derivatives **1** and **2** (eq 1) and are summarized in Table I.



(1)

1: $R_3 = t\text{-Bu(Me)}_2$
2: $R_3 = (i\text{-Pr})_3$
3: $R_3 = t\text{-Bu(Ph)}_2$

4

Comparison of experiments 1 and 2 indicates that H_2SiF_6 is a more effective desilylating agent than HF. Also, when compared to the recommended HF deprotection conditions (95:5 CH_3CN:40% aqueous HF),[1a] the fluorosilicic acid conditions are less acidic, which means that certain acid-labile protecting groups can be retained under the deprotection conditions (vide infra). Experi-

(1) (a) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1991. (b) Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 5743. (c) Olsson, L. I. *Acta Pharm. Sue.* **1986**, *23*, 370. (d) Otera, J.; Niibo, Y.; Nozaki, H.; Chikada, S. *Synthesis* **1988**, 328. (e) Solladé-Cavallo, A.; Khiar, N. *Synth. Commun.* **1989**, *19*, 1335. (f) Bou, V.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 567. (g) Cort, A. D. *Synth. Commun.* **1990**, *20*, 757. (h) Cormier, J. F. *Tetrahedron Lett.* **1991**, *32*, 187.

(2) (a) Prakash, C.; Samir, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19. (b) Monger, S. J.; Parry, D. M.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 381. (c) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(3) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817.

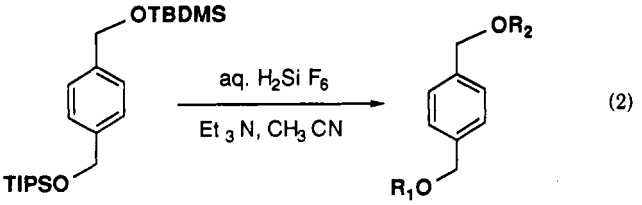
(4) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791.

(5) Fluorosilicic acid (H_2SiF_6) is not as acidic as traditional acid-deprotecting agents such as HF or HCl, and unlike tetrabutylammonium fluoride or alkali fluorides, it is not a threat to base-sensitive compounds. Fluorosilicic acid does not have the oxidizing properties of NBS or the strong nucleophilic properties of NaN_3.

(6) Refer to the following for information on the structure and reactivity of fluorosilicates. (a) Klanberg, F.; Muetterties, E. L. *Inorg. Chem.* **1968**, *7*, 155. (b) Rochow, E. G. In *Comprehensive Inorganic Chemistry*; Trotman-Dickenson, A. F., Ed.; Pergamon Press: New York, 1973; Vol. 1, pp 1465–1466. (c) Driesen, R. A. J.; Hulsbergen, F. B.; Vermin, W. J.; Reedijk, J. *Inorg. Chem.* **1982**, *21*, 3594. (d) Schomburg, D.; Krebs, R. *Inorg. Chem.* **1984**, *23*, 1378. (e) Corriu, R. J. P. *J. Organomet. Chem.* **1990**, *400*, 81.

ments 2 and 3 show that increasing the amount of fluorosilicic acid increases the reaction rate but does not affect selectivity significantly. The effects of additives and solvents were also surveyed. As seen in experiment 7, cleavage selectivity of fluorosilicic acid can be enhanced by adding an amine and increasing the quantity of acid. Triethylamine was found to give better results than pyridine, DMAP, or 2,6-di-*tert*-4-methylpyridine. Selectivity for the removal of TBDMS groups was also enhanced by increasing the concentration of water in the reaction mixture (experiment 10). However, the effects of an amine and water were not additive as demonstrated by experiment 11. Tetrahydrofuran and methylene chloride were also evaluated as solvents, but the reaction was sluggish in these solvents and appeared to be less selective under these circumstances.

A preparative-scale desilylation was performed after evaluating several reaction variables. Compound **5** was treated with H_2SiF_6 and Et_3N in CH_3CN at 0 °C (eq 2). After 1 h, the starting material had disappeared (99% by GC) and the reaction was quenched. Upon workup, the crude product mixture yielded 1% starting material **5**, 75% TIPS-protected product **6**, 17% diol **7**, and 7% TBDMS derivative **8** as indicated by GC. Purification by flash column chromatography provided alcohol **6** in 70% isolated yield.



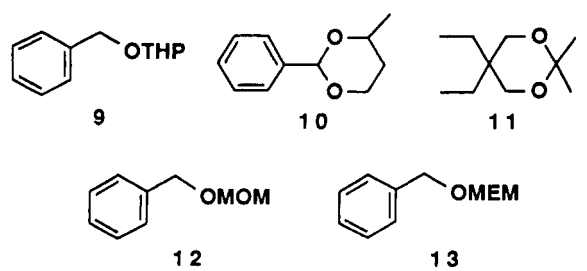
(2)

5

	R_1	R_2
6	TIPS	H
7	H	H
8	H	TBDMS

Having successfully differentiated between a TBDMS and a TIPS ether, the cleavage of TBDPS ethers with fluorosilicic acid was investigated. When compounds **1**, **2**, and **3** were treated separately with 1.0 F^- equiv of fluorosilicic acid in CH_3CN at 0 °C, 75% of the TBDMS ether was removed in 20 min. The TIPS ether required 20 h to reach 75% desilylation, while the TBDPS ether required 5 days to reach this point. This result indicates that this reagent can readily differentiate between these three common silyl derivatives. As expected, when a mixture of silyl ethers **1** and **3** was treated with H_2SiF_6 in CH_3CN at 0 °C, the TBDMS ether was deprotected completely in 50 min, leaving the TBDPS derivative intact.

A second set of experiments was performed in which TBDMS ether **1** was deprotected in the presence of various acid-labile protecting groups (structures **9**–**13**) to determine the stability of these protecting groups to the desilylation conditions. The results are listed in Table II. The apparent order of stability is MEM ≈ MOM ≫ benzylidene > THP ≫ acetonide.



9 **10** **11**

12 **13**

Although this method has not been completely optimized, we have demonstrated the utility of fluorosilicic acid for the selective deprotection of a variety of silyl ether and acid-labile protecting groups. The activity of the desilylating reagent cannot be attributed to the HF buffering effect of H_2SiF_6 according to the equilibrium expression in eq 3. For example, in experiment 2, 0.083 mmol of H_2SiF_6, which could release at most 0.17 mmol of HF, readily removes the silyl protecting group, whereas 0.500 mmol of HF (experiment 2) failed to effect desiylation in the same period of time.

$$H_2SiF_6 \rightleftharpoons HSiF_5 + HF \rightleftharpoons SiF_4 + 2HF \qquad (3)$$

An alternative mechanism for the desilylation process has a pentavalent silicon derivative acting as a Lewis acid, accepting the basic oxygen of the silyl ether as a sixth ligand, thus activating the silicon–oxygen bond to attack by fluoride or water. Formation of the sterically demanding octahedral silicon complex would favor less sterically demanding ROTBDMS as a ligand over the bulkier ROTIPS derivative. Water and amines may affect the deprotection by shifting the equilibrium and/or by acting as labile ligands on silicon. Our study suggests that fluorosilicic acid derivatives will be able to differentiate between other silyl ethers of a similar or greater difference in steric bulk. Future research will explore the capabilities of organofluorosilicates as selective deprotecting agents for silyl ethers.

Experimental Section

Stock solutions of the protected alcohols and a stock solution of naphthalene were made to be 0.10 M in hexane. All deprotection reactions were monitored by capillary gas chromatography. A 200-μL sample was neutralized in 1.5 mL of saturated Na_2CO_3 and then extracted with 1.5 mL of ether. The organic phase was assayed by GC using naphthalene as an internal standard. Flash column chromatography was performed using silica gel. ^1H NMR data were recorded at 200 MHz.

General Deprotection Procedure. In a typical deprotection reaction using H_2SiF_6, 5.0 mL of the Bn-O-TBDMS (Bn = benzyl) solution (0.50 mmol), 5.0 mL of the Bn-O-TIPS solution (0.50 mmol), and 5.0 mL of the naphthalene solution (0.50 mmol) were mixed in a heavy-walled polypropylene centrifuge tube. The hexane was removed at reduced pressure. Acetonitrile (5.0 mL) was then added. The mixture was stirred magnetically until homogeneous, and three 0.2-μL GC injections were made to determine the response factors. The tube was immersed in an ice bath and magnetic stirring was resumed. After the temperature equilibrated, 38.6 μL of H_2SiF_6 (0.104 mmol, 1.25 F^- equiv of a ~31% aqueous solution, d = 1.256) was added via a micropipette with a polyethylene tip. The reaction was monitored by GC. A typical deprotection reaction with 10% aqueous acetonitrile used as the solvent was performed in the same manner except that 4.5 mL of acetonitrile and 0.5 mL of water were used. A typical deprotection reaction using triethylamine was performed in the same manner except that 11.8 μL of Et_3N (0.0833 mmol, 0.167 equiv) was added before sampling for response factors and 77.2 μL of H_2SiF_6 (0.208 mmol, 2.50 F^- equiv) was used.

Preparation of Trialkylsilyl Derivatives of Benzyl Alcohol. Trialkylsilyl ethers **1**, **2**, and **3** were prepared by Corey's procedure[7] and purified by flash column chromatography (hexane) to give clear colorless oils.

[(*tert*-Butyldimethylsiloxy)methyl]benzene (1): 7.85 g, 88% yield, 99% pure by GC; IR (CCl_4) cm^{-1} 2957 (m), 2928 (m), 2858 (m), 1472 (m), 1461 (m), 1254 (m), 1110 (m), 1097 (m), 1010 (m), 841 (s); ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ar H), 4.73 (s, 2 H, -CH_2-), 0.93 (s, 9 H, Si-*t*-Bu), 0.08 (s, 6 H, $SiCH_3$).

[(Triisopropylsiloxy)methyl]benzene (2): 9.25 g, 91% yield, >99% pure by GC; IR (CCl_4) cm^{-1} 2944 (s), 2865 (s), 1463 (m), 1453 (m), 1112 (m), 1101 (m), 882 (m); ^1H NMR ($CDCl_3$) δ

(7) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

7.27-7.73 (m, 5 H, Ar H), 4.85 (s, 2 H, -CH_2-), 1.24-1.06 (m, 21 H, *i*-Pr).

[(*tert*-Butyldiphenylsiloxy)methyl]benzene (3): 9.68 g, 91% yield, 98% pure by GC; IR (CCl_4) cm^{-1} 2962 (m), 2931 (m), 2859 (m), 1474 (m), 1428 (m), 1113 (s), 1070 (m), 1028 (m); ^1H NMR ($CDCl_3$) δ 7.69-7.74 (m, 5 H, benzyl Ar H), 7.34-7.42 (m, 10 H, Si Ar H), 4.79 (s, 2 H, $PhCH_2O$), 1.11 (s, 9 H, *t*-Bu).

4-[(*tert*-Butyldimethylsiloxy)methyl][(triisopropylsiloxy)methyl]benzene (5). Methyl 4-(hydroxymethyl)benzoate (9.73 g, 58.6 mmol) was protected using TBDMS-Cl by Corey's procedure[7] to give 17.6 g of methyl 4-[(*tert*-butyldimethylsiloxy)methyl]benzoate (100% yield, 99% pure by GC) after workup and without further purification: oil; IR (CCl_4) cm^{-1} 2955 (s), 2930 (s), 2858 (s), 1728 (s), 1278 (s), 1258 (s), 1103 (s), 1091 (s), 840 (s); ^1H NMR ($CDCl_3$) δ 7.99 (d, 2 H, Ar H, J = 8.3 Hz), 7.37 (d, 2 H, Ar H, J = 8.3 Hz), 4.77 (s, 2 H, $ArCH_2$), 3.89 (s, 3 H, OCH_3), 0.93 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$). The TBDMS-protected material (16.34 g, 57.55 mmol) was dissolved in 70 mL of ether and stirred magnetically under N_2 while a $LiAlH_4$ solution (29 mL, 1.0 M in Et_2O, 29 mmol) was added via syringe over 15 min at a rate which maintained a mild reflux. The reaction mixture was quenched with 200 mL of H_2O after 1 h and then neutralized with 6 M HCl. The aqueous phase was extracted with 3 × 100 mL of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 11.75 g of 4-[(*tert*-butyldimethylsiloxy)methyl](hydroxymethyl)benzene (8) (97% pure by GC, 88% yield): oil; IR (CCl_4) cm^{-1} 3619 (m), 2956 (s), 2931 (s), 2858 (s), 1255 (s), 1091 (s), 840 (s); ^1H NMR ($CDCl_3$) δ 7.30 (s, 4 H, Ar H), 4.72 (s, 2 H, $ArCH_2OSi$), 4.65 (s, 2 H, $ArCH_2OH$), 0.92 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$).

4-[(*tert*-Butyldimethylsiloxy)methyl](hydroxymethyl)benzene (11.2 g, 43.7 mmol) was protected using TIPS-Cl by Corey's procedure.[7] The crude product was purified by flash column chromatography (hexane) to give 16.8 g of 5 (92% pure by GC, 87% yield): oil; IR (CCl_4) cm^{-1} 2947 (s), 2891 (s), 2867 (s), 1089 (s), 839 (s); ^1H NMR ($CDCl_3$) δ 7.28 (d, 4 H, Ar H, J = 1.1 Hz), 4.81 (s, 2 H, $ArCH_2OTIPS$), 4.71 (s, 2 H, $ArCH_2OTBDMS$), 1.13-1.03 (m, 21 H, *i*-Pr), 0.92 (s, 9 H, *t*-Bu), 0.75 (s, 6 H, $SiCH_3$).

Deprotection of Disilyl Ether 5. Compound 5 (10.0 mmol, 4.09 g), Et_3N (1.67 mmol, 232 μL), and 100 mL of CH_3CN were mixed in a 175-mL polyethylene bottle. The bottle was immersed in an ice bath and the solution was stirred magnetically while the temperature equilibrated. H_2SiF_6 (4.17 mmol, 1.54 mL of a ~31% aqueous solution, 2.50 F^- equiv) was added and the progress of the reaction was monitored by GC. At 99% completion (60 min), 10 mL of saturated $NaHCO_3$ was added. After evaporating the CH_3CN at reduced pressure, the concentrate was diluted with 100 mL of EtOAc and extracted with 3 × 50 mL of brine. The combined organic phases were dried ($MgSO_4$) and evaporated at reduced pressure to give a white solid in a colorless oil. Hexane was added to dissolve the soluble oil, which was then separated from the insoluble solid (pure diol 7) by filtration. Upon concentration at reduced pressure, the hexane solution provided 2.88 g of an oil which was 77% compound 6 by GC (75% crude yield). Other constituents of the oil included compound 8, *tert*-butyldimethylsilanol, triisopropylsilanol, *tert*-butyldimethylsilyl fluoride, triisopropylsilyl fluoride, and starting material 5. Purification by flash column chromatography (95:5 hexane:ether) yielded 2.05 g of alcohol 6 as a clear colorless oil (99% pure by GC, 70% yield): IR (CCl_4) cm^{-1} 3617 (w), 2944 (s), 2867 (s), 1117 (m), 1096 (m), 1069 (m), 1014 (m), 883 (m); ^1H NMR ($CDCl_3$) δ 7.32 (s, 4 H, Ar H), 4.82 (s, 2 H, $ArCH_2OSi$), 4.66 (s, 2 H, $ArCH_2OH$), 1.67 (s, 1 H, OH), 1.13-1.03 (m, 21 H, Si-*i*-Pr).

2-(Benzyloxy)tetrahydropyran (9). THP ether 9 was prepared from benzyl alcohol (20.0 mmol, 2.16 g) by Bernady's procedure[8] to give give 3.38 g of product (87% yield, >99% pure by GC) after workup and purification by flash column chromatography (hexane): oil; IR (CCl_4) cm^{-1} 2946 (s) 1455 (m), 1201 (m), 1037 (m), 1028 (m); ^1H NMR ($CDCl_3$) δ 7.28-7.39 (m, 5 H, Ar H), 4.80 (d, 1 H, $ArCH_2$, J = 12.0 Hz), 4.51 (d, 1 H, $ArCH_2$, J = 12.0 Hz), 4.72 (t, 1 H, -OCHO-, J = 3.6 Hz), 3.85-4.01 (m, 1 H, equatorial -CH_2O-), 3.46-3.62 (m, 1 H, axial -CH_2O-), 1.51-1.88 (m, 6 H).

***cis*-4-Methyl-2-phenyl-1,3-dioxane (10).** 2,4-Butanediol (10.9 mmol, 1.06 g), benzaldehyde (13.0 mmol, 1.38 g), TsOH (1.09 mmol, 0.206 g), and $MgSO_4$ (21.7 mmol, 2.61 g, 2.00 equiv) were combined in 10 mL of CH_2Cl_2. After the solution was stirred magnetically at rt for 4.75 h, the reaction mixture was filtered, and 20 mL of CH_2Cl_2 was added. The organic phase was extracted 3 times with 20 mL of saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated at reduced pressure. Purification of the crude product by flash column chromatography (hexane) gave 1.79 g of benzylidene 10 as an oil (91% yield, 99% pure by GC): IR (CCl_4) cm^{-1} 2976 (s), 2854 (s), 1376 (s), 1357 (s), 1247 (s), 1167 (s), 1114 (s), 1062 (s), 1028 (s), 999 (s), 968 (m); ^1H NMR ($CDCl_3$) δ 7.31-7.52 (m, 5 H, Ar H), 5.51 (s, 1 H, PhCH), 4.21-4.30 (m, 1 H, CHMe), 3.89-4.08 (m, 2 H, -OCH_2-), 1.70-1.90 (m, 1 H, equatorial MeCHCH_2), 1.43-1.57 (m, 1 H, axial MeCHCH_2), 1.32 (d, 3 H, Me, J = 6.2 Hz).

5,5-Diethyl-2,2-dimethyl-1,3-dioxane (11). Acetonide 11 was prepared from 2,2-diethyl-1,3-propanediol (50.0 mmol, 6.61 g) by Schmidt's procedure[11] (7.75 g, 90% yield, >99% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2967 (s), 2863 (m), 1386 (m), 1370 (m), 1199 (s), 1099 (s), 836 (m); ^1H NMR ($CDCl_3$) δ 3.56 (s, 4 H, -OCH_2C-), 1.41 (q, 4 H, CCH_2Me, J = 7.6 Hz), 1.40 (s, 6 H, MeCMe), 0.80 (t, 6 H, $MeCH_2C$, J = 7.5 Hz).

[(Methoxymethoxy)methyl]benzene (12). MOM ether 12 was prepared from benzyl alcohol (50.0 mmol, 5.41 g) by Fuji's procedure[9] (7.23 g, 91% yield, 95% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2950 (m), 2881 (m), 1455 (m), 1211 (m), 1150 (s), 1102 (s), 1050 (s), 1026 (s), 915 (m); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H, Ar H), 4.71 (s, 2 H, -OCH_2O-), 4.60 (s, 2 H, $ArCH_2$), 3.42 (s, 3 H, Me).

[[(Methoxyethoxy)methoxy]methyl]benzene (13). MEM ether 13 was prepared from benzyl alcohol (26.8 mmol, 2.89 g) using MEM-Cl by Corey's procedure[10] (5.57 g, 100% yield, 94% pure by GC) after workup without further purification: oil; IR (CCl_4) cm^{-1} 2929 (s), 2896 (s), 1450 (m), 1110 (s), 1048 (s); ^1H NMR ($CDCl_3$) δ 7.05 (m, 5 H, Ar H), 4.82 (s, 2 H, -OCH_2O-), 4.63 (s, 2 H, $ArCH_2$), 3.75 (m, 2 H, $MeOCH_2CH_2O$), 3.57 (m, 2 H, $MeOCH_2CH_2O$), 3.41 (s, 3 H, Me).

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Efficient Synthesis of 2-Chloro-, 2-Bromo-, and 2-Iodoindole

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Halogenation of simple indoles takes place preferentially at the 3-position,[1] and high-yielding syntheses of 3-chloro-,[2] 3-bromo-,[2-4] and 3-iodoindole[4-6] are today available. In

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