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Preparation of 10-g Quantities of 15-*O*-Acetyl-4-deoxynivalenol

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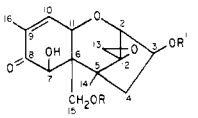
The most common trichothecenone produced by strains of *Fusarium graminearum* isolated from Eastern Canadian and United States grain is 15-*O*-acetyl-4-deoxynivalenol (15-*O*-acetyl-DON) (1, R = Ac, R^1 = H).[1] Although we have examined 51 isolates of this fungus for their ability to produce this mycotoxin in laboratory culture, the best yield obtained was only 40 mg L^{-1}. The relative inaccessibility of this compound has resulted in the use of deoxynivalenol (= DON = vomitoxin, 1, R = R^1 = H) for most toxicological studies with laboratory animals,[2] despite the known differences in partition coefficient (and hence pharmacology) of the acetate and alcohol in lipid–aqueous systems.



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By contrast, 3-*O*-acetyl-DON (1, R = H, R^1 = Ac) is readily available[3] and could serve as starting material for a partial synthesis of the 15-acetate. This conversion has now been achieved by two routes. The preferred route involves only two steps, hydrolysis of 3-*O*-acetyl-DON to DON with ammonium hydroxide followed by regiospecific Steglich esterification,[4] with acetic acid and dicyclohexylcarbodiimide (DCC) in the presence of 4-(dimethylamino)pyridine (DMAP), giving 15-*O*-acetyl-DON in 82% yield or 67% overall, together with a small amount of 3,15-di-*O*-acetyl-DON,[5] which is easily removed by column chromatography. This procedure was superior to acetylation with 1 equiv of acetic anhydride in the presence of DMAP,[6] which was also regiospecific, giving 15-*O*-acetyl-DON containing <5% 3-*O*-acetyl-DON but in only 69% yield. When pyridine was used instead of DMAP, the reaction was essentially nonspecific, giving the 15- and 3-acetates in the ratio 3:2.

The second route involves six steps using standard protecting group chemistry and gives the 15-acetate in 54% overall yield, but is more laborious and time-consuming. The 15-*tert*-butyldimethylsilyl ether (1, R = *t*-$BuMe_2Si$, R^1 = Ac) of 3-*O*-acetyl-DON was hydrolyzed with ammonium hydroxide to the diol (1, R = *t*-$BuMe_2Si$, R^1 = H), which readily formed the 3-tetrahydropyranyl (THP) ether (1, R = *t*-$BuMe_2Si$, R^1 = THP). Removal of the silyl group with tetrabutylammonium fluoride, regiospecific acetylation at position 15 of the resulting diol (1, R = H, R^1 = THP), and deprotection gave the 15-acetate (1, R = Ac, R^1 = H). With the exception of the silyl ether (1, R = *t*-$BuMe_2Si$, R^1 = Ac), the intermediate products were gums (this is normally the case with diastereoisomeric THP ethers) and were not analyzed. An envisaged six-step procedure using the trityl ether (1, R = Ph_3C, R^1 = Ac) broke down through failure to find a protecting group for the diol (1, R = Ph_3C, R^1 = H) that would both permit perferential removal of the trityl residue and also undergo fission without solvolysis of a 15-acetate residue. The 15-phenylurethane (1, R = CONHPh, R^1 = Ac) was also prepared.

Acetylation of 3-*O*-acetyl-DON under most conditions gives the known 3,7,15-triacetate,[7,8] but Steglich esterification gave the 3,15-diacetate (1, R = R^1 = Ac). This on mild alkaline hydrolysis gave a mixture of the 15- and 3-acetates in the ratio 3:2. The reaction between DON and 1 equiv of dihydropyran was also not regiospecific, and after acetylation of the product and deprotection, the 15- and 3-acetates were obtained in the ratio 1:1.

A crystalline precipitate consisting of about 80% 3-*O*-acetyl-DON can be obtained from the crude extract of *Fusarium culmorum* (HLX 1503) fermentations.[3] When this material was hydrolyzed on the 10-g scale and the resulting crude DON was acetylated under the preferred conditions described above, the 15-acetate (1, R = Ac, R^1 = H) was obtained, after chromatography in about 60% yield.

Experimental Section

A. Experimental Details for Work Carried Out at the University of Sussex. Melting points (Kofler block) are corrected. Merck silica gel 7734 was used in column chromatography. All reactions and chromatographic separations were monitored by analytical thin-layer chromatography (TLC) (UV detection) on Merck silica gel 60 F_{254} in chloroform–methanol (9:1). In this system DON has R_f 0.03, mono-*O*-acetyl-DON has R_f 0.55, and 3,15-di-*O*-acetyl-DON has R_f 0.73. Triethylamine was used, where possible, in preference to pyridine, which also has R_f 0.55.

In mixtures of 3-*O*-acetyl- and 15-*O*-acetyl-DON, integration of the ^{1}H NMR (80 MHz) signals from 3-*H*OAc at δ 5.28 ($CDCl_3$, Me_4Si internal standard) and 15-H_2OAc at δ 4.28 gave the ratio. The same could be checked by integration of the common H-10 signal at δ 6.68. Identifications were confirmed by comparison of the IR spectra which are for mulls in Nujol. Methylene chloride was distilled from calcium hydride.

Hydrolysis of 3α-Acetoxy-7α,15-dihydroxy-12,13-epoxytrichothec-9-en-8-one (1, R = H, R^1 = Ac; 3-*O*-Acetyl-DON). 3-*O*-Acetyl-DON (1.00 g) in methanol (20 mL) and ammonium hydroxide (1.5 N, 10 mL) was stirred at room temperature for 6 h. The solution was concentrated under reduced pressure (bath, 40 °C) to 6 mL and extracted with ethyl acetate saturated with water (10 × 6 mL). The recovered foam (895 mg) crystallized from ethyl acetate gave DON (722 mg, 82%), mp 150–152 °C (lit.[8] mp 151–153 °C).

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Acetylation of DON. (a) Steglich Esterification. To DON (592 mg, 2.00 mmol) in methylene chloride (250 mL) containing DMAP (40 mg) and acetic acid (125 μL, 2.20 mmol) was added DCC (412 mg, 2.00 mmol). After being stirred for 10 h at room temperature, the solution was washed with 1 N hydrochloric acid (10 mL) and dried (Na_2SO_4). Concentration afforded dicyclohexylurea (350 mg) and then, on recovery, a gum (ca. 850 mg). The latter was chromatographed on silica gel (25 g, 22 × 1.8 cm) made up in benzene. Elution with chloroform (10-mL fractions) gave, after a forerun (100 mL), (i) 20 mL, 32 mg, crystallized from ethyl acetate–petroleum ether, bp 60–80 °C, as needles of 3,15-di-*O*-acetyl-DON, mp 112–115 °C (lit.[5] mp 117 °C); (ii) 20 mL, dicyclohexylurea (170 mg); (iii) 180 mL, 553 mg, 82%, 15-*O*-acetyl-DON, mp 138–140 °C (lit.[1] mp 142–145 °C) by crystallization from ethyl acetate. It contained no 3-*O*-acetyl-DON by NMR analysis.

(b) DON (296 mg, 1.00 mmol) in methylene chloride (100 mL) and triethylamine (1 mL, 7.2 mmol) was stirred at room temperature with DMAP (20 mg) and acetic anhydride (95 μL, 1.00 mmol). After 5 h, TLC showed some material of R_f 0.73 (di-*O*-acetyl-DON) as well as unchanged DON. The solution was washed with hydrochloric acid (1 N, 20 mL) and sodium hydrogen carbonate solution (5 mL) and the solute recovered (260 mg, 77%). It was chromatographed on a silica gel column (9 g) made up in benzene. Elution with chloroform (5-mL fractions after removal of the forerun) gave (i) 15 mL, R_f 0.7, 35 mg, 3,15-di-*O*-acetyl-DON and (ii) 80 mL, R_f 0.55, 234 mg (69%), mp 130–133 °C, 15-*O*-acetyl-DON containing some 3-acetate (<5%).

(c) DON (65 mg, 0.21 mmol) in methylene chloride (25 mL) and pyridine (100 μL, 1.24 mmol) was stirred at room temperature with acetic anhydride (20 μL, 0.21 mmol) for 42 h. The solution was washed with hydrochloric acid and sodium hydrogen carbonate solution and the gummy product analyzed by NMR. This showed 15-*O*-acetyl-DON:3-*O*-acetyl-DON at ca. 3:2.

3α-Acetoxy-15-[(*tert*-butyldimethylsilyl)oxy]-12,13-epoxy-7α-hydroxytrichothec-9-en-8-one (1, R = *t*-BuMe$_2$Si, R^1 = Ac). 3-*O*-Acetyl-DON (1.00 g, 2.96 mmol) in methylene chloride (20 mL) was stirred at room temperature for 10 days with *tert*-butyldimethylsilyl chloride (500 mg, 3.32 mmol), triethylamine (461 μL, 3.32 mmol), and DMAP (18 mg, 0.15 mmol). The solution was washed with water (10 mL), and the solid product (1.33 g, 100%) was recrystallized from methanol, giving the silyl ether (1, R = *t*-BuMe$_2$Si, R^1 = Ac) as needles or plates: mp 180–182 °C; R_f 0.75; IR ν_{max} 3455, 1750, 1680 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.03 (Me_2), 0.93 (*t*-Bu), 1.17 (H_{14}), 1.96 (H_{16}), 2.15 (Ac), ca. 2.6 (H_4), 3.20 (H_{13}), 3.70 (H_{15}), 3.82 (OH), 3.95 (H_2), 4.85 (H_7), 4.90 (H_{11}), 5.25 (H_3), 6.65 (H_{10}). $C_{23}H_{36}O_7Si$ requires: C, 61.0; H, 8.0; M 452. Found: C, 61.3; H, 8.0; MH$^+$ 453.

Conversion of the Silyl Ether (1, R = *t*-BuMe$_2$Si, R^1 = Ac) to 15-*O*-Acetyl-DON. The silyl ether (1, R = *t*-BuMe$_2$Si, R^1 = Ac) (1.33 g) in methanol (200 mL) and ammonium hydroxide (1.5 N, 40 mL) was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure (bath, 40 °C) to 20 mL and extracted with ethyl acetate. Recovery afforded the diol (1, R = *t*-BuMe$_2$Si, R^1 = H) as a gum (1.00 g, 82%): R_f 0.62; IR ν_{max} 3460 (br), 1690 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.02 (Me_2), 0.90 (*t*-Bu), 1.15 (H_{14}), 1.95 (H_{16}), ca. 2.3 (H_4), 3.12 (H_{13}), 3.24 (H_{13}), 3.68 (H_2), 3.80 (H_{15}), 4.60 (H_3), 4.85 (H_7), 4.97 (H_{11}), 6.67 (H_{10}). $C_{21}H_{34}O_6Si$ requires: M 410. Found: MH$^+$ 411. The diol (1, R = *t*-BuMe$_2$Si, R^1 = H, 1.00 g, 2.44 mmol) in methylene chloride (20 mL) was stirred at room temperature for 6 h with dihydropyran (225 μL, 2.47 mmol) and toluene-4-sulfonic acid (10 mg). After washing with sodium hydrogen carbonate, recovery gave the THP ethers (1, R = *t*-BuMe$_2$Si, R^1 = THP) as a gum (1.16 g, 96%): R_f 0.75; IR ν_{max} 3460 (br), 1695 cm^{-1}.

The ether (1, R = *t*-BuMe$_2$Si, R^1 = THP, 1.06 g) was stirred at room temperature for 2 h with tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 7 mL). The dark solution was diluted with ethyl acetate (25 mL) and washed with water (10 mL). Recovery afforded the diol (1, R = H, R^1 = THP) as a gum (820 mg, 100%): IR ν_{max} 3450, 1690 cm^{-1}.

The diol (1, R = H, R^1 = THP) (760 mg, 2.00 mmol) in methylene chloride (10 mL) and triethylamine (1 mL) was stirred at room temperature for 4 h with acetic anhydride (200 μL, 2.12 mmol) and DMAP (10 mg). After dilution with methylene chloride (10 mL), the solution was washed with 1 *N* hydrochloric acid (10 °C, 2 × 5 mL) and sodium hydrogen carbonate solution. Recovery gave the acetate (1, R = Ac, R^1 = THP) as a gum (717 mg, 85%): IR ν_{max} 3450, 1745, 1685 cm^{-1}.

The acetate (1, R = Ac, R^1 = THP, 687 mg) in methanol (10 mL) and hydrochloric acid (1 N, 3 mL) was stirred at room temperature for 90 min. The solution was concentrated under reduced pressure (bath, 40 °C) to 3 mL, diluted with water (3 mL), and extracted with ethyl acetate, giving a gum (462 mg, 84%), which after column chromatography (see above) and recrystallization from ethyl acetate gave the 15-*O*-acetyl-DON (1, R = Ac, R^1 = H), mp 136–138 °C (443 mg, 81%).

Reaction of DON with Dihydropyran. DON (65 mg, 0.22 mmol) in methylene chloride (25 mL) was stirred at room temperature with toluene-4-sulfonic acid (2 mg) and dihydropyran (25 μL, 0.27 mmol) added at the rate of 5 μL every 10 min. After 90 min, the product was recovered and acetylated in methylene chloride with acetic anhydride–pyridine as described above, giving a gum (84 mg, 91%). This gum in methanol (2 mL) and hydrochloric acid (1 N, 1 mL) was stirred at room temperature for 2 h. After removal of the methanol under reduced pressure, extraction with ethyl acetate furnished a gum (50 mg, 68% overall) shown by NMR analysis to consist of a 1:1 mixture of the acetates 1, R = Ac, R^1 = H and 1, R = H, R^1 = Ac.

B. Experimental Details for Work Carried Out at the Atlantic Research Laboratory. Melting points are uncorrected. TLC was carried out on Merck silica gel plates (0.01-cm thick for analytical work, 0.5-mm thick for preparative) by using ethyl acetate–toluene (1:1) as the solvent. On analytical plates, trichothecenes were detected by UV and by spraying the plates lightly with a solution of ceric sulfate (10 mg) in water (5 mL) diluted with concentrated sulfuric acid to 25 mL. The plates were heated at 100 °C for 5 min when the trichothecenes appeared as purple spots that changed color on standing at room temperature as follows: (1, R = R^1 = Ac) slate grey; (1, R = Ac, R^1 = H) dark green; (1, R = H, R^1 = Ac) orange; (1, R = R^1 = H) violet. High-pressure liquid chromatography was used to determine the composition of mixtures of trichothecenes. The apparatus has been described:[9] a Du Pont Zorbax C_8 reversed-phase column (18 × 0.46 cm) was used, and water–methanol (usually 4:1) was the mobile phase. ^{1}H NMR spectra were obtained on solutions in $CDCl_3$ with Me_4Si as internal standard at 360 MHz at the Atlantic Region Magnetic Resonance Centre, Halifax, Nova Scotia. Methylene chloride was dried over calcium hydride and distilled from this desiccant before use. DCC was distilled [bp 108 °C (1 mm)], and ca. 5-mL lots were sealed into ampules. Petroleum ether was the fraction with bp 30–60 °C.

3α-Acetyl-12,13-epoxy-7α-hydroxy-15-(trityloxy)trichothec-9-en-8-one (1, R = Ph$_3$C, R^1 = Ac). Triphenylmethyl chloride (94.8 mg, 0.35 mmol) and 3-*O*-acetyl-DON (95.9 mg, 0.28 mmol) in pyridine (0.75 mL, 9.3 mmol) were kept at room temperature for 24 h. The solution was evaporated, and the residue on preparative TLC (solvent: diethyl ether–petroleum ether, 2:1) gave triphenylcarbinol (43 mg), 3-*O*-acetyl-DON (39 mg), and the trityl ether (1, R = Ph$_3$C, R^1 = Ac, 98 mg), which separated from diethyl ether–petroleum ether as stout rods: mp 186–187 °C; $[\alpha]^{20}_D$ +20° (*c* 2.01, $CHCl_3$); ^{1}H NMR δ 0.82 (3 H, H_{14}), 1.81 (3 H, H_{16}, $J_{16,10}$ = 1.5 Hz), 2.03 (H_4), 2.67 (H_4), 3.06 (H_{13}), 3.08 (H_{13}, $J_{13,13}$ = 4.3 Hz), 3.15 (H_{15}), 3.53 (H_{15}, $J_{15,15}$ = 10.7 Hz), 3.84 (H_2, $J_{2,3}$ = 4.5 Hz) 4.76 (H_7, $J_{7,7'}$ = 1.9 Hz), 4.93 (H_{11}, $J_{10,11}$ = 5.9 Hz), 5.20 (H_3), 6.57 (H_{10}), 7.20–7.36 (15 H). $C_{36}H_{36}O_7$ requires: C, 74.5; H, 6.25; O, 19.3. Found: C, 74.2; H, 6.3; O, 19.0.

3α,7α-Dihydroxy-12,13-epoxy-15-(trityloxy)trichothec-9-en-8-one (1, R = Ph$_3$C, R^1 = H). The trityl ether (1, R = Ph$_3$C, R^1 = Ac, 104 mg) in methanol (22.5 mL) and triethylamine (2.5 mL) was kept at room temperature for 5 days when it was evaporated. The residue on recrystallization from diethyl ether–petroleum ether (4:1) gave the diol (1, R = Ph$_3$C, R^1 = H): mp 189–192 °C; $[\alpha]^{20}_D$ −2.6° (*c* 1.72, $CHCl_3$). $C_{34}H_{34}O_6$ requires: C, 75.8; H, 6.4; O, 17.8. Found: C, 76.05; H, 6.45; O, 17.8.

3α-Acetoxy-12,13-epoxy-7α-hydroxy-15-[(phenylcarbamoyl)oxy]trichothec-9-en-8-one (1, R = CONHPh, R^1 = Ac). 3-*O*-Acetyl-DON (107 mg, 0.32 mmol) and phenyl isocyanate (0.08 mL, 0.74 mmol) were dissolved in hot benzene (2

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mL). After 7 days at room temperature, phenyl isocyanate (0.08 mL) was added, the solution was kept for 3 days, and water (0.2 mL) was then added. The mixture was stirred for 18 h, the diphenylurea collected, the fitrate evaporated, and the residue digested with cyclohexane (4 × 10 mL). The digests were combined and concentrated to 5 mL, and the precipitate was collected. This solid was purified by preparative TLC (ethyl acetate–toluene, 2:3) and recrystallization of the main band from cyclohexane and then from diethyl ether. The urethane (1, R = CONHPh, R^1 = Ac, 115 mg) separated from diethyl ether as minute needles: mp 79–82 °C; $[\alpha]^{21}_D$ +84° (*c* 1.19, $CHCl_3$); ^1H NMR δ 1.16 (3 H, H_{14}), 1.84 (3 H, H_{16}), 2.16 (3 H, Ac), 2.22 ($H_{4\beta}$, $J_{4,4}$ = 15.0 Hz, $J_{3,4\beta}$ = 11.2 Hz), 2.35 ($H_{4\alpha}$, $J_{3,4\alpha}$ = 4.4 Hz), 3.14 (H_{13}), 3.18 (H_{13}, $J_{13,13}$ = 4.2 Hz), 3.85 (H), 3.93 (H_2, $J_{2,3}$ = 4.3 Hz), 4.29 (H_{15}), 4.58 (H_{15}, $J_{15,15}$ = 12.0 Hz), 4.84 (H_{11}, $J_{10,11}$ = 5.7 Hz), 4.85 (H_7), 5.25 (H_3), 6.52 (H), 6.61 (H_{10}), 7.10–7.34 (5 H). $C_{24}H_{27}NO_8$ requires: C, 63.0; H, 5.95; N, 3.1. Found: C, 63.1; H, 6.0; N, 3.0.

Acetylation of 3-*O*-Acetyl-DON. To the acetate (339 mg, 1 mmol) in methylene chloride (20 mL) were added acetic acid (65 mg, 1.13 mmol), DCC (210 mg, 0.98 mmol), acetic anhydride (0.05 mL, 53 mmol), and DMAP (35 mg), and the solution was stirred overnight. The precipitated urea was filtered off and washed with methylene chloride, and the combined filtrate and washings were washed with ice-cold hydrochloric acid (1.5 N, 3 × 10 mL), sodium hydrogen carbonate solution (2 × 15 mL), and water. Recovery afforded a crystalline residue (380 mg), which was recrystallized from diisopropyl ether, giving needles, mp 117 °C,[5] of 3,15-di-*O*-acetyl-DON (1, R = R^1 = Ac).

Hydrolysis of 3,15-Di-*O*-acetyl-DON. (a) 3,15-Di-*O*-acetyl-DON (0.136 g, 0.36 mmol) in methyl alcohol (45 mL) was treated with triethylamine (5 mL) and kept at room temperature for 24 h. The solvents were evaporated, and the residue (0.11 g) recrystallized from ethyl acetate gave DON (0.098 g, mp 153 °C).

(b) 3,15-Di-*O*-acetyl-DON (47 mg, 0.12 mmol) in methyl alcohol (2 mL) was treated with ammonium hydroxide solution (1 N, 2 mL). Chromatography of the reaction mixture by HPLC, and by TLC, after 25 min revealed none of the starting material and a 1:1:1 mixture of DON, 3-*O*-acetyl-DON, and 15-*O*-acetyl-DON. The reaction mixture was evaporated, and the residue was absorbed from cyclohexane–chloroform (1:9) on silica gel (1.9 × 20 cm). The column was eluted with toluene–ethyl acetate (1:1), and fractions (20 mL) were collected. The 3-acetate (12 mg, mp 170–172 °C) was collected in fractions 30–35 and the 15-acetate (12 mg, mp 139–140 °C) in fractions 38–42, and vomitoxin (10 mg, mp 153 °C) was eluted with ethyl acetate–methyl alcohol (5:1).

Preparation of 15-*O*-Acetyl-DON from Crude Extracts of *F. culmorum* Cultures. The gum [50 g, 30–40% (1, R = H, R^1 = Ac)] from the methanol phase of the methanol–petroleum ether–water partition of the extract from 100 L of *F. culmorum* culture fluid[3] was dissolved in *tert*-butyl methyl ether (400 mL), the filtered solution treated with diisopropyl ether (400 mL), and the solution kept at −15 °C for 48 h. In about one in four cases, the solution required seeding with a crystal of the acetate. The crystalline precipitate [ca. 12 g 80–85% (1, R = H, R^1 = Ac)] was collected, the mother liquors were evaporated to about 200 mL, when a voluminous precipitate [ca. 6 g, 85–88% (1, R = H, R^1 = Ac)] was obtained. This was collected and combined with the crystals.

This material (10 g) was dissolved in methanol (200 mL) and ammonium hydroxide (1.5 N, 110 mL) added. The solution was kept at room temperature (ca. 24 °C) overnight, when the bulk of the methanol was evaporated, and then *tert*-butyl alcohol was added until a homogeneous solution was obtained. This solution was lyophilized and the resulting powder heated at 40 °C (0.01 mm) for 18 h to remove traces of ammonium acetate. The residue (8 g, 80–90% DON) was dispersed in methylene chloride (200 mL) by stirring for 2–3 h at room temperature. The dispersion was treated with DMAP (80 mg) and then dropwise, over 2 h, with a solution (50 mL) of DCC (6.1 g), acetic acid (1.7 g), and acetic anhydride (0.04 g) in methylene chloride. The mixture was stirred for 15 h, when a further 5 mL of the DCC–acetic acid solution and DMAP (40 mg) were added. The mixture was then stirred for 24 h and filtered, the filtrate evaporated, and the residue taken up in ethyl acetate (25 mL). A small quantity of dicyclohexylurea was filtered off, and the filtrate (12.5 mL) was diluted with toluene (12.5 mL). The solution was applied to a silica gel column (Merck "for TLC", 20 × 6.2 cm, made up in toluene), which was then eluted with ethyl acetate–toluene (1:1). In most cases, the eluate was discarded until a pale yellow band was eluted from the column (in other cases, the first 550 mL was discarded). The following fractions [ca. 15 mL (750 drops)] were collected: fractions 9–12 inclusive contained the 3,15-diacetate, fractions 31–40 the 3-acetate, and fractions 50–75 the 15-acetate. Fractions 50–75 were combined and evaporated, and the crystalline residue (2.56 g), mp 140–141 °C, >99%, 15-*O*-acetyl-DON (ca. 60% conversion on the calculated amount of 3-acetate used), was collected with the aid of a little diethyl ether.

Under these conditions, the 15-acetate is usually in the form of very fine needles that are easily dispersed in air. **Suitable precautions** should therefore be taken to avoid contamination of the laboratory and its staff.

Registry No. 1 (R = H, R^1 = Ac), 50722-38-8; 1 (R = R^1 = Ac), 56676-60-9; 1 (R = Ac, R^1 = H), 88337-96-6; 1 (R = *t*-$BuSiMe_2$, R^1 = Ac), 115032-19-4; 1 (R = *t*-$BuSiMe_2$, R^1 = H), 115032-20-7; 1 (R = *t*-$BuSiMe_2$, R^1 = THP), 115032-21-8; 1 (R = H, R^1 = THP), 115032-22-9; 1 (R = Ac, R^1 = THP), 115032-23-0; 1 (R = THP, R^1 = H), 115032-24-1; 1 (R = THP, R^1 = Ac), 115032-25-2; 1 (R = Ph_3C, R^1 = Ac), 115032-26-3; 1 (R = Ph_3C, R^1 = H), 115032-27-4; 1 (R = CONHPh, R^1 = Ac), 115032-28-5; DON, 51481-10-8.

Acyl-Substituent Effects on Ester Aminolysis

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Carbonyl-displacement reactions are a prevalent class of organic and biochemical reactions. Structure–reactivity relationships have been used extensively in mechanistic investigations of these acyl-transfer reactions.[1] For example, the dependence of the rate constants on the basicity (pK_a) of the nucleophile and of the leaving group has been useful in characterizing these reactions in terms of changes in effective charge on reactants in progressing from the ground state to the transition state.[2] Polar aliphatic acyl substituent effects can also be useful in describing the structure of the transition state in carbonyl-displacement reactions.[3,4] Unlike the effects of substituents on the nucleophiles (β_{nuc}) and on the leaving group (β_{lg}), the effects of substituents on the acyl group (ρ^*_{acyl}) depend not just on the charge development but also on the hybridization change upon reaching the transition state.[2,3] By comparing the effects of acyl substituents on the rate of acyl transfers from *p*-nitrophenol to hydroxide and to thiolate with calibrating equilibria (i.e., hydroxide or thiolate addition to a series of substituted aldehydes), we have shown that the magnitude of the Hammett–Taft reaction constant ($\rho^*_{acyl} \sim 3$) is influenced nearly equally by the development of a negative charge on the carbonyl oxygen and by saturation of the carbonyl bond.[3] In these reactions with negatively charged nucleophiles the transition state resembles the anionic tetrahedral intermediate.[3] To further investigate the potential use of the Hammett–Taft reaction constant as an index of transi-

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