7.72 (s, 1 H), 7.30 (d, 2 H, J = 8.3 Hz), 7.72 (d, 2 H, J = 8.3 Hz). Anal. Calcd for $C_{23}H_{29}NO_6S$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.81; H, 6.46; N, 2.93.

6,9-Dimethyl-7,10-dioxo-5,5-(ethylenedioxy)-8-methoxy-1-(*p*-tolylsulfonyl)-1,2,3,4,5,6,7,10-octahydro-1-benzazocine (13). To a solution of **12** (31 mg, 0.069 mmol) in 2 mL of dry DMF was added bis(salicylidene)ethylenediiminocobalt(II) (11 mg, 0.035 mmol). The dark suspension was stirred under an oxygen atmosphere for 3 h. The mixture was filtered through Celite to remove the catalyst, and the catalyst was washed with ethyl acetate. The filtrate and washings were combined, washed with water, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography with a 1:2 mixture of ethyl acetate and hexane as eluent to provide 30 mg (94%) of **13** as bright yellow crystals: mp 175–177 °C; IR ($CHCl_3$) 1660 cm^{-1}; 270-MHz NMR δ 1.60 (d, 3 H, J = 7.7 Hz), 1.6–1.8 (m, 1 H), 1.87 (s, 3 H), 2.1–2.3 (m, 1 H), 2.46 (s, 3 H), 3.12 (ddd, 1 H, J = 10.6, 4.4, 1.5 Hz), 3.6–4.2 (m, 8 H), 4.01 (s, 3 H), 7.33 (d, 2 H, J = 8.4 Hz), 7.64 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{23}H_{27}NO_7S$: C, 59.86; H, 5.90; N, 3.03. Found: C, 59.87; H, 5.95; N, 2.83.

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Registry No. **2**, 88609-66-9; **4**, 116437-99-1; **5**, 116438-00-7; **6**, 116438-01-8; **7**, 116438-02-9; **7** dibenzyl ether, 116438-04-1; **8**, 116438-03-0; **9**, 116438-05-2; **10**, 116438-06-3; **10** (debenzyl derivative), 116438-08-5; **10** (debenzyl deoxo derivative), 116438-09-6; **11**, 116438-07-4; **12**, 116438-10-9; **13**, 116438-11-0; **14**, 116438-12-1; mitomycin, 1404-00-8.

Supplementary Material Available: Crystal data for **8A,B**, the atomic numbering system used in the X-ray analysis, and tables of fractional coordinates, isotropic temperature factors, bond lengths, and bond angles for **8A,B** (6 pages). Ordering information is given on any current masthead page.

8-Ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-Glycosides by Acid-Catalyzed Glycosylation

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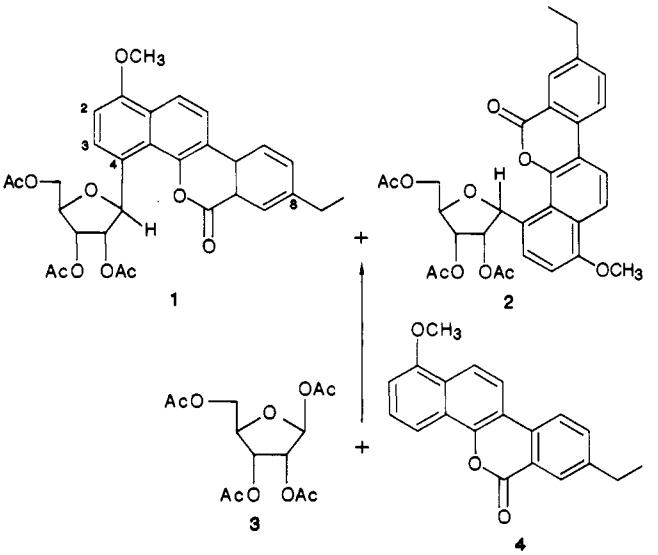
We recently reported[1,2] the first synthesis of *C*-glycosides[3] structurally related to the benzo[*d*]naphtho-[1,2-*b*]pyran-6-one *C*-glycoside antibiotics ravidomycin,[4] the gilvocarcins[5] (toromycin[6]), and the chrysomycins[7] (virenomycin,[8] the albacarcins[9]). The key reaction in these syntheses[1,2] was a palladium-mediated coupling[10] of a glycal (1,2-unsaturated carbohydrate) with a tri-*n*-butylstannyl derivative of the tetracyclic aglycone, which gives rise to 2′-deoxyfuranosyl or 2′-deoxypyranosyl *C*-glycosides. We now report a new, complementary procedure, which was used for preparation of 8-ethyl-1-methoxybenzo[*d*]-naphtho[1,2-*b*]pyran-6-one ribofuranosyl *C*-glycosides **1** and **2**. This procedure involves the direct formation of the *C*-glycosides by Lewis acid-catalyzed condensation of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[11] (**3**) with aglycon **4**.[12]



The aglycon 8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[12] (**4**) was prepared by a sequence developed by Chebaane et al.[13] involving acid-catalyzed condensation of 1,5-naphthalenediol (**5**) with 2-carbethoxy-4-ethylcyclohexanone[14] (**6**) to yield 8-ethyl-1-hydroxy-7,8,9,10-tetrahydrobenzo[*d*]naphtho[1,2-*b*]pyran-6-one (**7**). Methylation of the phenolic hydroxyl of **7** (dimethyl sulfate, potassium carbonate) produced **8**; the tetrahydro ring of this intermediate was aromatized with palladium on carbon to yield aglycon **4**.[12]

Treatment of equimolar portions of **4** and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[11] (**3**) in dry dichloroethane solution with stannic chloride at room temperature effected condensation with elimination of acetic acid to produce a 1:1 mixture of β- and α-*C*-glycosides **1** and **2** in 60% isolated yield. The *C*-glycoside anomers were separated by chromatography (silica gel) and characterized spectroscopically. Mass spectra of each isolated compound exhibited a molecular ion at m/z 562, establishing their isomeric nature and compositions.

The critical structural assignments of (a) the site of

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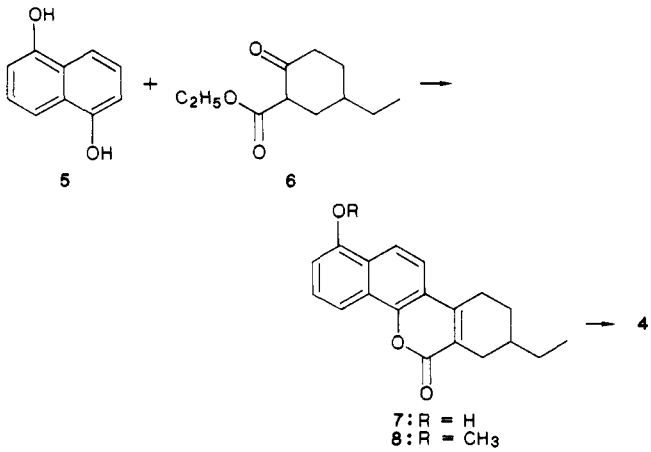

glycosidic linkage to the aglycon in each isomer and (b) the configurations of the ribofuranosyl anomeric centers of the respective isomers were made on the basis of detailed analysis of one and two dimensional nuclear magnetic resonance (NMR, 500 MHz) spectra of **1** and **2** and comparison with appropriate reference data. These analyses establish the site of aglycon glycosylation as C-4 (para to the activating methoxy group) for each isomer and permit assignment of **1** as the β *C*-glycoside anomer and **2** as the α-anomer.

In the ^{1}H NMR spectra of **1** and **2**, the aromatic hydrogen resonances at highest field (δ 6.86 and 6.93, respectively, doublets coupled to resonances at δ 8.05 and 7.94) are uniquely assignable to H-2 of the aglycons by comparison with spectra of known compounds. Invariably, in the ^{1}H NMR spectra of C-4-glycosylated benzo[*d*]naphtho[1,2-*b*]pyran-6-ones,[4-7] the resonance for H-2 is the aromatic resonance at highest field. In the ^{1}H NMR spectrum of gilvocarcin V,[15] the resonance for H-2 is observed at δ 6.92. In spectra of the synthetic C-4-glycosylated benzo[*d*]naphtho[1,2-*b*]pyranones we have prepared,[1,2] resonances for H-2 are observed at δ 6.93–7.00; whereas in spectra of isomeric C-2-glycosylated compounds, no resonance is present in the δ 6.9–7.0 region.[2]

Assignments of configurations at the anomeric centers (C-1′) of the ribofuranosyl groups of **1** and **2** made by comparison of NMR data with those of known *C*-glycosides were equally definitive. Discrimination between the isomers was most apparent from the ^{1}H chemical shifts of the carbohydrate *O*-acetyl methyl groups. In the spectrum of the β-anomer **1**, acetyl group methyl resonances were present at δ 2.29, 2.19, and 1.97; corresponding resonances for the α-anomer **2** were observed at δ 2.17, 2.02, and 1.53. The unusually high field acetyl methyl resonance (δ 1.53) in the spectrum of **2** is indicative of shielding by a neighboring (cis) aryl ring and establishes this *C*-glycoside as the α-anomer. This configurational relationship whereby a carbohydrate 2′-*O*-acetyl group cis to an electron-rich aromatic aglycon is shielded by ring π-electrons and gives rise to an unusually high field methyl resonance in the ^{1}H NMR spectrum is well recognized.[7,16,17] Such high-field ^{1}H resonances for a cis 2′-*O*-acetyl methyl group are observed for triacetylchrysomycin A (δ 1.20),[7] tetraacetylgilvocarcin V (δ 1.52)[5a] and diacetylravidomycin (δ 1.60).[4]

The successful Lewis acid catalyzed glycosylation of the benzo[*d*]naphtho[1,2-*b*]pyran-6-one aglycon system provides a remarkably direct synthetic route to *C*-glycosides of this important antibiotic class[1-9] in which the carbohydrate is fully functionalized. This synthesis complements the route involving palladium-mediated coupling of glycals with aglycons[1,2,10] which yields 2′-deoxy carbohydrate *C*-glycosides. Preparation of aromatic *C*-glycosides by Lewis acid catalyzed glycosylation, first demonstrated by Hurd and Bonner,[18] has been used for preparation of both furanosyl and pyranosyl *C*-glycosides of a variety of electron-rich aromatic compounds.[19-26]

Experimental Section

General Comments. Thin-layer chromatography (TLC) was carried out on prescored silica gel GF plates (Analtech). Preparative TLC was carried out on 1 mm thick, 20 × 20 cm, silica gel GF plates (Analtech). For flash chromatography, silica gel 60 (230–400 mesh ASTM, E. Merck) was used. Columns were eluted with a positive nitrogen pressure. Nuclear magnetic resonance spectra were obtained on a JEOL FX 90Q spectrometer or on a Bruker AM 500 spectrometer and are referenced to tetramethylsilane. Mass spectra (EI) were obtained with a Finnegan 4023 GC/MS/DS system operating at 70 eV with a direct insertion probe. Melting points were measured with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out by Dr. G. Robertson, Florham Park, NJ.

8-Ethyl-1-hydroxy-7,8,9,10-tetrahydrobenzo[*d*]naphtho[1,2-*b*]pyran-6-one (7). Dry hydrogen chloride was passes through a water bath cooled solution of 1,5-naphthalenediol[13] (**5**) (3.049 g, 19 mmol) and 2-carbethoxy-4-ethylcyclohexanone[14] (**6**) (5.334 g, 27.7 mmol) in 40 mL of anhydrous ethanol for 30 min. After 20 min the water bath was removed, and the reaction mixture was stirred at room temperature for 18 h. The precipitate that formed was then collected by filtration and recrystallized from acetone to yield 3.02 g (54%) of **7** as beige needles: mp 251–253 °C dec; MS, *m/z* 294; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.1–1.7 (br, 4 H, H_2-9, Et CH_2), 1.8–2.2 (m, 1 H, H-8), 2.4–3.1 (m, 4 H, H_2-7, H_2-10), 7.04 (dd, 1 H, $J_{2,3}$ = 7.5 Hz, $J_{2,4}$ = 0.8 Hz, H-2), 7.49 (dd, 1 H, $J_{3,4}$ = 8.2 Hz, H-3), 7.64 (d, 1 H, J = 8.8 Hz, H-11), 7.77 (dd, 1 H, H-4), 10.45 (br, 1 H, OH). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.6; H, 6.16. Found: C, 77.5; H, 5.91.

8-Ethyl-1-methoxy-7,8,9,10-tetrahydrobenzo[*d*]naphtho[1,2-*b*]pyran-6-one (8). Dimethyl sulfate (1.9 mL, 11.3 mmol) was added dropwise to a solution of **7** (2.165 g, 7.4 mmol) in 80 mL of acetone containing potassium carbonate (4.13 g, 30 mmol). The reaction mixture was heated under reflux for 12 h. Then 2 mL of ethanol was added to destroy unreacted dimethyl sulfate, and the solution was decanted and concentrated to 5–10 mL. This residue was partitioned between chloroform and water. The organic extract was washed with water and dried over sodium sulfate, and the solvent was removed. The resulting residue was recrystallized from acetone to yield 1.98 g (87%) of **8**: mp 156 °C; MS, *m/z* 308; ^{1}H NMR ($CDCl_3$) δ 2.7–3.0 (m, 4 H, H_2-7, H_2-10), 4.00 (s, 3 H), OCH_3), 6.94, (dd, 1 H, $J_{2,3}$ = 7.5 Hz, $J_{2,4}$ = 0.8 Hz, H-2), 7.51 (dd, 1 H, $J_{3,4}$ = 8.5 Hz, H-3), 7.54 (d, 1 H, $J_{11,12}$ = 8.8 Hz, H-11), 8.08 (dd, 1 H, $J_{4,12}$ = 0.8 Hz, H-12), 8.13 (ddd, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 11.29, (CH_3), 25.70 (CH_2), 27.21, 28.73, 30.14 (C-7), 34.42 (C-10), 55.55 (OCH_3), 105.88 (C-2), 114.16 (C-4), 115.46, 117.85, 118.61, 122.78, 124.02, 125.81, 126.95, 147.64, 148.02 (C-5), 155.01 (C-1), 161.67 (C=O). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.9; H, 6.54. Found: C, 77.7; H, 6.80.

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8-Ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one (4). A mixture of 8 (170 mg, 0.55 mmol) and 10% palladium on carbon (170 mg) was heated at 200 °C under vacuum for 10 h. During this period the reaction mixture was monitored by thin-layer chromatography (CH_2Cl_2, R_f(8) = 0.26, R_f(4) = 0.56). When the reaction was complete, the crude product was removed from the carbon by successive triturations with hot benzene and chloroform. The combined extract was evaporated to dryness, and the resulting residue was crystallized from cyclohexane–dichloromethane to yield 122 mg (72%) of 4 as fine, white needles: mp 174 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, CH_3) 2.81 (q, 2 H, benzylic), 4.02 (s, 3 H, OCH_3), 6.79 (d, 1 H, $J_{2,3}$ = 7.6 Hz, H-2), 7.41 (dd, 1 H, $J_{3,4}$ = 8.1 Hz, H-3) 7.54 (dd, 1 H, $J_{9,10}$ = 8.1 Hz, $J_{7,10}$ = 1.8 Hz, H-9), 7.77 (d, 1 H, $J_{11,12}$ = 9.0 Hz, H-11), 7.89 (d, 1 H, H-10), 7.96 (d 1 H, H-12), 7.98 (d, 1 H, H-4), 8.14 (d, 1 H, H-7); ^{13}C NMR ($CDCl_3$) δ 15.08 (CH_3), 28.51 (benzylic), 55.49 (OCH_3), 105.55 (C-2), 113.46, 114.06 (C-4), 118.01, 118.34 (C-11, C-12), 120.94, 122.02 (C-3), 124.67, 125.76, 127.00 (C-10), 128.87 (C-7), 132.80, 134.80 (C-9), 144.93, 146.34, 155.07 (C-1), 161.30 (C=O). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.71; H, 5.29.

8-Ethyl-1-methoxy-4-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (1) and 8-Ethyl-1-methoxy-4-(2′,3′,5′-tri-*O*-acetyl-α-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one (2). To a stirred solution of 4 (600 mg, 1.97 mmol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[11] (3) (628 mg, 1.97 mmol) in 40 mL of dichloroethane was added stannic chloride (0.7 mL, 6 mmol). After 24 h at room temperature, the reaction mixture was poured into an aqueous sodium bicarbonate solution. The organic phase was separated and washed with water. The extract was dried (sodium sulfate), and the solvent was evaporated; the resulting residue was separated by preparative thin-layer chromatography (dichloromethane–ether, 14:1). Unreacted 4 (145 mg, 23%), 351 mg (32%) of **2**, off-white crystals (mp 200 °C), and 315 mg (29%) of 1, off-white crystals (mp 193 °C), were obtained. For 1: MS, *m/z* 562 (1.6%, M$^{\bullet+}$), 383 (100%, M$^{\bullet+}$ - 2AcOH - OAc); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7.6 Hz, CH_3), 1.97, 2.19, 2.29 (3 s, 9 H, acetyl), 2.76 (q, 2 H, benzylic), 4.00 (s, 3 H, OCH_3), 4.46 (dd, 1 H, *J* = 12.2 Hz, *J* = 5.0 Hz, H-5′), 4.53 (dd, 1 H, *J* = 2.6 Hz, H-5′), 4.56 (ddd, 1 H, $J_{4',3'}$ = 9.5 Hz, $J_{4',5'}$ = 2.6 Hz, $J_{4',5'}$ = 5.0 Hz, H-4′), 5.16 (dd, 1 H, $J_{2',3'}$ = 4.2 Hz, H-3′), 5.59 (d, 1 H, H-2′), 6.58 (brs, 1 H, H-1′), 6.86 (d, 1 H, $J_{2,3}$ = 8.4 Hz, H-2), 7.65 (dd, 1 H, $J_{9,10}$ = 8.3 Hz, $J_{9,7}$ = 1.9 Hz, H-9), 8.03 (d, 1 H, $J_{11,12}$ = 9.0 Hz, H-11), 8.05 (d, 1 H, H-3), 8.09 (d, 1 H, H-10), 8.15 (d, 1 H, H-7), 8.23 (d, 1 H, H-12); ^{13}C NMR ($CDCl_3$) δ 15.19 (CH_3), 20.50, 20.95, 21.21 (acetyl), 28.56 (benzylic), 55.73 (OCH_3), 63.16 (C-5′), 69.59 (C-3′), 76.37, 76.47 (C-2′,C-4′), 82.60 (C-1′), 104.81 (C-2), 115.25 (C-4), 118.79 (C-12), 119.28 (C-11), 120.36 (C-8), 122.01, 122.43 (C-3), 125.62 (C-10), 126.77, 127.28, 128.75 (C-7), 132.80, 135.09 (C-9), 145.42 (C-6a), 147.32 (C-5), 154.97 (C-1), 160.31 (C-6), 169.72, 170.66, 170.76 (acetyl C=O). Anal. Calcd for $C_{31}H_{30}O_{10}$: C, 66.2; H, 5.38. Found: C, 66.0; H, 5.14.

For 2: MS, *m/z* 562 (7.1%, M$^{\bullet+}$), 383 (100%, M$^{\bullet+}$ - 2AcOH - OAc); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, *J* = 7.6 Hz, CH_3), 1.53, 2.02, 2.17 (3 s, 9 H, acetyl), 2.80 (q, 2 H, benzylic), 4.02 (s, 3 H, OCH_3), 4.34 (dd, 1 H, $J_{5',5'}$ = 12.2 Hz, $J_{5',4'}$ = 5.1 Hz, H-5′), 4.48–4.52 (m, 2 H, H-4′, H-5′), 5.69 (dd, 1 H, $J_{3',2'}$ = 4.8 Hz, $J_{3',4'}$ = 7.6 Hz, H-3′), 6.35 (dd, 1 H, *J* = 3.5 Hz, H-2′), 6.72 (d, 1 H, H-1′), 6.93 (d, 1 H, $J_{3,2}$ = 8.4 Hz, H-2), 7.68 (dd, 1 H, $J_{9,7}$ = 1.9 Hz, $J_{9,10}$ = 8.3 Hz, H-9), 7.94 (d, 1 H, H-3), 8.02 (d, 1 H, $J_{11,12}$ = 9.1 Hz, H-11), 8.11 (d, 1 H, H-10), 8.23 (d, 1 H, H-12), 8.24 (d, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 15.21 (CH_3), 20.14, 20.55, 20.93 (acetyl), 28.59 (benzylic), 55.68 (OCH_3), 64.40 (C-5′), 73.02, 73.66, 77.71 (C-2′, C-3′, C-4′), 80.59 (C-1′), 104.83 (C-2), 114.81 (C-4), 118.44 (C-12), 118.99 (C-11), 120.41 (C-8), 122.43 (C-3 and quaternary), 124.09, 126.60, 126.98 (C-10), 128.82 (C-7), 132.99, 135.10 (C-9), 145.42 (C-6a), 147.41 (C-5), 154.68 (C-1), 160.35 (C-6), 169.04, 169.54, 171.00 (acetyl C=O). Anal. Calcd for $C_{31}H_{30}O_{10}$: C, 66.2; H, 5.38. Found: C, 66.0; H, 5.10.

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Registry No. 1, 116596-78-2; 2, 116596-79-3; 3, 13035-61-5; 4, 114862-65-6; 5, 83-56-7; 6, 116596-80-6; 7, 114862-61-2; 8, 114862-62-3.

Aryl Exchange via Reversible Friedel–Crafts Reaction in the Synthesis of a Diarylacetic Acid

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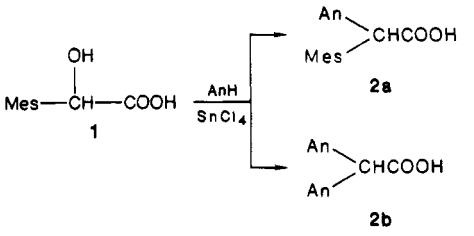
Friedel–Crafts alkylations are reversible processes as judged by transalkylation and reorientation reactions and the formation of the thermodynamically more stable product if the processes take place for sufficient time.[1]

In the course of an attempted preparation of a diarylacetic acid via a Friedel–Crafts type alkylation of an aromatic substrate by an arylglycolic acid, we observed a product which suggests that exchange of an aryl group between the two precursors takes place. We believe that this is due to the reversibility of the Friedel–Crafts reaction after an initial proton transfer. Alkyl transfers are known,[1] and aryl "replacement" reactions were reported in the $AlCl_3$-catalyzed reaction of few β,β-diarylpropionic acids with aromatic solvents[2] or in the $AlCl_3$-catalyzed addition of ArH to cinnamic acids, which presumably proceeds via the β,β-diarylpropionic acids.[2] Since we did not find a precedent for this behavior in our particular system, we report this interesting variant of the reaction here.

Reflux of mesitylglycolic acid (1)[3] with anisole as the solvent (16-fold excess over 1) in the presence of excess anhydrous stannic chloride gave 70% yield of an acid, which is not the expected anisylmesitylacetic acid (**2a**) since it showed no mesityl-methyl signals in the NMR. The acid was identified as 2,2-di-*p*-anisylacetic acid (**2b**) (eq 1).



(1)

Mes = 2,4,6-$Me_3C_6H_2$; An = 4-$MeOC_6H_4$

In order to see if this results from the large concentration of anisole, the same reaction was conducted in refluxing CS_2 with only a slight excess of anisole and with the same or a different order of mixing the reagents. Both **2a** and **2b** were formed under these conditions, either in a 1:1 ratio when $SnCl_4$ is dripped into the anisole–CS_2 solution, or in a 4.8-fold excess of **2a** when the anisole is dripped into the $SnCl_4$–CS_2 solution (eq 1).

The reaction conditions are those of a Friedel–Crafts reaction where the carbenium ion **3a** generated from **1** with the Lewis acid catlayst $SnCl_4$ electrophilically attacks the activated anisole to give cation **4a**. The parallel formation of **2a** and **2b** and the exclusive formation of **2b** with excess

(1) (a) Olah, G. A. Friedel–Crafts Chemistry; Wiley: New York, 1972; e.g. pp 36 and 179. (b) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984; Chapter 7, pp 673 and 680. (c) Streitwieser, A., Jr.; Reif, L. *J. Am. Chem. Soc.* **1964**, *86*, 1988.

(2) (a) Fuson, R. C.; Kozacik, A. P.; Eaton, J. T. *J. Am. Chem. Soc.* **1933**, *55*, 3799. (b) Dippy, J. F. J.; Young, J. T. *J. Chem. Soc.* **1952**, 1817; **1955**, 3919. (c) Koncos, R.; Friedman, B. S. In *Friedel–Crafts and Related Reactions*, Olah, G. A., Ed.; Interscience: New York, 1963; Vol. II, Chapter XV, pp 324–326. We are indebted to a referee for bringing these references to our attention.

(3) Riebsomer, J. L.; Irvine, J.; Andrews, R. *J. Am. Chem. Soc.* **1938**, *60*, 1015.

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