Synthesis of Tetra- and Pentasubstituted Benzenes from Dimedone and Derivatives[1]

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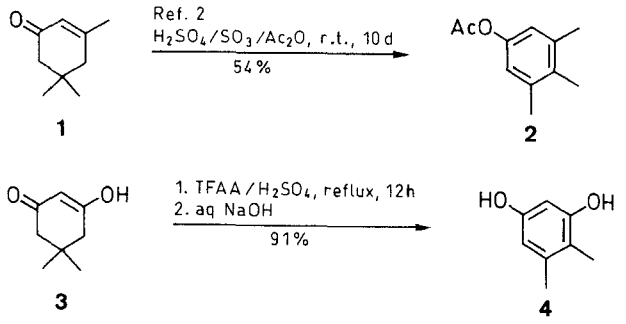
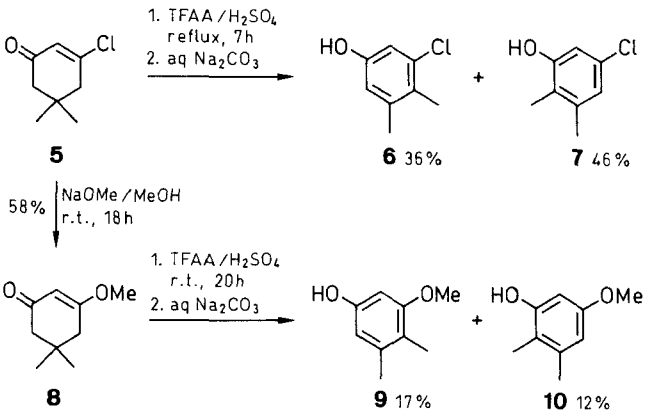
Treatment of dimedone (5,5-dimethylcyclohexane-1,3-dione) and derivatives with one molar equivalent of sulfuric acid in trifluoroacetic anhydride leads, via sulfonation and a 1,2-methyl group migration, to a variety of dimethylresorcinol derivatives. The reaction has been performed on substrates bearing ester, alkoxy, halo and amino substituents to produce a variety of polysubstituted benzenes. Transient sulfonated intermediates were observed by NMR.

The conversion of some cyclohexanone and cyclohexenone derivatives to benzenoid compounds under sulfonating conditions was first reported by von Doering.[2] Treatment of 3,3,5-trimethylcyclohex-5-en-1-one (**1**) with 5% oleum in acetic anhydride gave a 54% yield of 3,4,5-trimethylphenyl acetate (**2**) (Scheme 1). In this and related reactions, sulfur dioxide was evolved and intermediate sulfonic acids, convertible to the benzenoid final products by treatment with acetic anhydride at reflux, could be isolated. Subsequently,[3] it was shown that cyclohexanediones were converted to the corresponding diacetoxybenzenes by treatment with sulfuric acid in refluxing acetic anhydride. Under these conditions, dimedone (5,5-dimethylcyclohexane-1,3-dione, **3**) was converted into the diacetate of 4,5-dimethylresorcinol **4**. We have examined the scope and limitations of the latter reaction, and report our findings herein.



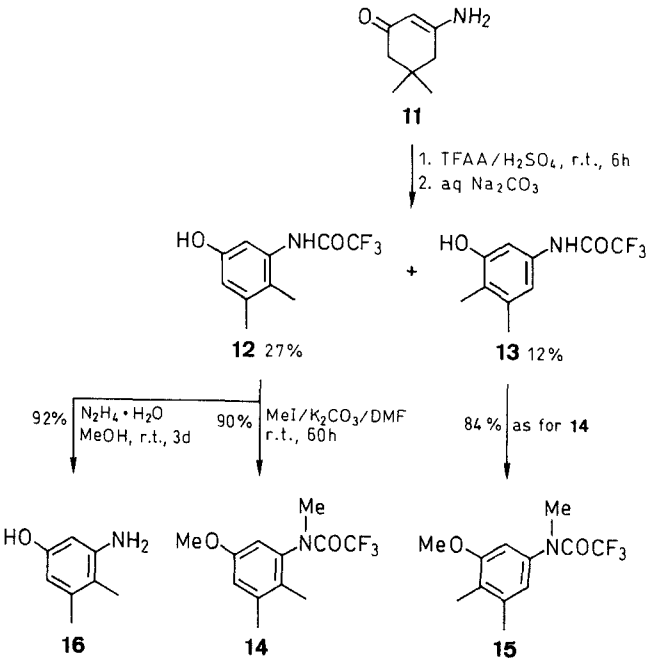
Scheme 1

Attempted aromatization of dimedone, under the conditions of Reference 3, produced, after basic hydrolysis and chromatography, a 44% yield of **4**, together with 17% of 2-acetyldimedone, a product not reported in the original work. Despite efforts to exclude oxygen,[3] the reaction mixture was black and the workup was difficult. In an attempt to avoid the formation of dark products, trifluoroacetic anhydride was used instead of acetic anhydride, and under these conditions a clean conversion to **4** (ca. 90% yield) was obtained. The reaction could be performed at room temperature (3–5 days) or at reflux (12 hours); on a multigram scale, completion of the reaction was indicated by the cessation of sulfur dioxide evolution. A number of workup procedures were employed (see Experimental Section). Ultimately it was found easiest to remove trifluoroacetic anhydride at room temperature under a modest vacuum, and then to subject the crude product, in which the phenolic hydroxy groups were present as trifluoroacetate esters, to a mild hydrolysis.



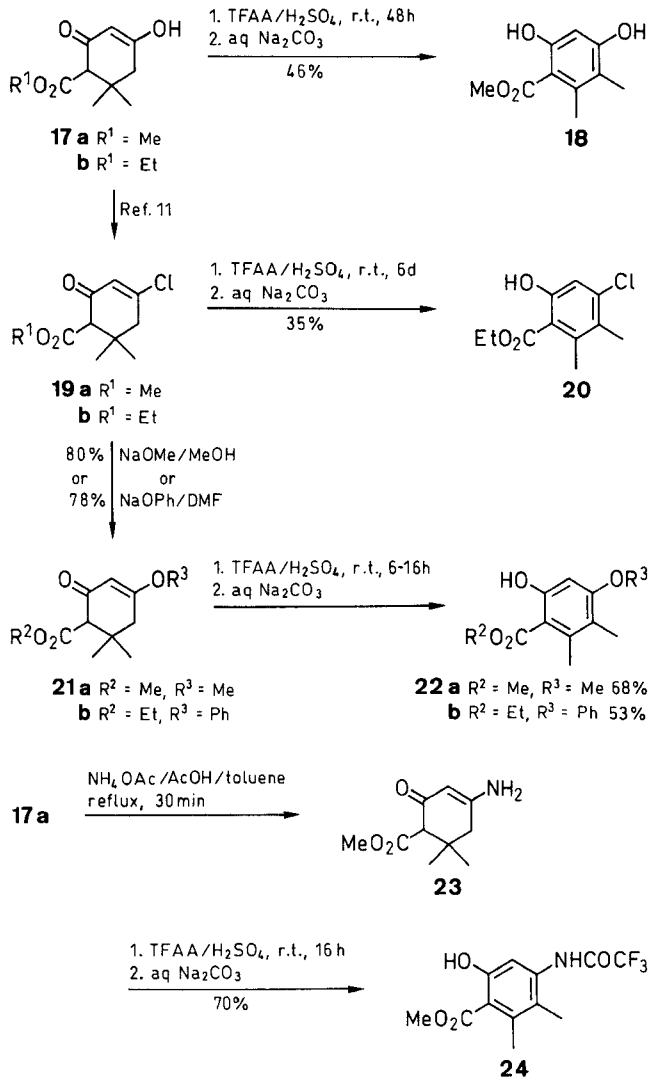
Scheme 2

Using the improved procedure, chloro, methoxy (Scheme 2) and amino (Scheme 3) derivatives of dimedone were converted into the corresponding benzenoid compounds. In the latter cases, the methyl group migration which accompanies aromatization occurred in both of the available directions, and two products, separable by chromatography, were obtained. The anilines (Scheme 3) were isolated as the trifluoroacetyl amides **12** and **13**, and were converted into *N,O*-dimethyl derivatives to facilitate structure determination by NMR. Removal of the trifluoroacetyl moiety was effected by transacylation with hydrazine.



Scheme 3

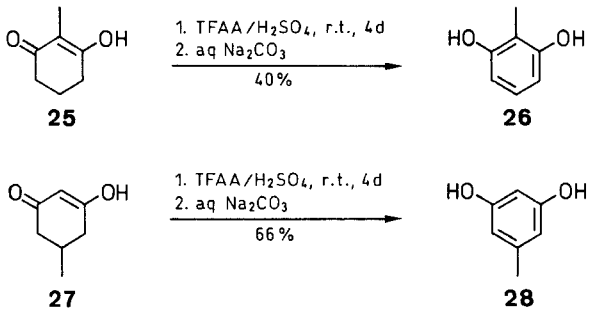
More specific results were obtained when 2,2-dimethyl-4,6-dioxocyclohexane-1-carboxylates, and compounds derived therefrom, were subjected to the aromatization procedure, (Scheme 4). In these cases, methyl group migration is constrained to one direction, and only one aromatic product was obtained. Since the vinylogous acid chlorides **5** and **19** react smoothly with a variety of nucleophiles, the method can be used to prepare diverse tetra- and pentasubstituted benzenes whose syntheses by conventional routes would require many steps.



Scheme 4

2- and 5-Methylcyclohexane-1,3-diones were converted respectively into 2- and 5-methylresorcinols (Scheme 5), confirming previous results,[2,3] and indicating the broad potential scope of the aromatization procedure. The structures of the isomeric products of Schemes 2–4 were determined by ^1H and ^{13}C NMR, with appropriate NOE difference experiments.[4]

All reactions were performed under N_2. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$). Trifluoroacetic anhydride (TFAA) (99%) was purchased from Aldrich Chemical Co. The 299.9 MHz ^1H and 75.4 MHz ^{13}C NMR data were acquired on a Bruker ACF 300 spectrometer using TMS as internal reference. The ^{13}C NMR assignments were aided by the use of long-range ^1H-^{13}C heteronuclear correlation spectroscopy. The NOE difference experiments were performed on a Bruker WM 300 NMR spectrometer using the standard Bruker microprogrammes HOMNOEDF and HOMNOEPR and were not quantified.



Scheme 5

4,5-Dimethylresorcinol (4):

To an ice-cooled magnetically stirred solution of 5,5-dimethylcyclohexane-1,3-dione (**3**;[5] 49.6 g, 0.35 mol) in TFAA (30 mL), was added H_2SO_4 (36 g, 0.37 mol), over 10 min. The mixture was allowed to warm to r.t., and was then refluxed for 12 h, by which time gas evolution, monitored by a bubbler attached to the reflux condenser, stopped. The cooled solution was then added dropwise to an ice cooled stirred solution of NaOH (160 g, 4.0 mol) in H_2O (750 mL), at such a rate that the temperature was below 25 °C. The resultant alkaline solution was left for 30 min then acidified by the addition of conc. HCl (50 mL). The resultant solution was extracted with Et_2O (2 × 300 mL), and the extract was dried and evaporated to yield **4**; yield 45.5 g, 91% mp 134–136 °C (toluene) (Lit.[6] mp 134–135 °C).

3-Chloro-4,5-dimethylphenol (6) and 5-Chloro-2,3-dimethylphenol (7):

3-Chloro-5,5-dimethylcyclohex-2-enone (**5**,[7] 5.0 g, 0.315 mol) was added to TFAA (50 mL) cooled in ice. H_2SO_4 (3.26 g, 0.033 mol) was then added. The solution was refluxed for 7 h. The TFAA was distilled into a dry-ice cooled receiver under a vacuum of ca. 70 Torr, and the residual oil was added to ice (50 g). The resultant solution was basified by addition of solid Na_2CO_3 until CO_2 evolution no longer occurred. After 30 min, the solution was acidified by addition of 2 N HCl (25 mL) and extracted with EtOAc (100 mL). The extract was dried and evaporated and the residue (5.3 g) was chromatographed on silica gel (500 g), eluting with hexane/Et_2O (12:1) to produce firstly, **6**; yield 1.8 g, 36%; mp 88–91 °C (Et_2O/hexane) (Lit.[8] mp 88 °C).

C_8H_9ClO (156.6) calc. C 61.35 H 5.79
found 60.98 5.88

^1H NMR ($CDCl_3$/TMS): δ = 2.22 (s, 3H, C4-CH_3), 2.24 (s, 3H, C5-CH_3), 6.56 (d, 1H, J = 2.6 Hz, H-6), 6.73 (d, 1H, 2.6 Hz, H-2).

^{13}C NMR ($CDCl_3$/TMS): δ = 15.34 (q, C4-CH_3), 21.03 (q, C5-CH_3), 113.70 (d, C-2), 115.64 (d, C-6), 126.61 (s, C-4), 134.68 (s, C-3), 139.45 (s, C-5), 153.20 (s, C-1).

and then **7**; yield 2.3 g, 46% mp 78–81 °C (Et_2O/hexane). (Lit.[9] mp 81–82 °C).

C_8H_9ClO (156.6) calc. C 61.35 H 5.79
found 60.96 5.81

^1H NMR ($CDCl_3$/TMS): δ = 2.09 (s, 3H, C2-CH_3), 2.22 (s, 3H, C3-CH_3), 6.63 (d, 1H, J = 1.9 Hz, H-6), 6.74 (d, 1H, J = 1.9 Hz, H-4).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.25 (q, C2-CH_3), 20.05 (q, C3-CH_3), 113.01 (d, C-6), 121.22 (s, C-2), 122.37 (d, C-4), 130.78 (s, C-5), 139.67 (s, C-3), 154.06 (s, C-1).

4,5-Dimethyl-3-methoxyphenol (9) and 2,3-Dimethyl-5-methoxyphenol (10):

5,5-Dimethyl-3-methoxycyclohex-2-enone (**8**):

Na (450 mg, 0.0196 mol) was added to MeOH (50 mL) to produce a solution of NaOMe, to which was added **5** (3.3 g, 0.016 mol). After

18 h the solution was diluted with Et_2O (200 mL) and washed with H_2O (3 × 100 mL). The ethereal solution was dried and evaporated and the residual oil was chromatographed on silica gel (50 g), eluting with hexane/EtOAc (3:1), to produce **8** as an oil; yield 1.9 g, 58%.

$C_9H_{14}O_2$ (154.2) calc. C 70.05 H 9.15 found 69.77 8.99

^1H NMR ($CDCl_3$/TMS): δ = 1.08 (s, 6H, CH_3), 2.22 (s, 2H, H-6), 2.28 (s, 2H, H-4), 3.71 (s, 3H, OCH_3), 5.38 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$/TMS): δ = 28.24 (q, C5-diCH$_3$), 32.54 (s, C-5), 42.46 (t, C-4), 50.67 (t, C-6), 55.74 (q, OCH_3), 101.06 (d, C-2), 177.38 (s, C-3), 203.76 (s, C-1).

Aromatization of **8** *to give* **9** *and* **10**

Compound **8** (2.86 g, 0.0135 mol) was dissolved in ice-cooled TFAA (30 mL) and H_2SO_4 (2.0 g, 0.014 mol) was added with vigorous magnetic stirring. After 20 h at r.t., the reaction was worked up as described above for the preparation of **6** and **7**. The oily product (2.0 g) was chromatographed on silica gel (200 g), eluting with hexane/Et_2O (3:1), to afford firstly **10**; yield 476 mg, 17%; mp 82–83 °C (hexane).

$C_9H_{12}O_3$ (168.2) calc. C 71.02 H 7.94 found 69.78 7.85

^1H NMR ($CDCl_3$/TMS): δ = 2.08 (s, 3H, C4-CH_3), 2.24 (s, 3H, C5-CH_3), 3.74 (s, 3H, OCH_3), 6.25 (d, 1H, J = 2.4 Hz, H-2), 6.35 (d, 1H, J = 2.4 Hz, H-6).

^{13}C NMR ($CDCl_3$/TMS): δ = 10.96 (q, C4-CH_3), 20.56 (q, C5-CH_3), 55.36 (q, OCH_3), 99.10 (d, C-2), 108.12 (d, C-6), 114.58 (s, C-4), 139.01 (s, C-5), 154.37 (s, C-3), 158.00 (s, C-1).

then **9**; yield 344 mg, 12%; mp 71–73 °C (hexane).

$C_9H_{12}O_3$ (168.2) calc. C 71.02 H 7.94 found 71.11 7.94

^1H NMR ($CDCl_3$/TMS): δ = 2.04 (s, 3H, C4-CH_3), 2.19 (s, 3H, C5-CH_3), 3.75 (s, 3H, OCH_3), 4.99 (s, 1H, OH), 6.26 (s, 2H, H-2, H-6).

^{13}C NMR ($CDCl_3$/TMS): δ = 10.98 (q, C4-CH_3), 20.21 (q, C5-CH_3), 55.63 (q, OCH_3), 96.56 (d, C-2), 108.73 (d, C-6), 117.13 (s, C-4), 138.60 (s, C-5), 153.76 (s, C-1), 158.50 (s, C-3).

Mixed fractions containing 210 mg of **9** and **10** were obtained.

4,5-Dimethyl-3-(trifluoroacetylamino)phenol (12) and 2,3-Dimethyl-5-(trifluoroacetylamino)phenol (13):

3-Amino-5,5-dimethylcyclohex-2-enone (**11**;[10] 5.0 g, 0.036 mol) was added to ice-cooled TFAA (40 mL). To the resultant solution was added H_2SO_4 (3.88 g, 0.04 mol). The mixture was left at r.t. for 60 h, then worked up as described above for the preparation of **6** and **7**. The crude product (4.8 g) was chromatographed on silica gel (300 g), eluting with hexane/EtOAc (4:1), to afford first **13**; yield 980 mg, 12%; mp 126–130 °C (EtOAc/hexane).

$C_{10}H_{10}F_3NO_2$ (233.2) calc. C 51.51 H 4.32 N 6.01 found 51.55 4.46 6.00

^1H NMR ($CDCl_3$/TMS): δ = 2.13 (s, 3H, C4-CH_3), 2.25 (s, 3H, C3-CH_3), 6.71 (d, 1H, J = 1.9 Hz, H-2), 7.24 (d, 1H, J = 2.1 Hz, H-6).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.19 (q, C4-CH_3), 19.98 (q, CH_3), 105.47 (d, C-6), 113.32 (d, C-2), 115.80 (s, J_{CF} = 288.6 Hz, CF_3), 120.97 (s, C-4), 133.10 (s, C-1), 138.22 (s, C-3), 154.68 (s, J_{CF} = 37.4 Hz, NHCO), 154.94 (s, C-5).

and then **12**; yield 2.29 g, 27%; mp 116–117 °C (Et_2O/hexane).

$C_{10}H_{10}F_3NO_2$ (233.2) calc. C 51.51 H 4.32 N 6.01 found 51.37 4.20 5.81

^1H NMR ($CDCl_3$/TMS): δ = 2.09 (s, 3H, C2-CH_3), 2.26 (s, 3H, C3-CH_3), 6.63 (d, 1H, J = 2.5 Hz, H-4), 7.17 (d, 1H, J = 2.5 Hz, H-6).

^{13}C NMR ($CDCl_3$/TMS): δ = 12.92 (q, C2-CH_3), 20.50 (q, C3-CH_3), 110.08 (d, C-6), 116.15 (s, J_{CF} = 288.6 Hz, CF_3), 116.69 (d, C-4), 121.80 (s, C-2), 133.06 (s, C-1), 138.74 (s, C-3), 154.73 (s, C-5), 155.65 (s, J_{CF} = 36.8 Hz, NHCO).

Methylation of 12 and 13:

Compound **12** (500 mg, 0.0021 mol) was stirred in DMF (3 mL) containing K_2CO_3 (500 mg, 0.0036 mol) and MeI (1.5 g, 0.0106 mol) for 60 h. The mixture was added to H_2O (50 mL) and extracted with Et_2O (50 mL). The extract was dried and filtered through a short column of silica gel (ca. 10 g). The eluate was evaporated to yield **14**; yield 505 mg, 92%; mp 69–71.5 °C (acetone/hexane).

$C_{12}H_{14}F_3NO_2$ (261.2) calc. C 55.17 H 5.40 N 5.36 found 55.29 5.46 4.82

^1H NMR ($CDCl_3$/TMS): δ = 2.05 (s, 3H, C2-CH_3), 2.29 (s, 3H, C3-CH_3), 3.26 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 6.55 (d, 1H, J = 2.4 Hz, H-6), 6.78 (d, 1H, J = 2.6 Hz, H-4).

^{13}C NMR ($CDCl_3$/TMS): δ = 13.29 (q, C2-CH_3), 20.63 (q, C3-CH_3), 38.42 (q, NCH_3), 55.39 (q, OCH_3), 110.95 (d, C-6), 116.36 (s, J_{CF} = 288.1 Hz, CF_3), 116.76 (d, C-4), 126.13 (s, C-2), 139.61 (s, C-3), 139.77 (s, C-1), 157.19 (s, J_{CF} = 35.5 Hz, NHCO), 157.52 (s, C-5).

Using the same procedure, compound **13** gave **15**; yield 470 mg, 85%; mp 86–88 °C (aq MeOH).

$C_{12}H_{14}F_3NO_2$ (261.2) calc. C 55.17 H 5.40 N 5.36 found 54.44 5.49 5.08

^1H NMR ($CDCl_3$/TMS): δ = 2.14 (s, 3H, C4-CH_3), 2.27 (s, 3H, C3-CH_3), 3.33 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.54 (br s, 1H, H-6), 6.65 (br s, 1H, H-2).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.57 (q, C4-CH_3), 20.07 (q, C3-CH_3), 39.07 (q, NCH_3), 55.71 (q, OCH_3), 106.94 (d, C-6), 116.52 (s, J_{CF} = 287.6 Hz, CF_3), 120.73 (d, C-2), 126.09 (s, C-4), 138.38 (s, C-1), 138.72 (s, C-3), 157.01 (s, J_{CF} = 35.3 Hz, NHCO), 157.99 (s, C-5).

Hydrolysis of 12 to 3-Amino-4,5-dimethylphenol (16):

Compound **12** (200 mg, 0.00086 mol) was dissolved in MeOH (5 mL) containing 85% $N_2H_4 \cdot H_2O$ (150 mg, 0.0025 mol). After 48 h, the solution was cooled to −20 °C and the product was separated by filtration to afford **16**, yield 109 mg, 91%; mp 220–226 °C (aq MeOH). (Lit.[11] mp 210–211 °C).

$C_8H_{11}NO$ (137.2) calc. C 70.04 H 8.08 N 10.21 found 69.73 8.00 10.09

^1H NMR (DMSO-d_6/TMS): δ = 1.84 (s, 3H, C2-CH_3), 2.05 (s, 3H, C3-CH_3), 4.53 (br s, 2H, NH_2), 5.86 (d, 1H, J = 2.4 Hz, H-4), 5.95 (d, 1H, J = 2.4 Hz, H-6), 8.49 (s, 1H, OH).

^{13}C NMR (DMSO-d_6/TMS): δ = 11.83 (q, C2-CH_3), 20.29 (q, C3-CH_3), 99.36 (d, C-6), 105.80 (d, C-4), 110.08 (s, C-2), 136.35 (s, C-3), 146.95 (s, C-1), 154.91 (s, C-5).

Methyl 4,6-Dihydroxy-2,3-dimethylbenzoate (18):

Methyl 2,2-dimethyl-4,6-dioxocyclohexane-1-carboxylate (**17a**,[12] 5.0 g, 0.025 mol) was added to TFAA (50 mL), cooled in ice. H_2SO_4 (2.59 g, 0.026 mol) was added. After 48 h at r.t., workup as for **6** and **7** above gave a semi-crystalline product (4.3 g), which was chromatographed on silica gel (200 g), eluting with hexane/EtOAc (2:1), to give **18**; yield 2.29 g, 46%; mp 123–126 °C (acetone/hexane) (Lit.[13] mp 120–122 °C).

$C_{10}H_{12}O_4$ (196.2) calc. C 61.85 H 6.19 found 61.57 6.17

^1H NMR ($CDCl_3$/TMS): δ = 2.09 (s, 3H, C3-CH_3), 2.42 (s, 3H, C2-CH_3), 3.92 (s, 3H, OCH_3), 6.30 (s, 1H, H-5), 6.45 (br m, 1H, OH), 11.37 (s, 1H, OH).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.51 (q, C3-CH_3), 18.93 (q, C2-CH_3), 51.97 (q, CO_2CH_3), 100.75 (d, C-5), 106.30 (s, C-1), 116.48 (s, C-3), 141.37 (s, C-2), 159.06 (s, C-4), 161.42 (s, C-6), 172.36 (s, CO_2).

Ethyl 4-Chloro-6-hydroxy-2,3-dimethylbenzoate (20):

Ethyl 4-chloro-2,2-dimethyl-6-oxocyclohex-4-ene-1-carboxylate (**19b**)[14] (prepared from **17b**[14]) (3.0 g, 0.0132 mol) was dissolved in TFAA (40 mL) and H_2SO_4 (1.41 g, 0.0145 mol) was added with stirring. After 6 d, workup as described above for **6** and **7** gave a semi-crystalline product (2.4 g) which was chromatographed on

silica gel (200 g), eluting with hexane/Et_2O (7:1), to give **20** as an oil; yield 1.04 g, 35%; mp 83–85°C (hexane) and then unchanged **19b** (0.99 g).

$C_{11}H_{13}ClO_3$	calc.	C 57.78	H 5.73
(228.5)	found	57.85	5.83

^1H NMR ($CDCl_3$/TMS): δ = 1.42 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.28 (s, 3H, C3-CH_3), 2.47 (s, 3H, C2-CH_3), 4.43 (q, 2H, J = 7.1 Hz, OCH_2), 6.90 (s, 1H, H-5), 10.63 (s, 1H, OH).

^{13}C NMR ($CDCl_3$/TMS): δ = 14.15 (q, OCH_2CH_3), 16.35 (q, C3-CH_3), 19.74 (q, C2-CH_3), 61.89 (t, OCH_2), 112.89 (s, C-1), 115.73 (d, C-5), 126.54 (s, C-3), 140.37 (s, C-4), 140.54 (s, C-2), 171.09 (s, CO_2).

Methyl 6-Hydroxy-4-methoxy-2,3-dimethylbenzoate (22a):

Methyl 4-Methoxy-2,2-dimethyl-6-oxocyclohex-4-ene-1-carboxylate **(21a)**:

Compound **19a**[14] (8.5 g, 0.0383 mol) was added to a solution of NaOMe (2.07 g, 0.0383 mol) in MeOH (60 mL). After 6 h, the solution was diluted with Et_2O (200 mL) and washed with H_2O. The ethereal solution was dried and evaporated to yield an oil (7.5 g), which was chromatographed on silica gel (200 g), eluting with hexane/EtOAc (1:1), to afford **21a** as an oil; yield 6.8 g, 80%.

$C_{11}H_{16}O_4$	calc.	C 62.25	H 7.99
(212.2)	found	62.01	7.69

^1H NMR ($CDCl_3$/TMS): δ = 1.12 (s, 3H, C3-CH_3), 1.14 (s, 3H, C3-CH_3), 2.17 (d, 1H, J = 17.4 Hz, H-4), 2.71 (d, 1H, J = 17.4 Hz, H-4), 3.16 (s, 1H, H-2), 3.71 (s, 3H, CO_2CH_3), 3.73 (s, 3H, C5-OCH_3), 5.41 (s, 1H, H-6).

^{13}C NMR ($CDCl_3$/TMS): δ = 25.41 (q, C3-CH_3), 28.32 (q, C3-CH_3), 34.32 (s, C-3), 40.98 (t, C-4), 51.87 (q, CO_2CH_3), 55.81 (q, C5-OCH_3), 63.42 (d, C-2), 100.12 (d, C-6), 169.52 (s, CO_2), 177.56 (s, C-5), 193.9 (s, C-1).

Aromatization of **21a** *to give* **22a**:

Compound **21a** (6.3 g, 0.03 mol) was dissolved in TFAA (50 mL) and H_2SO_4 (3.2 g, 0.033 mol) was added. After 6 h, TFAA was removed under vacuum and the residue was dissolved in MeOH (25 mL). The solution was basified by addition of sat aq Na_2CO_3. After 1 h, H_2O (20 mL) and 2 N HCl (20 mL) were added. The precipitate was removed by filtration, washed with H_2O and dried under high vacuum to yield **22a**: yield 4.3 g, 68%; mp 82–84°C (EtOAc/hexane) (Lit.[15] mp 82–83°C).

$C_{11}H_{14}O_4$	calc.	C 62.85	H 6.71
(210.2)	found	62.92	6.75

^1H NMR ($CDCl_3$/TMS): δ = 2.08 (s, 3H, C3-CH_3), 2.43 (s, 3H, C2-CH_3), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, CO_2CH_3), 6.34 (s, 1H, H-5), 11.33 (s, 1H, OH).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.48 (q, C3-CH_3), 18.85 (q, C2-CH_3), 51.84 (q, CO_2CH_3), 55.51 (q, OCH_3), 96.80 (d, C-5), 105.69 (s, C-1), 117.86 (s, C-3), 139.92 (s, C-2), 162.28 (s, C-4), 162.48 (s, C-6), 172.36 (s, CO_2).

Ethyl 6-Hydroxy-2,3-dimethyl-4-phenoxybenzoate (22b):

Ethyl 2,2-Dimethyl-6-oxo-4-phenoxycyclohex-4-ene-1-carboxylate **(21b)**:

60% NaH in oil (383 mg, 0.0096 mol) was added to a solution of phenol (899 mg, 0.0096 mol) in DMF (20 mL). After 40 min, **19b** (2.0 g, 0.0087 mol) was added. The mixture was placed in a 70°C oil bath for 45 min, then cooled and added to 1 N HCl (200 mL). The solution was extracted with Et_2O (100 mL) and the extract was dried and evaporated to give an oil (2.6 g) which was chromatographed on silica gel (200 g), eluting with hexane/Et_2O (3:1) to afford **21b** as an oil; yield 1.95 g, 78%.

$C_{17}H_{20}O_4$	calc.	C 70.81	H 6.99
(288.3)	found	70.73	6.27

^1H NMR ($CDCl_3$/TMS): δ = 1.19 (s, 3H, C3-CH_3), 1.21 (s, 3H, C3-CH_3), 1.28 (t, 3H, J = 7.3 Hz, $CO_2CH_2CH_3$), 2.40 (d, 1H, J = 17.6 Hz, H-4), 2.95 (d, 1H, J = 17.6 Hz, H-4), 3.15 (s, 1H, H-2), 4.18 (q, 2H, J = 7.3 Hz, $CO_2CH_2CH_3$), 5.16 (s, 1H, H-6), 7.05 (br d, 2H, J = 8.0 Hz, OPh), 7.24 (br t, 1H, J = 8.0 Hz, OPh), 7.39 (br t, 2H, J = 8.0 Hz, OPh).

^{13}C NMR ($CDCl_3$/TMS): δ = 14.18 (q, $CO_2CH_2CH_3$), 25.66 (q, C3-CH_3), 28.38 (q, C3-CH_3), 35.06 (s, C-3), 40.76 (t, C-4), 61.02 (t, $CO_2CH_2CH_3$), 63.61 (d, C-2), 104.07 (d, C-6), 121.33 (d, OPh) 126.20 (d, OPh), 130.04 (d, OPh), 152.74 (s, OPh), 168.97 (s, $CO_2CH_2CH_3$), 177.32 (s, C-5), 194.20 (s, C-1).

Aromatization of **21b** *to give* **22b**:

Compound **21b** (1.6 g, 0.0056 mol) was dissolved in TFAA (20 mL) at 0°C and H_2SO_4 (599 mg, 0.0061 mol) was added. After 16 h at r.t., work-up as for **5** and **6** gave an oil (1.4 g) which was chromatographed on silica gel (60 g), eluting with hexane/Et_2O (8:1), to give **22b** as an oil; yield 840 mg, 53%.

$C_{17}H_{18}O_4$	calc.	C 71.31	H 6.34
(286.3)	found	70.73	6.27

^1H NMR ($CDCl_3$/TMS): δ = 1.42 (t, 3H, J = 7.2 Hz, OCH_2CH_3, 2.20 (s, 3H, C3-CH_3), 2.51 (s, 3H, C2-CH_3), 4.41 (q, 2H, J = 7.2 Hz, OCH_2), 6.23 (s, 1H, H-5), 6.99 (br d, 2H, J = 7.7 Hz, OPh), 7.14 (t, 1H, J = 7.7 Hz, OPh), 7.33 (t, 2H, J = 7.7 Hz, OPh), 11.07 (br m, 1H, OH).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.85 (q, C3-CH_3), 14.04 (q, OCH_2CH_3), 18.88 (q, C2-CH_3), 61.29 (t, OCH_2), 102.95 (d, C-5), 108.47 (s, C-1), 119.42 (s, C-3), 119.55 (d, OPh), 123.88 (d, OPh), 129.72 (d, OPh), 141.07 (s, C-2), 155.65 (s, OPh), 160.22 (s, C-4), 160.23 (s, C-6), 171.38 (s, CO_2).

Methyl 6-Hydroxy-2,3-dimethyl-(trifluoroacetylamino)benzoate (24):

Compound **17a** (7.92 g, 0.04 mol), NH_4OAc (6.1 g, 0.08 mol), AcOH (2.0 mL, 0.035 mol) and toluene (100 mL) were refluxed using a H_2O separator, for 30 min.[16] The mixture was cooled and H_2O (100 mL) was added. The aqueous layer was separated and $NaHCO_3$ was added until no more CO_2 was evolved; the aqueous solution was extracted with EtOAc (3 × 50 mL). The extract was dried and evaporated to give a yellow gum (4.4 g) consisting of the desired product, **23**, together with some unchanged **17a**.

A 2.3 g sample of this material was dissolved in TFAA (30 mL) cooled in ice, and H_2SO_4 (1.14 g) was added with stirring. After 16 h at r.t. the solution was added dropwise to ice (160 g) to give a suspension of a solid. The product was isolated by filtration, washed with H_2O and dried to afford **24**; yield 1.6 g, 70%; mp 128–130°C (aq MeOH);

$C_{12}H_{12}F_3NO_4$	calc.	C 49.49	H 4.15	N 4.81
(291.3)	found	49.59	4.19	4.69

^1H NMR ($CDCl_3$/TMS): δ = 2.13 (s, 3H, C3-CH_3), 2.47 (s, 3H, C2-CH_3), 3.97 (s, 3H, CO_2CH_3), 7.37 (s, 1H, H-5), 7.88 (br s, 1H, NH), 10.56 (s, 1H, OH).

^{13}C NMR ($CDCl_3$/TMS): δ = 13.73 (q, C3-CH_3), 18.33 (q, C2-CH_3), 52.13 (q, CO_2CH_3), 111.54 (d, C-5), 116.02 (s, J_{CF} = 288.4 Hz, CF_3), 116.77 (s, C-1), 123.26 (s, C-3), 136.53 (s, C-2), 138.30 (s, C-4), 155.37 (s, J_{CF} = 37.8 Hz, NHCO), 156.28 (s, C-6), 170.37 (s, CO_2).

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