with 100 mL of CH_2Cl_2 and once with 100 mL of ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel, eluting with 50% EtOAc/hexane, to afford 3.36 g (88%) of the desired ketone (-)-**3b**. $[\alpha]_D = -51.3$ ($c = 1$, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.11; H, 7.20; N, 4.90. ^1H NMR in $CDCl_3$ was identical with racemic **3b**.

Ethyl (+)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-3b). As for (-)-**3b**, 5.9 g (15.7 mmol) of **14**, 1.98 g (23.5 mmol) of $NaHCO_3$, and 12.5 mL (24.4 g, 156.7 mmol) of iodoethane in 31 mL of DMF gave 3.96 g (89%) of (+)-**3b**. $[\alpha]_D = +53.4$ ($c = 1$, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.50; H, 7.46; N, 4.72. ^1H NMR in $CDCl_3$ was identical with racemic **3b**.

Determination of Optical Purity of 13 and 14. To a suspension of 63 mg (0.17 mmol) of **13** in 1.5 mL of CH_2Cl_2 at 0 °C was added 22 μL (0.17 mmol) of isobutyl chloroformate. After being stirred for 30 min, 37 μL (0.34 mmol) of *N*-methylmorpholine was added and the mixture stirred for another 2 h. Another 11 μL of isobutyl chloroformate was added and the mixture stirred for another 20 min, and then 22 μL of (*R*)-α-methylbenzylamine was added and the mixture stirred overnight while warming to rt. TLC (10% HOAc/EtOAc) showed complete reaction. To the reaction mixture was added 10 mL of CH_2Cl_2 and 10 mL of 10% aqueous $NaHSO_4$, and the aqueous layer was separated and extracted twice with 5 mL each of CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. GC[8] of the crude material shows a 99:1 ratio of epimers (98% ee). By use of the same experimental conditions, **14** showed a >99:<1 ratio of epimers (by GC,[8] >99% ee).

Acknowledgment. We thank the Physical Chemistry Department of Lilly Research Laboratories for spectral data and elemental analyses, as well as Jack Campbell for his assistance with the hydrogenations.

Synthesis of 1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC). A Promising Agent for the Treatment of Acquired Immune Deficiency Syndrome

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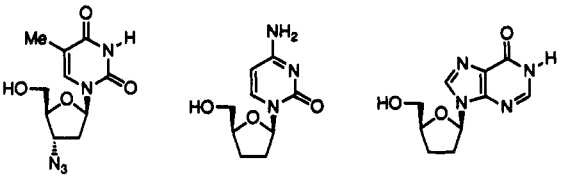
A new and practical synthesis of a fluorinated analogue of 2',3'-dideoxycytidine (ddC), 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC), is described. The key feature in the synthesis is the use of the selectively protected 2,4,5-trihydroxypentanoic acid derivative **15** as a chiral pool synthon.

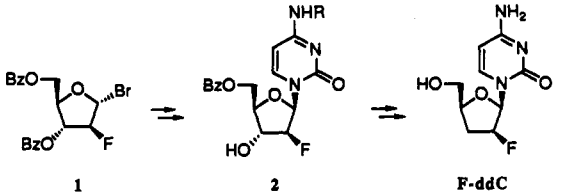
A variety of fluorinated 2',3'-dideoxynucleosides has been prepared by several groups[1] in order to seek out agents that effectively inhibit HIV reverse transcriptase. Other reverse transcriptase inhibitors, such as 3'-deoxy-3'-azidothymidine (AZT),[2] 2',3'-dideoxycytidine (ddC),[3] and 2',3'-dideoxyinosine (ddI)[4] have thus far proven to be the most effective therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS).[5] As part of our program concerned with finding new ways to prepared dideoxynucleosides with anti-HIV activity,[6] a fluorinated analogue of ddC, 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC) was prepared. F-ddC has shown significant anti-HIV activity[1b-d] and potentially could show diminished clinical side effects.



AZT ddC ddI

Results and Discussion

In the original preparation of F-ddC,[1a-c] protected 1-(2-deoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine **2** was prepared from 3,5-*O*-dibenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**1**),[7] and then the 3-hydroxy group was removed by Barton's deoxygenation reaction.



1 2 F-ddC

The requirement for tributyltin hydride in the deoxygenation step is especially vexing as it results in tin contam-

(1) (a) Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1743. (b) Martin, J. A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. *J. Med. Chem.* **1990**, *33*, 2137. (c) Watanabe, K. A.; Harada, K.; Zeidler, J.; Matulic-Adamic, J.; Takahashi, K.; Ren, W.-Y.; Cheng, L.-C.; Fox, J. J.; Chou, T.-C.; Zhu, Q.-Y.; Polsky, B.; Gold, J. W. M.; Armstrong, D. *J. Med. Chem.* **1990**, *33*, 2145. (d) Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150. (e) Fleet, G. W. J.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625. (f) Puech, F.; Gosselin, G.; Imbach, J. L. *Tetrahedron Lett.* **1989**, *30*, 3171.

(2) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.

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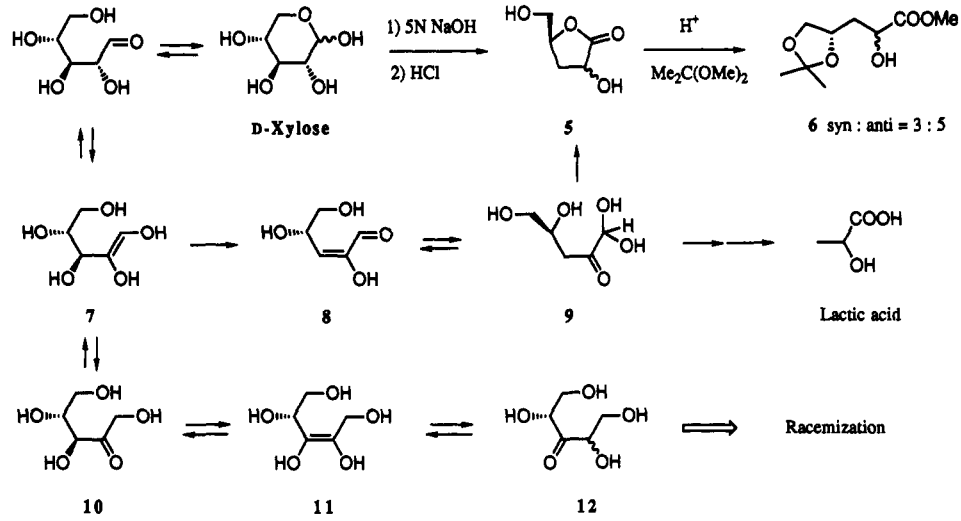
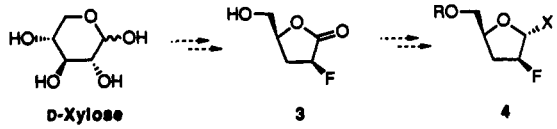


ination of the final product. Additional steps are required to ensure that the final product is free from this contamination. We also felt that it should be better to introduce cytosine in a later stage since it is the most expensive ingredient of F-ddC. We, therefore, decided to prepare compound 4, the complete sugar portion of F-ddC, first and then couple it with cytosine to produce F-ddC. D-Xylose, the cheapest pentose of all, was chosen as the starting material. We planned to remove the C-3 hydroxy group in an early stage and oxidize to the corresponding γ-lactone in order to secure the requisite five-membered ring. The presence of a carbonyl group at the C-1 position would also help the introduction of fluorine at the C-2 position.

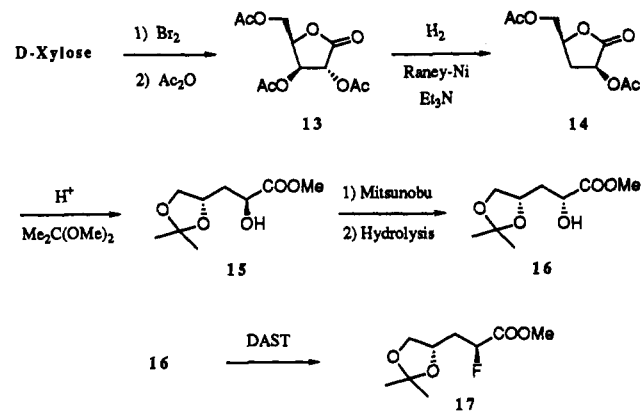


At first we employed the alkaline degradation of D-xylose,[8] in which the 3-hydroxy group (β from the aldehyde in the acyclic form) is eliminated to form the keto aldehyde 8 followed by (presumably) a hydride shift from C-1 to form 2,4,5-trihydroxypentanoic acid, which lactonizes to 5. A major byproduct was lactic acid, which formed via a retro-aldol reaction. After treatment of the crude degradation products with 2,2-dimethoxypropane, the suitably protected ester 6 was obtained in 30% yield after distillation. Even though the stereochemical integrity at C-2 was lost, deoxygenation at C-3 and oxidation at C-1 have already been achieved. Since the stereochemistry at C-2 can be taken care of in a later stage by epimerization and because this process is so cheap, we thought it could be developed. However the enantiomeric purity of 6 at C-4 was found to be only 77%! This was improved to 84% by using 10 N NaOH at room temperature instead of 5 N NaOH at 55 °C in the degradation step, but the process is nevertheless rendered useless by this unanticipated partial racemization. Using less basic conditions such as 3 N NaOH or CaO caused more racemization. Presumably, because the elimination of the 3-hydroxy group (7 to 8) is a rate-determining step and requires strongly basic conditions, under weakly basic conditions the transformation is sluggish and further isomerization via the 2-keto form 10 to the 3-keto form 12 becomes a major path that leads to racemization.

(8) Nef, J. U. *Ann.* **1910**, *376*, 46. Other D-pentoses also can be used instead of D-xylose.

Thus, we took a different approach. Oxidation of D-xylose with bromine followed by acetylation gave crystalline tri-*O*-acetyl-D-xylono-1,4-lactone 13 in 65% yield. Catalytic hydrogenation of 13 in ethyl acetate and triethylamine using Raney-Ni as catalyst afforded diacetate 14[9] in 92% yield. There is a small amount of the epimeric acetate detected by NMR, and it can be removed by recrystallization. Other D-pentoses, such as arabinose, ribose, or lyxose, can be used as the starting material according to the cited paper.[9]

The diacetate 14 was treated with 2,2-dimethoxypropane and methanol in the presence of a catalytic amount of *p*-TsOH·H_2O to afford the alcohol 15 in 88.5% yield. Inversion of the stereochemistry at C-2 by Mitsunobu reaction[10] followed by the treatment of the alcohol 16 (74% from 15) with (diethylamino)sulfur trifluoride (DAST) afforded the anti isomer 17. However, the use of these reagents could be troublesome for a larger scale preparation and may not be economically feasible.



Therefore, the alcohol 15 was converted to the mesylate and the mesyloxy group was displaced by fluoride ion to afford the corresponding fluoride 18 as a mixture of the C-2 epimers (syn:anti = 8–9:1) in 55.4% yield from 15 (29.4% from D-xylose). The desired anti isomer 17 was then enriched (25% de, syn:anti = 3:5) by the treatment of 18 with NaOMe (5–7 mol %) in toluene.[11] Further enrichment of the anti isomer 17 was achieved by fractional distillation. The early fractions containing the syn isomer as a major component were isomerized to the anti-enriched

(9) Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scan.* **1981**, *B35*, 155.
(10) Mitsunobu, O. *Synthesis* **1981**, 1.
(11) In a small scale, the diastereomers can be easily separated at the lactone 20 stage by chromatography.

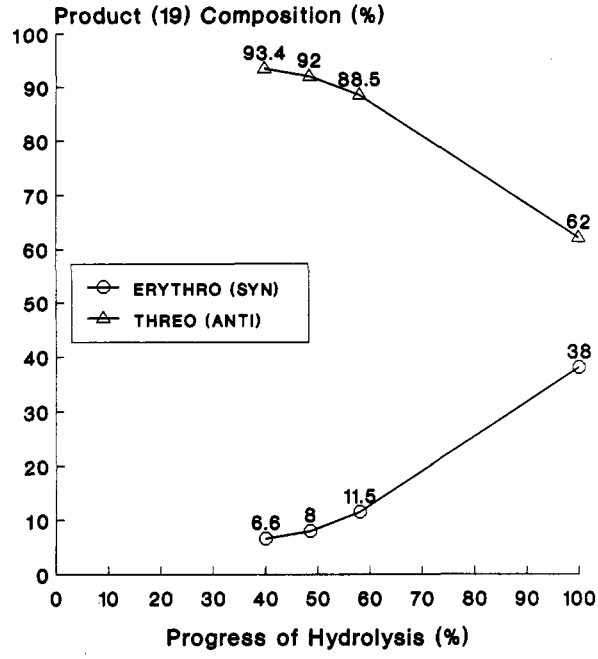
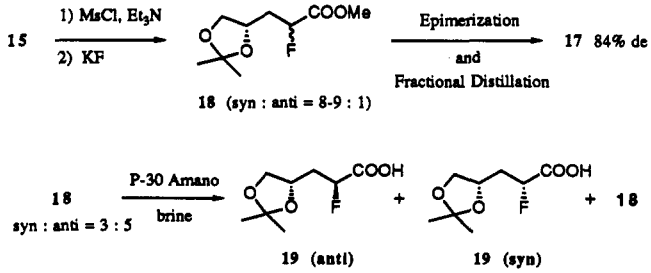


Figure 1. Lipolysis of (*S,S**)-α-fluoro-2,2-dimethyl-1,3-dioxane-4-propanoic acid methyl ester (18).

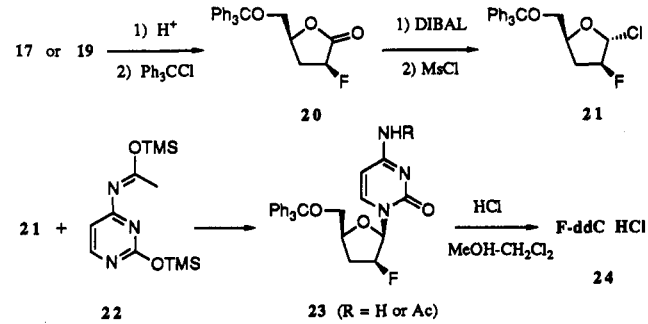
material by NaOMe. The anti isomer 17 of 83.5% de was thus obtained in 9.7% overall yield from D-xylose. If the overall yield is corrected for the amount of 18 recovered (ca. 29% de), it becomes 24.2%. The anti isomer 17 of still higher diastereomeric excess (such as 94% de) was originally prepared by distillation, but later we found it was not necessary since purification can be easily achieved in a later step. The fluoride 17 prepared by this method was found to have at least 99.6% ee at C-4 by the GLC analysis of the corresponding Mosher ester of the alcohol prepared by $LiAlH_4$ reduction of 17.[12]

Alternatively, the anti isomer was enriched by enzymatic hydrolysis[13] of 18 (syn:anti = 3:5). The anti isomer of the corresponding acid 19 of 80.4% de was obtained in 42% yield when brine was used as the reaction medium. A water–*tert*-butyl alcohol medium[14] also gave a similar result. Media with DMSO,[15] DMF, or no additive did not give satisfactory results (only 60–70% de). The surviving ester rich in the syn isomer could be redigested after alkaline reequilibration.

The diastereomeric excess of fluoro acid 19 produced by this enzymatic hydrolysis showed the dependence on the extent of hydrolysis depicted in Figure 1.



The anti isomer 17 was lactonized on treatment with 2.5 mol % of 1 N HCl (ca. 1.5 equiv of water) under reduced pressure, and the resulting free hydroxy group of 3 was protected as a triphenylmethyl ether. The protected lactone 20 was reduced by DIBAL in CH_2Cl_2 to give the β-lactol, which was converted stereospecifically to the α-chloride 21 by mesyl chloride.[16] The coupling of 21 with bis-TMS-cytosine in refluxing chloroform gave an anomeric mixture of nucleosides 23 (R = H) (α:β = 1:5). This anomeric ratio was significantly improved (α:β = 1:>15) by using bis-TMS-*N*-acetylcytosine 22 instead of bis-TMS-cytosine.[17] The protecting groups were removed by treatment with concd HCl in methanol–dichloromethane, resulting in precipitation of pure F-ddC hydrochloride salt 24,[18] which on treatment with basic ion-exchange resin produced F-ddC. Recrystallization from ethanol afforded crystalline F-ddC in 40.2% yield based on the lactone 20 and 7.9% overall yield from D-xylose.



Since the base portion is installed in the last stage of the synthesis, the overall yield of F-ddC based on cytosine (the most expensive ingredient) is significantly improved over the approaches employing Barton's deoxygenation reaction and this procedure can easily be extended to the preparation of other 2′β-fluoronucleosides.

The ready availability of the selectively protected 2,4,5-trihydroxypentanoic acid derivatives of defined stereochemistry, such as 15, either from a D- or L-pentose (preferably, D-xylose or L-arabinose), coupled with Mitsunobu inversion provides chiral pool synthons with the promise of broad utility.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian XL-200 and XL-400 instruments and are reported in parts per million from tetramethylsilane(s). Electron-impact mass spectra were determined on a VG ZAB-1F instrument at 70 eV. Elemental analyses were carried out in our Microanalytical Laboratory under the direction of Dr. F. Scheidl.

(4*S-rac*)-α-Hydroxy-2,2-dimethyl-1,3-dioxolane-4-propanoic Acid Methyl Ester (6, 77% ee at C-4). A mixture of D-xylose (750 g, 5.0 mol) and 5 N NaOH (3.0 L, 15 mol) was stirred at 55 °C for 2.5 h. After being cooled with an ice–water bath, the mixture was acidified with 1.2 L of concd HCl and concentrated. The residue was further dried at 80 °C under reduced pressure (aspirator) for 30 min and dissolved in 750 mL of methanol while still hot. The salt was removed by filtration and washed with 1 L of methanol. The methanolic solutions were combined, concentrated, and dried at 80 °C under reduced pressure (aspirator). The residue was diluted with DMF (450 mL) and 2,2-dimethoxypropane (1.65 L, 13.4 mol) followed by dropwise

(12) The corresponding C-4 epimers were prepared from L-arabinose using a similar procedure. The Mosher acid purchased from Aldrich was assumed to have 100% ee.

(13) Kalaritis, P.; Regenye, R. W. *Org. Synth.* **1990**, *69*, 10.

(14) Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *38*, 4639.

(15) Björkling, F.; Boutelje, J.; Hjalmarsson, M.; Hult, K.; Norin, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1041.

(16) The 2-fluorine at the C-2 position has a strong directing effect on the incoming nucleophile at the anomeric center. See refs 7b and c. In case of a 2,2-difluoride, the corresponding mesylate was isolated: Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406.

(17) The β-selectivity was shown to be strongly influenced by the base portion. The coupling of the bromide 1 with bis-TMS-thymine gave nucleosides with high β-selectivity (α:β = 1:19);[7c] however, the same bromide 1 reacted with bis-TMS-cytosine under the same conditions to give the α to β ratio of only 1:6.4.[1b]

(18) Pure F-ddC hydrochloride salt 24 was also isolated even from 17 of only 71% de by this procedure without any difficulties.

addition of concd H_2SO_4 (37.5 mL). Then, the mixture was refluxed for 3 h. After being cooled, Na_2CO_3 (75 g), EtOAc (2 L), and water (2 L) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated at 80 °C under reduced pressure. The residue was distilled under high vacuum to give 335 g (32.8% yield) of 6; bp 95–105 °C (0.3 mmHg).

The enantiomeric purity of 6 at C-4 was determined by the following method. A sample of 6 was converted to fluoro ester 18 and then reduced to the corresponding fluoro alcohol with $LiAlH_4$. The Mosher ester derived therefrom was analyzed by capillary GC.

Tri-*O*-acetyl-D-xylono-1,4-lactone (13). After a solution of D-xylose (300 g, 2.0 mol) in 800 mL of water was cooled with an ice–water bath, K_2CO_3 (340 g, 2.32 mol) was added in portions, keeping the temperature below 25 °C. Then, bromine (120 mL, 2.16 mol) was added dropwise over 2 h, keeping the temperature between 4 and 11 °C. After being stirred at that temperature for 30 min, the mixture was stirred at room temperature overnight. The reaction was quenched by careful addition of 95% formic acid (20 mL) over 20 min. After being stirred for 30 min, the mixture was concentrated at 50 °C under reduced pressure. The residual water was removed azeotropically with 200 mL of acetic acid at 50 °C under reduced pressure (aspirator). The residue was then diluted with acetic acid (400 mL) and heated to 50 °C. Then, acetic anhydride (1.8 L, 19.1 mol) was added dropwise over 2 h, keeping the temperature between 50–55 °C. After the mixture was stirred at 50 °C overnight, the salt was removed by filtration and washed with 400 mL of warm acetic acid. The combined filtrate and washings were concentrated at 50 °C under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and water, and the resulting mixture was neutralized with Na_2CO_3. The organic layer was separated and the aqueous layer was back-extracted. The combined extracts were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was recrystallized from EtOAc–hexane to afford 357 g (65.1% yield) of 13: mp 97–98 °C (lit.[9] mp 94–95 °C); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 2.14 (s, 3 H), 2.19 (s, 3 H), 4.27 (dd, J = 12.8 and 2.9 Hz, 1 H), 4.39 (dd, J = 12.8 and 2.9 Hz, 1 H), 5.00 (dt, J = 7.7 and 2.9 Hz, 1 H), 5.62 (t, J = 7.8 Hz, 1 H), 5.69 (d, J = 7.9 Hz, 1 H); IR (KBr) 1805, 1792, 1750 cm^{-1}; MS m/e 275 (MH^+). Anal. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 47.97; H, 5.01.

Di-*O*-acetyl-3-deoxy-D-arabino-1,4-lactone (14). To a solution of 13 (274 g, 1.0 mol) in EtOAc (2.5 L) was added freshly prepared Raney-Ni (27 g) and triethylamine (220 mL, 1.58 mol), and the mixture was immediately pressurized with 1000 psi of hydrogen. After 24 h at 30 °C, the catalyst was removed by filtration (caution: fire hazard!) and washed with EtOAc. The combined filtrate and washings were washed with water, and the aqueous layer was back-extracted with EtOAc. The combined extracts were then washed with 1 N HCl, saturated $NaHCO_3$, and brine and then dried and concentrated to afford 199 g (92.0%) of 14.

This crude diacetate 14 was used for the next step without further purification. An analytical sample was prepared by recrystallization from EtOAc–hexane: mp 69–70 °C (lit.[9] mp 69–71 °C); ^1H NMR ($CDCl_3$) δ 2.07 (dt, J = 12.8 and 10.3 Hz, 1 H), 2.12 (s, 3 H), 2.18 (s, 3 H), 2.78 (ddd, J = 12.8, 8.8, and 6.0 Hz, 1 H), 4.19 (dd, J = 12.5 and 5.8 Hz, 1 H), 4.38 (dd, J = 12.5 and 3.1 Hz, 1 H), 4.68 (m, 1 H), 5.51 (dd, J = 10.3 and 8.8 Hz, 1 H); IR (KBr) 1791, 1745 cm^{-1}; MS m/e 143 ($M^+ - CH_2OAc$). Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 49.55; H, 5.54.

(*S*,*S)-α-Hydroxy-2,2-dimethyl-1,3-dioxolane-4-propanoic Acid Methyl Ester (15).** A mixture of 14 (199 g, 0.92 mol), methanol (400 mL), 2,2-dimethoxypropane (200 mL), and *p*-toluenesulfonic acid monohydrate (19 g) was stirred at 30 °C overnight. Then, more 2,2-dimethoxypropane (200 mL) was added and the mixture was stirred at 30 °C for 90 min. The reaction was quenched with NaOAc (10 g) followed by $NaHCO_3$ (5 g). After being stirred for 30 min, the mixture was concentrated. The residue was dissolved in EtOAc and saturated $NaHCO_3$. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to afford 166 g (88.5%) of 15.

This crude alcohol 15 was used in the next step without further purification. An analytical sample was prepared by distillation: bp 95–105 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.43 (s, 3 H), 1.81 (ddd, J = 13.9, 9.3, and 4.5 Hz, 1 H), 2.11 (ddd, J = 13.9, 8.4, and 3.1 Hz, 1 H), 3.01 (d, J = 5.9 Hz, 1 H), 3.60 (dd, J = 8.2 and 6.8 Hz, 1 H), 3.80 (s, 3 H), 4.11 (dd, J = 8.2 and 6.0 Hz, 1 H), 4.32 (m, 1 H), 4.39 (m, 1 H); IR (neat) 3455, 1742, 1378, 1368 cm^{-1}; MS m/e 189 ($M^+ - CH_3$). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.83; H, 7.96.

Mitsunobu Inversion of 15. A mixture of 15 (prepared from 14 using material purified by recrystallization; 1.02 g, 5.0 mmol), triphenylphosphine (2.62, 10 mmol), and anhydrous THF (25 mL) was cooled with a dry ice–acetone bath followed by the addition of acetic acid (0.57 mL, 10 mmol) and diethyl azodicarboxylate (1.6 mL, 10 mmol). The mixture was slowly warmed to room temperature over 3 h and then concentrated. The residue was purified by chromatography on silica gel, eluting with 20% EtOAc in hexane to afford 1.07 g (87% yield) of the corresponding acetate of 16 as an oil: ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.40 (s, 3 H), 2.05 (dt, J = 14.4 and 5.6 Hz, 1 H), 2.15 (s, 3 H), 2.23 (dt, J = 14.4 and 6.6 Hz, 1 H), 3.63 (dd, J = 8.2 and 6.4 Hz, 1 H), 3.76 (s, 3 H), 4.09 (dd, J = 8.2 and 6.0 Hz, 1 H), 4.23 (m, 1 H), 5.18 (t, J = 5.6 Hz, 1 H); IR (neat) 1745, 1372 cm^{-1}; MS m/e 231 ($M^+ - CH_3$).

The acetate (1.07 g) was treated with 5 mol % of NaOMe in methanol to give 0.76 g (85.5% yield) of 16 after distillation (bath temperature 75 °C (0.05 mmHg)): ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.40 (s, 3 H), 2.05 (t, J = 6.1 Hz, 2 H), 3.15 (d, J = 3.8 Hz, 1 H), 3.63 (dd, J = 8.2 and 6.7 Hz, 1 H), 3.80 (s, 3 H), 4.10 (dd, J = 8.2 and 6.1 Hz, 1 H), 4.31 (m, 1 H), 4.35 (m, 1 H); IR (neat) 3525, 1738, 1381, 1371 cm^{-1}; MS m/e 189 ($M^+ - CH_3$).

(*S*,*S)-α-Fluoro-2,2-dimethyl-1,3-dioxolane-4-propanoic Acid Methyl Ester (17).** To a solution of 16 (0.76 g, 3.7 mmol) in CH_2Cl_2 (4 mL) at −10 °C was added (diethylamino)sulfur trifluoride (2 mL, 15 mmol).[19] The mixture was stirred at room temperature for 2 h. After being cooled to −60 °C, methanol (2 mL) was added and the mixture was warmed to room temperature. After dilution with CH_2Cl_2, the solution was washed with saturated $NaHCO_3$ and brine, then dried, concentrated, and distilled (bath temperature 75 °C (1.0 mmHg)) to give a mixture of 16 and 17 (0.48 g). 17 (0.20 g, 26% yield) was isolated by chromatography on silica gel, eluting with 33% EtOAc in hexane: ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.43 (s, 3 H), 2.0–2.3 (m, 2 H), 3.61 (dd, J = 8.0 and 6.5 Hz, 1 H), 3.81 (s, 3 H), 4.12 (dd, J = 8.0 and 6.2 Hz, 1 H), 4.30 (m, 1 H), 5.12 (ddd, J = 49.2, 10.3 and 2.6 Hz, 1 H); IR (neat) 1768, 1748, 1382, 1378 cm^{-1}; MS m/e 191 ($M^+ - CH_3$). Anal. Calcd for $C_9H_{15}O_4F$: C, 52.42; H, 7.33; F, 9.21. Found: C, 52.15; H, 7.39; F, 9.18.

(*S*,*S)-α-[(Methanesulfonyl)oxy]-2,2-dimethyl-1,3-dioxolane-4-propanoic Acid Methyl Ester.** A mixture of 15 (286 g, 1.4 mol), Et_3N (293 mL, 2.1 mol), and CH_2Cl_2 (1.2 L) was cooled to 5 °C followed by the dropwise addition of mesyl chloride (141 mL, 1.8 mol), keeping the temperature below 10 °C. The reaction mixture was allowed to warm to 18 °C over 90 min, before being washed with water twice. The aqueous washings were back-extracted. The combined organic layers were washed with brine, dried, and concentrated to afford 395 g (100%) of the crude mesylate.

This crude mesylate was used for the next step without further purification. An analytical sample was prepared by chromatographic purification: an oil; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.43 (s, 3 H), 2.02 (ddd, J = 13.5, 10.8, and 3.8 Hz, 1 H), 2.19 (ddd, J = 13.5, 9.1, and 3.0 Hz, 1 H), 3.16 (s, 3 H), 3.61 (dd, J = 8.2 and 6.0 Hz, 1 H), 3.82 (s, 3 H), 4.12 (dd, J = 8.2 and 6.0 Hz, 1 H), 4.26 (m, 1 H), 5.21 (dd, J = 10.8 and 3.0 Hz, 1 H); IR (neat) 1762, 1368, 1178 cm^{-1}; MS m/e 267 ($M^+ - CH_3$). Anal. Calcd for $C_{10}H_{18}O_7S$: C, 42.55; H, 6.43; S, 11.36. Found: C, 42.36; H, 6.39; S, 11.07.

(4*S*-*rac*)-α-Fluoro-2,2-dimethyl-1,3-dioxolane-4-propanoic Acid Methyl Ester (18). A mixture of acetamide (1 kg), spray-dried KF (150 g, 2.58 mol), and toluene (200 mL) was refluxed for 4.5 h to remove water azeotropically. Then, the crude mesylate (395 g, 1.4 mol) prepared previously was added with the

(19) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

aid of toluene (200 mL). The mixture was refluxed for 2.5 h. The mixture was then diluted with toluene and water. The aqueous layer was back-extracted three times with toluene. The combined organic layers were washed with brine, dried, and concentrated. The residue was distilled under high vacuum to give 160 g (55.4% yield) of 18: bp 64 °C (0.2 mmHg), 78.8% de of the syn isomer. An analytical sample was prepared by redistillation: ^{1}H NMR ($CDCl_3$; syn isomer) δ 1.35 (s, 3 H), 1.40 (s, 3 H), 2.0–2.3 (m, 2 H), 3.65 (dd, J = 8.2 and 6.4 Hz, 1 H), 3.81 (s, 3 H), 4.12 (m, 1 H), 4.29 (m, 1 H), 5.08 (dt, J = 48.1 and 5.9 Hz, 1 H); IR (neat) 1765, 1749 cm^{-1}; MS m/e 191 ($M^+ - CH_3$). Anal. Calcd for $C_9H_{15}O_4F$: C, 52.42; H, 7.33; F, 9.21. Found: C, 52.49; H, 7.01; F, 8.96.

Enrichment of the Anti Isomer 17. To a solution of 18 (160 g, 776 mmol) in toluene (776 mL) was added 25 wt % NaOMe in methanol (10 mL) dropwise. After being stirred at room temperature for 4 h, the reaction was quenched with acetic acid (2.5 mL). Then, the mixture was washed with brine, dried, and concentrated to give 17 of 25% de.

17 of 25% de was distilled under reduced pressure through a 4-ft Goodloe column with a reflux ratio of 20. The early fractions containing the syn isomer as a major component were treated with NaOMe as in the previous text and transferred back to the distillation pot. Then, distillation was resumed. After this procedure was repeated several times, the material in the pot was collected and distilled through a 10-cm Vigreaux column under a reduced pressure (65 °C (0.3 mmHg)) to give 52.7 g of 17 (83.5% de). The early fractions were saved for a future distillation (a total of 96.0 g, 29% de of anti isomer 17).

The overall yield of 17 (83.5% de) from D-xylose was 24.2% on the basis of previously recovered material.

Enzymatic Hydrolysis of 18.[13] A mixture of 18 (syn:anti = 3:5; 5.7 g, 28 mmol), pH 7 phosphate buffer (16 mL), and brine (22 mL) was adjusted to pH 7 followed by the addition of Amano P-30 lipase (100 mg). The pH of the mixture was maintained within the 6.85–6.95 range by the addition of 1 N NaOH (11.5 mL) over 75 min. Then, the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water, dried, and concentrated to recover 2.8 g of 18 (syn:anti = 5:3). The aqueous layer and the wash were combined, adjusted to pH 2 with concd HCl, and extracted with EtOAc (3 × 35 mL). The combined extracts were washed with brine, dried, and concentrated at 20 °C to give 2.2 g (41.5%) of 19 (80.4% de) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.42 (s, 3 H), 1.9–2.4 (m, 2 H), 3.62 (m, 1 H), 4.10 (m, 1 H), 4.32 (m, 1 H), 5.16 (ddd, J = 49.2, 10.0 and 3.0 Hz, 1 H).

(3*S*-*cis*)-3-Fluoro-5-[(triphenylmethoxy)methyl]-2-tetrahydrofuranone (20). A mixture of 17 (41.2 g, 200 mmol; 83.5% de) and 1 N HCl (5 mL) was stirred at 50–55 °C (bath temperature) under atmospheric pressure for 30 min and then under a reduced pressure of 60 mmHg overnight. The excess water was removed by stirring at that temperature under high vacuum (0.3 mmHg) for 1.5 h. This crude lactone 3 was used in the next step. An analytical sample was prepared by distillation. 3: bp 150 °C (bath) (0.6 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.02 (b t, J = 6.6 Hz, 1 H), 2.45 (ddt, J = 23.4, 13.4, and 9.5 Hz, 1 H), 2.71 (m, 1 H), 3.73 (m, 1 H), 3.99 (m, 1 H), 4.55 (m, 1 H), 5.30 (dt, J = 51.3 and 9.0 Hz, 1 H); IR (neat) 3390, 1780 cm^{-1}; MS m/e 103 ($M^+ - CH_2OH$). Anal. Calcd for $C_5H_7O_3F$: C, 44.78; H, 5.26; F, 14.17. Found: C, 44.65; H, 5.51; F, 13.90.

The crude lactone 3 prepared previously was diluted with pyridine (100 mL) followed by the addition of triphenylmethyl chloride (61.3 g, 220 mmol). The mixture was stirred at 45 °C overnight. After dilution with EtOAc, the mixture was washed with water. The aqueous layer was back-extracted. The combined extracts were washed with water and brine, dried, and concentrated. The residue was recrystallized from EtOAc and hexane (1:1; hexane was added after dissolution) to afford 48.4 g (64.3% yield) of 20 (mp 174–176 °C) contaminated with a small amount of the C-2 epimer (3.02 and 3.65 ppm, dd, 1 H each). A further 12.9 g (81.4% total) of 20 (mp 173–175 °C) obtained from the mother liquor was free from the epimer: ^{1}H NMR ($CDCl_3$) δ 2.38 (m, 1 H), 2.64 (m, 1 H), 3.29 (dd, J = 10.7 and 5.0 Hz, 1 H), 3.41 (dd, J = 10.7 and 3.4 Hz, 1 H), 4.53 (m, 1 H), 5.25 (dt, J = 51.3 and 8.9 Hz, 1 H), 7.2–7.5 (m, 15 H); IR (KBr) 1790 cm^{-1}; MS m/e 376 (M^+). Anal. Calcd for $C_{24}H_{21}O_3F$: C, 76.58; H, 5.62; F, 5.05. Found: C, 76.33; H, 5.73; F, 5.12.

(2*R*,3*S*,5*S*)-3-Fluoro-5-[(triphenylmethoxy)methyl]-2-tetrahydrofuranol. After a solution of 20 (61.3 g, 163 mmol) in CH_2Cl_2 (400 mL) was cooled to −75 °C, 1.5 N DIBAL in toluene (130 mL, 195 mmol) was added dropwise, keeping the temperature below −65 °C. After being stirred for 15 min, the reaction was quenched by the careful addition of methanol (6 mL). After the cooling bath was removed, 90 mL of saturated Na_2SO_4 was added dropwise and the mixture was allowed to warm to room temperature. After the mixture was stirred at room temperature for 2 h, 45 g of Na_2SO_4 was added and the mixture was stirred for 1 h. Then, the salt was filtered off and washed with CH_2Cl_2. The combined solutions were concentrated to afford 65.6 g (106% yield) of the crude lactol as a syrup. An analytical sample was obtained by chromatographic purification: mp 43–46 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (m, 1 H), 2.41 (m, 1 H), 2.46 (b s, 1 H), 3.12 (dd, J = 9.7 and 4.8 Hz, 1 H), 3.29 (dd, J = 9.7 and 6.4 Hz, 1 H), 4.50 (m, 1 H), 4.97 (dd, J = 52.7 and 5.4 Hz, 1 H), 5.58 (dd, J = 9.4 and 2.5 Hz, 1 H), 7.2–7.5 (m, 15 H); IR (KBr) 3385, 708 cm^{-1}; MS m/e 378 (M^+). Anal. Calcd for $C_{24}H_{23}O_3F$: C, 76.17; H, 6.13; F, 5.02. Found: C, 75.73; H, 6.24; F, 4.86.

(2*R*,3*S*,5*S*)-2-Chloro-3-fluoro-5-[(triphenylmethoxy)-methyl]tetrahydrofuran (21). After a mixture of the previous crude lactol (65.6 g, ca. 163 mmol), CH_2Cl_2 (163 mL), Et_3N (36.4 mL, 261 mmol), and Bu_3N (7.8 mL, 32.6 mmol) was cooled to −35 °C, 16.4 mL (212 mmol) of mesyl chloride was added dropwise, keeping the temperature below −10 °C. After being stirred for 1 h at room temperature, the mixture was diluted with CH_2Cl_2, washed with water and brine, and then dried and concentrated to give 71 g of the crude chloride 21 containing tributylamine. This crude chloride was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.06 (m, 1 H), 2.59 (m, 1 H), 3.31 (m, 2 H), 4.66 (m, 1 H), 5.30 (dd, J = 55.1 and 5.8 Hz, 1 H), 6.34 (d, J = 10.1 Hz, 1 H), 7.2–7.5 (m, 15 H).

***N*-Acetylcytosine.** A mixture of cytosine (121 g, 1.09 mol), pyridine (600 mL, 7.4 mol), and acetic anhydride (500 mL, 5.3 mol) was heated to reflux (ca. 125 °C) and stirred at that temperature for 2.5 h. After the mixture was cooled to room temperature, 500 mL of EtOAc was added and the mixture was stirred for 30 min. The white solid was filtered, washed with EtOAc, and dried to afford 162 g (97.2% yield) of *N*-acetylcytosine: ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3 H), 7.10 (d, J = 6.7 Hz, 1 H), 7.80 (d, J = 6.7 Hz, 1 H).

Coupling of 21 with Bis-TMS-*N*-acetylcytosine 22. A mixture of *N*-acetylcytosine (32.4 g, 212 mmol), hexamethyldisilazane (133 mL, 636 mmol), and ammonium sulfate (133 mg) was refluxed for 3 h and then cooled to 55 °C before adding a solution of the crude chloride 21 (71 g) prepared previously, in 200 mL of chloroform (ethanol free). The mixture was refluxed overnight and, cooled with an ice–water bath, and then methanol (34.3 mL, 848 mmol) was added dropwise, keeping the temperature below 20 °C. The resulting suspension was stirred at room temperature for 30 min. The precipitate was then filtered off and washed with chloroform. The combined filtrate and washings were washed with water, dried, and concentrated to give 110 g of the crude nucleoside as a sticky solid. This crude nucleoside was used in the next step without further purification.

An analytical sample of the pure nucleoside 23 (R = H) was obtained by chromatographic purification after deacetylation with propylamine: mp 271 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.18 (m, 1 H), 2.42 (m, 1 H), 3.29 (dd, J = 9.8 and 3.9 Hz, 1 H), 3.34 (dd, J = 9.8 and 6.4 Hz, 1 H), 4.34 (m, 1 H), 5.26 (dm, J = 54.5, 1 H), 5.60 (d, J = 7.5 Hz, 1 H), 6.11 (dd, J = 9.5 and 2.8 Hz, 1 H), 7.2–7.5 (m, 15 H), 7.62 (dd, J = 7.5 and 1.6 Hz, 1 H); IR (KBr) 3460, 3340, 1650, 705 cm^{-1}; MS m/e 471 (M^+). Anal. Calcd for $C_{25}H_{26}N_3O_3F$: C, 71.32; H, 5.56; N, 8.91; F, 4.03. Found: C, 71.28; H, 5.54; N, 8.86; F, 3.96.

1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine Hydrochloride (24). The crude nucleoside (110 g) prepared previously was dissolved in CH_2Cl_2–MeOH (1:1; 320 mL). After being cooled with an ice–water bath, 18 mL of concd HCl was added dropwise over 15 min and the mixture was stirred at room temperature overnight. The suspension was then diluted with 200 mL of acetone and stirred for 15 min before the precipitate was filtered and washed with acetone. After being dried at 80 °C under high vacuum, 19.8 g (40.2% based on the lactone 20)

of **24** was obtained: mp 227–229 °C dec; ^{1}H NMR (CD_3OD) δ 2.20 (m, 1 H), 2.54 (m, 1 H), 3.68 (dd, J = 12.1 and 5.8 Hz, 1 H), 3.76 (dd, J = 12.1 and 3.2 Hz, 1 H), 4.30 (m, 1 H), 5.35 (dm, J = 54.2, 1 H), 6.07 (dd, J = 16.4 and 3.4 Hz, 1 H), 6.09 (d, J = 8.0 Hz, 1 H), 8.21 (dd, J = 8.0 and 1.2 Hz, 1 H); IR (KBr) 3395, 1673 cm^{-1}; MS m/e 229 (M^+ – HCl); $[\alpha]_{589nm}$ +141.21° (c 0.99, 0.1 N HCl). Anal. Calcd for $C_9H_{12}N_3O_3F$–HCl: C, 40.69; H, 4.93; F, 7.15. Found: C, 39.22; H, 4.85; F, 6.55.

This material was used in the next step without further purification.

1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC). An aqueous solution of **24** (19.8 g, 74.5 mmol) in 320 mL of water was passed through an ion-exchange column (200 mL of Bio-Rex 9, OH^- form, 20–50 mesh; Bio-Rad) using 600 mL of 66% aqueous methanol as eluent. The combined fractions containing F-ddC were concentrated, and the residue was recrystallized from ethanol to give 15.0 g (87.8% yield) of F-ddC: mp 205–208 °C (lit.[1b] mp 205–208 °C); ^{1}H NMR (CD_3OD) δ 2.14 (dddd, J = 28.2, 14.9, 5.3, and 1.9 Hz, 1 H), 2.52 (dddd, J = 34.4, 14.9, 8.5, and 5.7 Hz, 1 H), 3.68 (dd, J = 12.0 and 6.0 Hz, 1 H), 3.72 (dd, J = 12.0 and 3.9 Hz, 1 H), 4.24 (m, 1 H), 5.28 (dm, J = 54.3 Hz, 1 H), 5.88 (d, J = 7.5 Hz, 1 H), 6.01 (dd, J = 8.2 and 3.2 Hz, 1 H), 7.87 (dd, J = 7.5 and 1.5 Hz, 1 H); IR (KBr) 3465–3200, 1640 cm^{-1}; MS m/e 229 (M^+); $[\alpha]_{365nm}$ +710.15° (c 1.027, H_2O). Anal. Calcd for $C_9H_{12}N_3O_3F$: C, 47.16; H, 5.28; N, 18.33; F, 8.29. Found: C, 46.92; H, 5.25; N, 18.05; F, 8.21.

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Benzotriazole as a Synthetic Auxiliary: Advantageous Syntheses of Substituted Diarylmethanes and Heterocyclic Analogues

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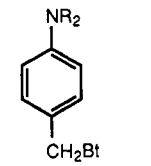
4-(Benzotriazol-1-ylmethyl)-*N*,*N*-dimethylaniline (**1b**) can be substituted at the CH_2 link via lithiation. Both the parent and substituted derivatives react with a variety of electron-rich benzenoid and heteroaromatic compounds in a novel approach to leuco dyes. Other 4-(benzotriazol-1-ylmethyl)anilines react similarly.

Introduction

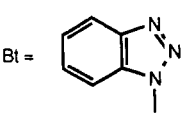
Di- and triarylmethanes containing electron-donating groups in ortho or para positions are of considerable importance. Thus they are leuco dyes which on hydride abstraction by oxidizing agents give colored cations of the type of Michler's hydrol, Crystal Violet, and Malachite Green. Previous synthesis of such di- and triarylmethanes generally involved the treatment of a one-carbon electrophilic reagent (formaldehyde, chloroform, etc.) with arene nucleophiles (usually substituted by electron donors such as NR_2, NHR, NH_2, OH) via an S_E2 mechanism.[1] Numerous reported vinylogous di- and triarylmethane dyes include a few heteroaromatic analogues.[2] For example, Naef[2b] synthesized trihetaryl dyes in yields of 20–85% by treatment of unsymmetrical dihetaryl ketones with 1,2-dimethylindole in the presence of phosphorus oxychloride. Other hetaryl dyes that have been prepared are diindolylpyridylmethanes,[2c] which afford colored compounds upon proton abstraction and hence cannot be considered as leuco dyes.

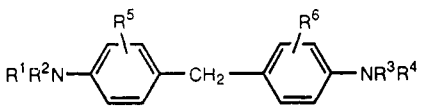
Compounds of type **2** have found numerous other applications in industry. They are used as curing agents for epoxy resins and urethane elastomers, as intermediates in the preparation of polyurethanes, in the synthesis of polyamides and in the production of dyes and recording materials.[3] Alteration of the molecule, such as by changing an aryl ring to a heterocyclic ring, or by introducing a functional group onto the methylene carbon, should modify the properties of these materials and perhaps widen their synthetic applications. Proper selection of these groups could lead to potential leuco dyestuffs.

Previous work[4] in our laboratory has shown that aniline or *N*,*N*-dialkylanilines are readily alkylated by 1-(hydroxymethyl)benzotriazole to give 4-(benzotriazol-1-ylmethyl)anilines **1**. Subsequent displacement of the benzotriazole group by arylamines or *N*,*N*-dialkylanilines gives either symmetrical or unsymmetrical 4,4′-methylenebis(*N*,*N*-dialkylanilines) **2**. Thus the displacement of benzotriazole by a variety of nucleophiles was investigated.



1a R = H
1b R = Me
1c R = Et





2

R^1-R^4 = H, alkyl
R^5, R^6 = H, alkyl, halogen

N-Benzylbenzotriazole has been shown to undergo lithiation at the benzylic carbon atom.[5] Although *N*,*N*-dimethylaniline and 4,4′-methylenebis(*N*,*N*-dimethylaniline) both undergo ortho-metalation (due to chelation effects),[6] it was anticipated that the electron-withdrawing nature of benzotriazole could assist in directing lithiation toward the benzylic position in **1**. We now report our results on the reaction of 4-(benzotriazol-1-ylmethyl)-

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