

dimethyl-*N*-tosylformohydrazide (20–30 %) and *N,N'*-dimethyl-*p*-toluenesulfonohydrazide. *N,N'*-Dimethyl-*N*-tosylformohydrazide 4b. *N,N'*-Dimethyl-*p*-toluenesulfonohydrazide (0.02 mol) was stirred at room temperature for 2.5 h with (0.23 mol) acetic formic anhydride formylating mixture prepared by heating equimolar amounts of acetic acid anhydride and formic acid for 2 h. After cooling to 0 °C the mixture was poured into H<sub>2</sub>O (150 ml), the precipitate was filtered off. Yield 80 %, m.p. 79–80 °C (from ethanol), Anal. C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S: C, H, N. MS *m/e* (% of base peak): 242(9) M<sup>+</sup>, 91(27), 87(100), 65(25), 59(78), 43(55). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.96 (1 H, s), 7.8–7.2 (4 H, m), 2.63 (6 H, s), 2.46 (3 H, s).

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## An Improved Synthesis of 2-Methyl-4,6-dihydroxybenzoic Acid (Orsellinate) Esters and Homologues

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In connection with ongoing research in this Laboratory directed toward the synthesis of natural products based on the 2-alkyl-4,6-dihydroxybenzoic acid system (*I*), we became attracted by the route<sup>1</sup> shown in Scheme 1 (reagent a). In our hands, however, the reaction failed to give the reported yields. For example, ethyl 2-methyl-4,6-dihydroxybenzoate (orsellinate) *1a* was obtained<sup>1</sup> in 38 % yield whereas our yields were consistently less than 10 %.

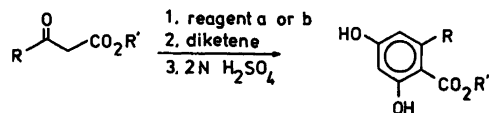
Thallium(I) salts of β-dicarbonyl systems have been used for *C*-alkylations and *C*-acylations in very high yields.<sup>2</sup> We were, therefore, led to test the Tl(I) salt of various β-keto esters in the diketene reaction, and now report that ethyl orsellinate and homologues are obtainable in acceptable yields (Scheme 1, reagent b; isolated yields are shown). As seen from the second entry (*Ib*), the reaction can be further improved by the use of *t*-butyl<sup>3</sup> instead of ethyl β-keto esters.

Applications of the β-keto ester/Tl(I)/diketene route to the synthesis of naturally occurring orsellinate-type compounds will be reported shortly.

**Experimental. General procedure.** Thallium(I) salts of β-keto esters were made either with TlOH in aqueous solution<sup>4</sup> or with TlOEt in light petroleum.<sup>5</sup> The crystalline Tl(I) salts were dried for 6 h under high vacuum at 25 °C.

Freshly distilled diketene (0.091 ml, 1.2 mmol) was added with a syringe into 1 mmol of the Tl(I) salt under Ar in THF (CaH<sub>2</sub>-dried, 5 ml) at 0 °C. The mixture was stirred for 40 h at 0 °C, poured on 2 N H<sub>2</sub>SO<sub>4</sub> (20 ml) and extracted twice with ether. The combined extracts were washed with water, dilute aqueous NaHCO<sub>3</sub>, dried and evaporated. Preparative TLC (Merck silica gel PF<sub>254</sub>, elution with CHCl<sub>3</sub>) then gave the orsellinate or homologue, recrystallized from light petroleum 40–60 °C.

**Individual products.** The compounds *1a–1d* are known,<sup>1</sup> and had physical properties in accord with their structure and reported data. *Ethyl-2-(8-*t*-butyldimethylsilyloxy)nonyl-4,6-dihydroxybenzoate*. A. Ethyl 7-bromoheptanoate (2.5 g) was treated in dry toluene (50 ml) at –80 °C with diisobutylaluminium hydride (20 % in hexane, 11.0 ml, 1.02 eq). After 5 h at –80 °C, the cold solution was poured with stirring on 2 N H<sub>2</sub>SO<sub>4</sub> (50 ml). Extraction (Et<sub>2</sub>O) and washing (aqueous NaHCO<sub>3</sub>), drying and evaporation of the combined organic layers gave crude 7-bromoheptanal (1.85 g), used



reagent a = NaH

b = TiOEt or TiOH

R	R'	
1a Me	Et	(49 %)
1b Me	Bu- <i>t</i>	(60 %)
1c (CH <sub>2</sub> ) <sub>4</sub> Me	Et	(42 %)
1d C <sub>6</sub> H <sub>5</sub>	Et	(45 %)
1e (CH <sub>2</sub> ) <sub>7</sub> CHMe	Et	(32 %)

OSiMe<sub>2</sub>Bu-*t*

directly for the next step, TLC and IR showing the near absence of by-products.

B. Crude 7-bromoheptanal (1.85 g) was treated in dry Et<sub>2</sub>O under Ar at 0 °C with methylolithium (1.6 M in ether, 6.0 ml, 1.0 eq). After 1 h at 0 °C, the solution was poured with stirring on 2 N H<sub>2</sub>SO<sub>4</sub> (80 ml). Extraction (Et<sub>2</sub>O) and washing (aqueous NaHCO<sub>3</sub>), drying and evaporation of the combined organic layers gave crude 8-bromo-2-octanol (1.95 g) which was used as such for the next step.

C. Crude 8-bromo-2-octanol (1.95 g), *t*-butylchlorodimethylsilane (1.50 g) and imidazole (0.70 g) in dry DMF (20 ml) were stirred for 20 h. The solution was then poured on water, extracted twice with ether, the combined extracts washed with water (4 times) and dried. After evaporation, the residue was chromatographed on preparative TLC plates (as above, elution with light petroleum 40–60 °C) to give 2-(8-bromooctyl) *t*-butyldimethylsilyl ether (2.71 g, 82 % overall from ethyl 7-bromohexanoate),  $\delta$  0.03 (6 H, s), 0.83 (9 H, s), 1.05 (3 H, d,  $J=5.5$  Hz), 1.30 (10 H, m), 1.65 (2 H, m), 3.42 (2 H, t,  $J=6$  Hz), 3.73 (1 H, m).

D. Ethyl acetoacetate (1.12 g) was added under Ar at 0° to lithium diisopropylamide (2.05 eq, from 2.42 ml of *i*-Pr<sub>2</sub>NH and 8.0 ml of 2.16 M BuLi/hexane in 30 ml of dry THF). After 0.5 h, the preceding silyl ether (2.70 g, 1 eq) was added with a syringe, and the solution kept for 20 h at 0 °C. Aqueous work-up, drying and evaporation gave crude material which was purified on preparative TLC plates (as above, elution with chloroform-light petroleum 40–60° 1:1) to give ethyl 10-*t*-butyldimethylsilyloxy-3-oxo-undecanoate (2.11 g, 70 %),  $\bar{\nu}$  1750, 1735 cm<sup>-1</sup>,  $\delta$  0.03 (6 H, s), 0.90 (9 H, s), 1.05 (3 H, d,  $J=6$  Hz), 1.3 (15 H, m), 2.51 (2 H, t,  $J=7$  Hz), 3.42 (2 H, s), 3.79 (1 H, m), 4.20 (2 H, qr,  $J=7$  Hz).

E. Ti(I)/diketene cyclisation of the above keto ester, as described under the general procedure, gave ethyl 2-(8-*t*-butyldimethylsilyloxyonyl)-4,6-dihydroxybenzoate, m.p. 87–

89 °C,  $\bar{\nu}$  1645 cm<sup>-1</sup>,  $\delta$  0.03 (6 H, s), 0.84 (9 H, s), 1.06 (3 H, d,  $J=5.5$  Hz), 1.25 (15 H, m), 2.83 (2 H, t,  $J=6.5$  Hz), 4.45 (2 H, qr,  $J=7$  Hz), 6.28 (2 H, br s), 7.15 (1 H, br, exch. D<sub>2</sub>O), 10.88 (1 H, s, exch. D<sub>2</sub>O).

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