also gave the same impression, but at 100 or 360 MHz (Figure 1) it is clear that a mixture is present. This is as might be expected since we have noted[7] that addition of methyl nicotinate to pure β-D-glucose in D_2O accelerates the rate of mutarotation at least twofold. Thus, buchananine might be expected to catalyze its own mutarotation. On the basis of the above observations we conclude that buchananine as described by Sharma and co-workers[5] exists as a mixture of α and β isomers, though, of course, we cannot comment upon its precise identity in nature.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. With the exception of the 60-MHz spectrum shown in Figure 1A, all NMR spectra were run at 360 MHz, using a Nicolet NT-360 spectrometer. Ultraviolet spectra were measured on a Cary 15 spectrophotometer, and infrared spectra were determined on a Beckman IR8. Optical rotations were recorded on a Jasco DIP-180 automatic polarimeter. High-pressure LC was performed on a Waters Associates instrument consisting of a Model 6000A solvent delivery system, U6K injector, and a Perkin-Elmer LC55B variable-wavelength detector connected to an external strip recorder. The detector was set at 215 nm and a normal phase column (Waters Associates) packed with μPorasil was used for separations, eluting with ethyl acetate/cyclohexane (2:3).

1,2-*O*-Isopropylidene-6-*O*-nicotinoyl-D-glucofuranose (3). To a solution of 220 mg (1×10^{-3} mol) of 1,2-*O*-isopropylidene-D-glucofuranose (**2**) (Aldrich) in 5 mL of dry pyridine was added 177 mg (1×10^{-3} mol) of nicotinoyl chloride hydrochloride, and the mixture was stirred overnight at ambient temperature. The solution was then poured into water and extracted into butanol. Washing of the organic phase with water and saturated aqueous sodium bicarbonate, followed by drying (anhydrous $MgSO_4$) and evaporation to dryness, gave a crystalline solid (250 mg, 77%): mp 134–136 °C; $[\alpha]^{20}_D$ +4.5° (*c* 4.3, EtOH); mass spectrum, *m/e* (%) 325 (3, M^+), 310 (100); IR (Nujol) 3500 (OH), 1690 (CO), 1600 (Ar) cm^{-1}; UV (EtOH) 257 nm (ε 70000), 262 (72000), 269 (56000); ^1H NMR (CD_3OD) δ 9.21 (1 H, d, *J* = 1.4 Hz, C_2ArH), 8.78 (1 H, dd, *J* = 1.65, 6.0 Hz, C_6ArH), 8.40 (1 H, dt, *J* = 1.9, 8.0 Hz, C_4ArH), 7.60 (1 H, m, C_5ArH), 5.93 (1 H, d, *J* = 3.6 Hz, $C_1'H$), 4.28 (3 H, m, sugar H), 1.47, 1.33 (each 3 H, s, CMe_2).

Anal. Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.84; N, 4.30. Found: C, 55.38; H, 5.86; N, 4.22.

6-*O*-Nicotinoyl-D-glucopyranose (4). 1,2-*O*-Isopropylidene-6-*O*-nicotinoyl-D-glucofuranose (**3**, 200 mg, 0.6×10^{-3} mol) was stirred in 2 mL of 5 N hydrochloric acid for 4 h at ambient temperature. Solid sodium carbonate was added to neutralize the solution and the water was removed under reduced pressure to give a residue which was triturated with ethyl acetate and then absolute ethanol. Removal of the ethanol gave a solid which was crystallized from aqueous methanol to give the product (92 mg, 53%): mp 136–140 °C; $[\alpha]^{20}_D$ +38° (*c* 3.08, H_2O); IR (Nujol) 3300 (OH), 1730 (CO), 1600 (Ar) cm^{-1}; UV (EtOH) 257 nm (ε 35300), 262 (38600), 269 (30000); ^1H NMR (D_2O) δ 8.80 (1 H, s, C_2ArH), 8.47 (1 H, d, *J* = 4.81 Hz, C_6ArH), 8.11 (1 H, dd, *J* = 1.66, 7.96 Hz, C_4ArH), 7.38 (1 H, m, C_5ArH), 5.12 (<1 H, d, *J* = 3.56 Hz, $C_1'H$, α isomer), 4.54 (<1 H, d, *J* = 7.87 Hz, $C_1'H$, β isomer), 3.75 (1 H, m, sugar H), 3.62 (1 H, m, sugar H), 3.35 (1 H, m, sugar H), 3.15 (1 H, t, *J* = 7.92 Hz, $C_2'H$).[11]

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-D-glucopyranose (5). 6-*O*-Nicotinoyl-D-glucopyranose (**4**, 250 mg) was acetylated by using 2 mL of acetic anhydride in 2 mL of pyridine at ambient temperature for 3 h. Workup with aqueous sodium bicarbonate gave an oil (415 mg, 64%) which was separated by high-pressure LC (μPorasil column, elution with ethyl acetate/cyclohexane, 2:3) into the α and β isomers. **β-Isomer**: mp 136–139 °C; mass spectrum, *m/e* 454 ($M^+ + 1$, 100%); ^1H NMR ($CDCl_3$) δ 9.16 (1 H, s, C_2ArH), 8.80 (1 H, d, *J* = 4.42 Hz, C_6ArH), 8.22 (1 H, dd, *J* = 1.67, 8.0 Hz, C_4ArH), 7.41 (1 H, m, C_5ArH), 5.97 (1 H, d, 8.2 Hz, $C_1'H$, 5.42 (2 H, m, sugar H), 5.21 (1 H, t, *J* = 8.0 Hz, sugar H), 4.22 (1 H, dd, *J* = 2.0, 12.0 Hz, $C_6'H$), 4.04 (1 H, m, $C_5'H$), 2.13, 2.04, 1.92 (3 H, s, 6 H, s, and 3 H, s, 4 COMe).

Anal. Calcd for $C_{20}H_{23}NO_{11}$: C, 52.98; H, 5.07; N, 3.09. Found: C, 52.96; H, 5.23; N, 2.93.

α-Isomer: mp 135–138 °C; ^1H NMR ($CDCl_3$) δ 6.35 (1 H, d, *J* = 3.5 Hz, $C_1'H$).

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-β-D-glucopyranose Methiodide. 1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-β-D-glucopyranose (**5**, 20 mg) was stirred with 1 mL of methyl iodide in 2 mL of dry acetonitrile for 18 h at ambient temperature. Evaporation of the solvent gave a yellow solid which was recrystallized from ethyl acetate/ether to give the methiodide hydrate (18 mg, 66%): mp 196–198 °C; ^1H NMR (CD_3OD) δ 9.58 (1 H, s, C_2ArH), 9.17 (1 H, d, *J* = 6.1 Hz, C_6ArH), 9.09 (1 H, d, *J* = 8.0 Hz, C_4ArH), 8.29 (1 H, m, C_5ArH), 5.95 (1 H, d, *J* = 8.0 Hz, $C_1'H$), 5.63 (1 H, t, *J* = 9.4 Hz, sugar H), 5.47 (1 H, t, *J* = 9.5 Hz, sugar H), 5.24 (1 H, t, *J* = 8.7 Hz, sugar H), 4.56 (3 H, s, ^+NMe), 4.40 (2 H, m, $C_6'H$), 4.26 (1 H, m, $C_5'H$), 2.16, 2.11, 2.10, 1.98 (each 3 H, s, 4 COMe).

Anal. Calcd for $C_{21}H_{26}INO_{11}\cdot H_2O$ (hygroscopic): C, 41.10; H, 4.56; N, 2.28. Found: C, 41.25; H, 4.23; N, 2.16.

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-D-glucopyranose (5) (from 1,2,3,4-*O*-Tetraacetyl-D-glucopyranose, 6). To a solution of 800 mg (2.2×10^{-3} mol) of 1,2,3,4-*O*-tetraacetyl-D-glucopyranose[10] (**6**) in 5 mL of dry pyridine was added 177 mg (2.2×10^{-3} mol) of nicotinoyl chloride, and the mixture was stirred at ambient temperature for 18 h. An aqueous sodium bicarbonate workup gave an oil (760 mg, 80%) for which the IR, NMR, high-pressure LC, and TLC were identical with those reported above for the material synthesized from 6-*O*-nicotinoyl-D-glucopyranose (**4**).

3-*O*-Nicotinoyl-1,2,5,6-diisopropylidene-D-glucofuranose (8). This compound was synthesized from 1,2,5,6-diisopropylidene-D-glucofuranose, using the method described for the preparation of compound (**3**), and was isolated as an oil: NMR ($CDCl_3$) δ 9.86 (1 H, d, *J* = 1.4 Hz, C_2ArH), 8.78 (1 H, dd, *J* = 1.18, 4.66 Hz, C_6ArH), 8.26 (1 H, dt, *J* = 8.0, 1.18 Hz, C_4ArH), 7.39 (1 H, m, C_5ArH), 5.93 (1 H, d, *J* = 3.67 Hz, $C_1'H$), 5.49 (1 H, d, *J* = 2.71 Hz, sugar H), 4.61 (1 H, d, *J* = 3.69 Hz, sugar H), 4.30 (2 H, m, sugar H), 4.05 (2 H, m, sugar H), 1.52, 1.38, 1.29, and 1.23 (each 3 H, s, 2 CMe_2).

3-*O*-Nicotinoyl-D-glucopyranose (7). This compound was obtained from the foregoing diacetonide, using 5 N HCl, as described above: ^1H NMR (D_2O) δ 8.86 (1 H, s, C_2ArH), 8.54 (1 H, d, *J* = 4.21 Hz, C_6ArH), 8.17 (1 H, d, *J* = 7.93 Hz, C_4ArH), 7.46 (1 H, m, C_5ArH), 5.18 (<1 H, d, *J* = 3.7 Hz, $C_1'H$, α-isomer), 4.60 (<1 H, d, *J* = 8.7 Hz, $C_1'H$ β-isomer), 3.75 (1 H, m, sugar H), 3.40 (1 H, m, sugar H), 3.20 (1 H, t, *J* = 8.7 Hz, sugar H).

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Conversion of Pyrimidine Nucleoside 2',3'-Orthoacetates into Pyrimidine 2'-Azido-2'-deoxynucleosides

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Among the nucleoside antibiotics produced by microorganisms only three are known to possess aminodeoxyribofuranose structures, puromycin,[1] 3'-amino-3'-deoxyadenosine,[1] and 2'-amino-2'-deoxyguanosine.[2] The last is the only known occurrence of 2'-amino-2'-deoxy-

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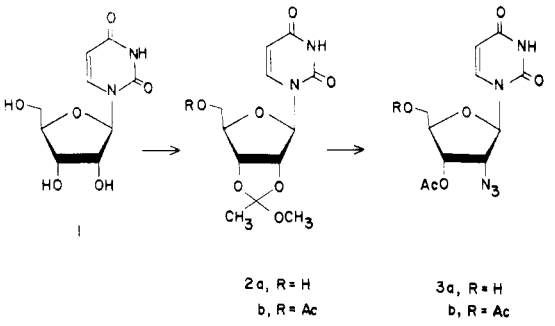
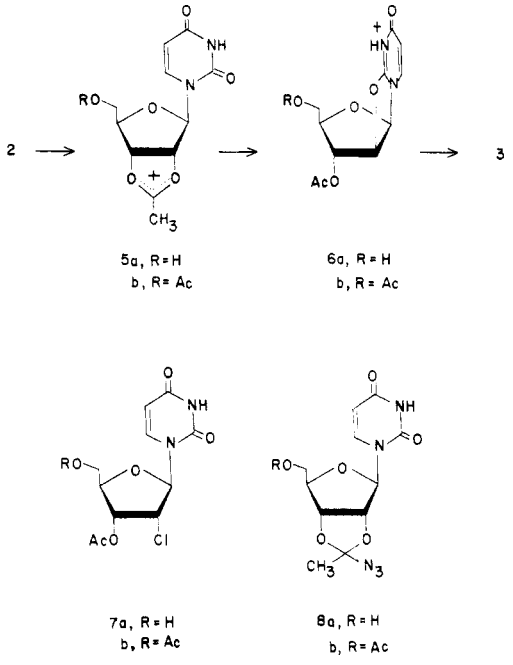
Scheme I



Scheme II



ribose in nature. The occurrence and biological activities of these aminodeoxynucleosides has promoted considerable interest in the synthesis of other aminodeoxynucleosides.[3-8] The least studied of the aminodeoxynucleosides have been the pyrimidine 2′-amino-2′-deoxyribonucleosides.[3,5]

In this paper we describe a facile synthesis of 3′,5′-di-*O*-acetyl-2′-azido-2′-deoxyuridine (**3b**) in good yield from 2′,3′-*O*-(methoxyethylidene)uridine (**2a**) by a one-flask procedure. Azide **3b** serves as a ready high-yield precursor for the production of 2′-amino-2′-deoxyuridine via catalytic reduction over palladium[3] or the triphenylphosphine route.[9] A related synthesis of **3b** from uridine (1) has previously been described;[3] however, the overall yield is low (32%) and the procedure requires the use of hexamethylphosphoramide (HMPA), a cancer-suspect solvent.[10] A recent modification[4] of this procedure produces 2′-azido-2′-deoxyuridine in 50% yield, but it also uses the solvent HMPA. Other routes to derivatives of 2′-azido-2′-deoxyuridine from the action of ammonium azide in dimethylformamide (DMF) on 2,2′-anhydro-1-(5-*O*-trityl-β-D-arabinofuranosyl)uracil[5a] or 1-(3,5-di-*O*-benzoyl-2-*O*-methanesulfonyl-β-D-arabinofuranosyl)uracil[5b] are relatively lengthy, only slightly higher in yield, and require inconvenient starting materials.

We have previously shown that **2a** can be converted into 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine upon treatment with chlorotrimethylsilane.[11] It therefore appeared reasonable that **2a** might be converted into **3a** by the same reagent in the presence of azide ion. Thus, treatment of a solution of **2a** in DMF with excess sodium azide and Me_3SiCl for 14 h at 95 °C followed by 7.5 h at 150 °C produced **3b** in 40% yield after acetylation of the initially formed **3a** (Scheme I). Although **3a** can be isolated as such from the reaction mixture, we prefer to isolate **3a** as its 5′-*O*-acetyl derivative (**3b**) since **3b** is much easier to manipulate. Neither shorter nor longer reaction time at these temperatures resulted in improved yields; in fact, such changes were detrimental. Since the sodium azide is mostly undissolved under the reaction conditions, we decided to repeat the reaction in the presence of an equimolar (to N_3^-) amount of tetramethylammonium chloride (TMAC). Under these conditions **3b** was isolated in 79% yield. For some unexplained reason, the order of addition of the reagents to the DMF solution of **2a** is crucial. In every instance, the yields of **3b** were lower (~68%) when the Me_3SiCl was added before the TMAC and sodium azide rather than after them.

In order to determine whether or not the 5′-hydroxyl of **2a** has an effect on the reaction, **2a** was acetylated to **2b**. When **2b** was subjected to the same reagents for 0.5 h at 85 °C and 14 h at 100 °C, **3b** was isolated in 81% yield. Hence, there is no difference in yield whether the acetylation is performed prior to or subsequent to the reaction; however, milder conditions and shorter reaction times result when **2b** is used instead of **2a**.

With regard to the mechanism for the conversion of **2** to **3**, we have ruled out the intermediacy of Me_3SiN_3 since all attempts to convert **2** to **3** with Me_3SiN_3 were unsuccessful. The failure of **2** to produce **3** upon treatment with Me_3SiN_3 is puzzling because this very type of reaction has recently been reported to readily occur with simple 2-methoxy-2-methyl-1,3-dioxolanes.[12] We favor a mechanism such as the one outlined in Scheme II where **5** is formed by the action of Me_3SiCl on **2**, and **3** results from nucleophilic attack of N_3^- on the 2′-carbon of **6**. We have previously shown that **6a** is produced in 72% yield upon treatment of **2a** with Me_3SiCl in refluxing acetonitrile[11] and now report that **3b** is produced, quantitatively, when the free base form of **6b** is treated with sodium azide in DMF at 95 °C for 5 h and then at 150 °C for 5 h. However, the intermediacy of chloronucleoside **7** can not be ruled out as **7b** produces **3b** in 50% yield when heated with sodium azide in DMF. Azide **8** is also a possible intermediate in the reaction, being formed by the trapping of the 1,3-dioxolan-2-ylium ion **5** by azide ion. Regardless of whether or not **7** and/or **8** are intermediates, they can lead to the formation of **3** only through their prior conversion to **6**.

In summary, the present methodology offers greatly improved yields and simplified procedures for the synthesis

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of pyrimidine 2'-azido-2'-deoxynucleosides.

Experimental Section

All chemicals were of reagent grade and used as received except that DMF was dried by distillation under reduced pressure and storage over 4-A molecular sieves and Me_3SiCl was freshly distilled. Column chromatography was performed on E. Merck silica gel 60 (7734) and all TLC was performed on E. Merck silica gel 60 plates (5539). IR spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were recorded on a Varian EM 390 spectrometer with Me_4Si as an internal reference. UV spectra were recorded on a Cary Model 14 spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected.

2',3'-*O*-(Methoxyethylidene)uridine (2a).[13] To a magnetically stirred suspension of 300 mg (1.23 mmol) of 1 in 1.5 mL of $CH_3C(OMe)_3$ was added 28.6 mg (0.15 mmol) of *p*-toluenesulfonic acid monohydrate. After 16 h at room temperature, excess MeOH-washed Amberlite IR-45 exchange resin ($^-$OH form) suspended in several milliliters of MeOH was added. After 15 min, the mixture was filtered and the filtrate evaporated to dryness on a rotary evaporator. The residue was coevaporated several times with benzene to give a colorless glass. TLC of this material showed two spots for the epimers of **2a** and the complete absence of 1. This material was used in subsequent reactions without any further purification.

5'-*O*-Acetyl-2',3'-*O*-(methoxyethylidene)uridine (2b).[14] Standard acetylation of **2a** with acetic anhydride in pyridine gave **2b** in quantitative yield and this material was used directly as isolated without further purification.

3',5'-Di-O-acetyl-2'-azido-2'-deoxyuridine (3b). Method A. To a magnetically stirred solution of 480 mg (1.6 mmol) of **2a** in 5 mL of dry DMF were added 488 mg (7.5 mmol) of NaN_3 and 0.95 mL (7.5 mmol) of Me_3SiCl. The resulting mixture was then heated for 14 h at 95 °C and then for 7.5 h at 150 °C. The DMF was removed under reduced pressure and the residue was treated with 2 mL of pyridine and 1 mL of acetic anhydride for 5 h at room temperature. The excess anhydride was destroyed by adding a few grams of ice and the mixture was extracted with CH_2Cl_2. After evaporation to dryness under reduced pressure, the residue was chromatographed on a 1.5 × 40 cm column of silica gel, eluting with 9:1 $CHCl_3$–EtOH (v/v), to give 226 mg (40%) of **3b** as a colorless syrup which was homogeneous on TLC: IR ($CHCl_3$) 2114 cm^{-1}; UV (MeOH) λ_{max} 259 nm (ϵ 9100) [lit.[3] (MeOH) λ_{max} 259 nm (ϵ 9200)]; NMR ($CDCl_3$) is identical with that previously reported.[3]

Method B. Procedure A was followed except for the addition of TMAC to the initial reaction mixture. A mixture of 480 mg (1.6 mmol) of **2a**, 0.95 mL (7.5 mmol) of Me_3SiCl, 488 mg (7.5 mmol) of NaN_3, and 821 mg (7.5 mmol) of TMAC in DMF with the reagents added to DMF in the order listed gave 385 mg (68%) of **3b**.[15]

Method C. Procedure B was followed, except for a change in the order of addition of the reagents to the solution of **2a** in DMF (NaN_3, TMAC, and Me_3SiCl, in order), to give 446 mg (79%) of **3b**.[15]

Method D. To a magnetically stirred solution of 85.5 mg (0.25 mmol) of **2b** in 5 mL of dry DMF were added 81.3 mg (1.25 mmol) of NaN_3, 41 mg (0.374 mmol) of TMAC, and 0.15 mL (1.18 mmol) of Me_3SiCl, respectively. The mixture was heated for 0.5 h at 85 °C and then for 14 h at 100 °C. The DMF was removed under reduced pressure and the residue was chromatographed on a 1.5 × 40 cm column of silica gel, eluting with 9:1 $CHCl_3$–EtOH (v/v), to give 72 mg (81%) of **3b**.[15]

Method E. A magnetically stirred solution of 347 mg (1 mmol) of **7b** and 325 mg (5 mmol) of NaN_3 in 5 mL of dry DMF was heated for 5 h at 95 °C and then for 5 h at 150 °C. Removal of the DMF under reduced pressure and chromatography of the residue on a 1.5 × 40 cm column of silica gel, eluting with 9:1 $CHCl_3$–EtOH (v/v), gave 177 mg (50%) of **3b**.[15]

Method F. Treatment of 155 mg (0.5 mmol) of the free base form of **6b** with 163 mg (2.5 mmol) of NaN_3 in 5-mL of dry DMF according to procedure E gave 177 mg (100%) of **3b**.[15]

3',5'-Di-*O*-acetyl-2'-chloro-2'-deoxyuridine (7b).[16] Acetylation of **7a**[11] with acetic anhydride and pyridine gave **7b** in quantitative yield as a chromatographically homogeneous syrup:[17] NMR ($CDCl_3$) δ 2.13 (s, 3, OAc), 2.16 (s, 3, OAc), 4.37 (br s, 2, H-5'), 4.37 (m, 1, H-4') 4.63 (t, 1, $J_{1',2'} = J_{2',3'} = 5$ Hz, H-2'), 5.24 (t, 1, $J_{3',4'} = 5$ Hz, H-3'), 5.80 (d, 1, $J_{5,6} = 8$ Hz, H-5), 6.07 (d, 1, $J_{1',2'} = 5$ Hz, H-1'), 7.56 (d, 1, H-6).

2,2'-Anhydro-1-(3,5-di-*O*-acetyl-β-D-arabinofuranosyl)uracil.[18] Acetylation of **6a**[11] with acetic anhydride and pyridine gave the free base form of **6b** in quantitative yield as a chromatographically homogeneous syrup: NMR ($CDCl_3$)[19] δ 1.98 (s, 3, OAc), 2.17 (s, 3, OAc), 3.99 (dd, 1, $J_{5'a,5'b} = 12$ Hz, $J_{4',5'a} = 4$ Hz, H-5'a), 4.24 (dd, 1, $J_{4',5'b} = 5$ Hz, H-5'b), 4.50 (m, 1, H-4'), 5.37 (d, 1, $J_{3',4'} = 1.5$ Hz, H-3'), 5.50 (d, 1, $J_{1',2'} = 6$ Hz, H-2'), 5.99 (d, 1, $J_{5,6} = 7.5$ Hz, H-5), 6.45 (d, 1, H-1'), 7.48 (d, 1, H-6). Crystallization from methanol gave colorless prisms, mp 184.6–185.7 °C (lit. mp 186–187 °C[18a] and 183–185 °C[18b]).

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Registry No. 1, 58-96-8; **2a**, 16667-57-5; **2b**, 75149-69-8; **3a**, 34407-68-6; **3b**, 26889-43-0; **6a**, 75149-70-1; **6b** (free base), 75149-71-2; **7a**, 42973-35-3; **7b**, 10190-39-3; NaN_3, 26628-22-8; $CH_3C(OMe)_3$, 1445-45-0.

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(14) **2b** has been prepared from 5'-*O*-acetyluridine as an intermediate without isolation.[13]

(15) Identical in all respects with **3b** prepared by method A.

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(17) **7b** has been reported as a difficulty obtained crystalline solid.[16] We were unable to obtain **7b** in crystalline form, but its NMR spectrum is essentially identical with that previously reported.[16b]

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(19) This NMR spectrum is essentially identical with that reported in $(CD_3)_2SO$ at 60 MHz.[18c]

A Simple and Convenient Phenol Annelation

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Conventional synthetic approaches to substances possessing a phenol ring(s) invariably start with the aromatic ring intact. Subsequent steps construct the remaining aliphatic molecular framework around this aromatic template or steps are taken to introduce the appropriately substituted intact aromatic ring at an early stage in the synthetic sequence. Though these approaches admirably serve most purposes, often they are plagued by serious shortcomings. Aside from the difficulties associated with the regiospecific preparation of substituted phenols, the adaptation of the synthetic work for the preparation of closely related natural products or synthetic analogues with even the simplest aromatic modification often necessitates an independent total synthesis.[2]

(1) National Institutes of Health (NIH) predoctoral trainee, NIH Trainee Grant No. GM-07775.

(2) For representative work and relevant discussions, see: (a) Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098; Kende, A. S.; Curran, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 1857; McDonald, E.; Martin, R. T. *Tetrahedron Lett.* **1978**, 4723; (b) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324; Palmer, D. C.; Strauss, M. *J. Chem. Rev.* **1977**, *77*, 1.

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