A One-Pot Synthesis of Dibenzosuberones via the Parham Cycliacylation Reaction

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Dibenzosuberone (10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-one, **6a**) is important as an intermediate in the preparation of psychotropic agents[1,2], thus there is a need for a convenient synthesis, which is also suitable for the preparation of derivatives. A possible route appeared to be via the Parham cycliacylation[3,4] of the lithium salt **3a** of 2-bromo-2'-bibenzylcarboxylic acid (**4a**). While the acid **4a** was unknown, its synthesis was simplified by an observation made earlier in this laboratory[5]. It had been shown that the addition of one equivalent of butyllithium to *o*-bromobenzyl bromide (**1a**) at −100 °C, followed by hydrolysis led to 2-bromobibenzyl, and it was assumed that the intermediate was 2-bromo-2'-lithiobibenzyl (**2a**). Repetition of the experiment, except carbonating the reaction mixture with solid carbon dioxide before hydrolysis, afforded the desired acid **4a** in 58% yield. When the acid was treated with two equivalents of butyllithium at −100 °C, halogen-metal exchange was complete in 15 min and cyclization took place in 6 h at room temperature (39% yield).

A more convenient and productive procedure involved carbonation of **2a** with gaseous carbon dioxide below −85 °C,

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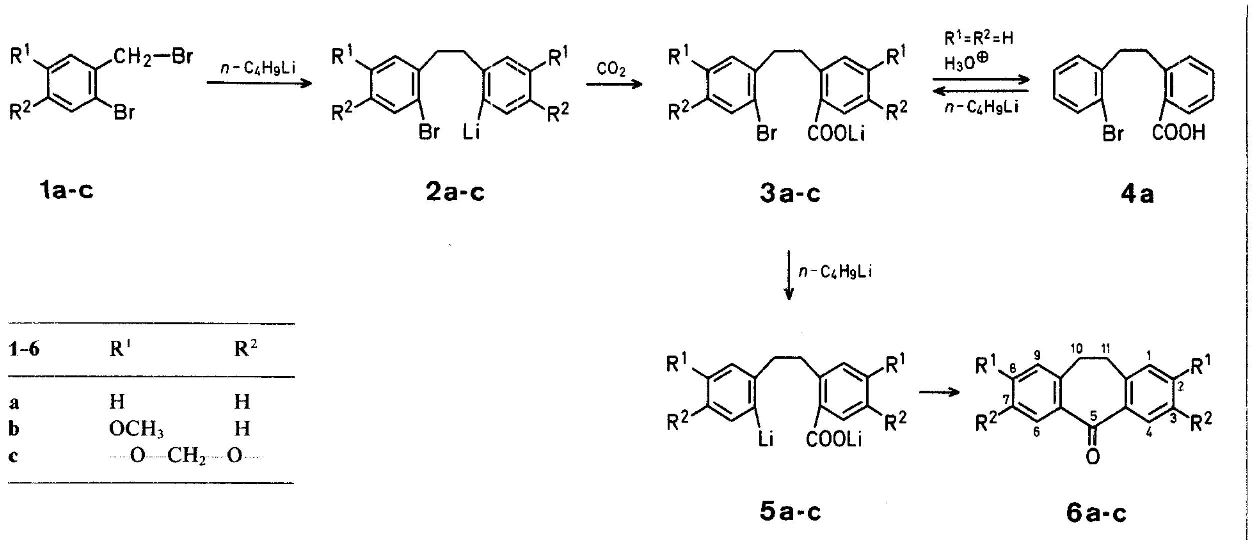
warming the mixture to room temperature, followed by recooling to $-100\,^{\circ}$C, and addition of 1.2 equivalents (excess) of butyllithium. After 6 h at room temperature followed by the usual workup, the overall yield of **6a** (G.L.C.) was 56%.



1-6	R^1	R^2
a	H	H
b	OCH$_3$	H
c	—O—CH$_2$—O—	

Two previously unknown symmetrically substituted dibenzosuberones were prepared by this one-pot procedure; 2,8-dimethoxydibenzosuberone (**6b**) in 55% yield from **1b**[6] and 2,3,7,8-bis[methylenedioxy]dibenzosuberone (**6c**) in 30% yield from **1c**[7]. This new synthetic method provides a convenient route to symmetrically substituted dibenzosuberones.

2-Bromobibenzyl-2'-carboxylic Acid (4a):

o-Bromobenzyl bromide (**1a**, 12.5 g, 50 mmol) is converted to 2-bromo-2'-lithiobibenzyl (**2a**) as described by Parham et al.[5], and 1 h after addition of butyllithium the reaction mixture is poured on a slurry of solid carbon dioxide (10 g) in ether (150 ml). The organic phase is concentrated and partitioned for 24 h between ether and 20% sodium hydroxide solution. Acidification of the alkaline layer yields colorless crystals of **4a**; yield: 4.40 g (58%); m. p. 149–152 °C (pure, m. p. 151–153 °C).

$C_{15}H_{13}BrO_2$	calc.	C 59.04	H 4.29	Br 26.19
(305.2)	found	59.22	4.12	25.96

I. R. (Nujol mull): $\nu = 2650$ (OH); 1670 (C=O) cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/(CD$_3$)$_2$SO): $\delta = 2.90$–3.50 (m, 4, CH$_2$CH$_2$); 7.00–8.10 (m, ArH); 9.65 ppm (bs, 1, OH).

Dibenzosuberone (10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one, 6a):

o-Bromobenzyl bromide (**1a**, 12.5 g, 50 mmol) is dissolved in tetrahydrofuran (325 ml) and hexane (100 ml) in a 1 l three-neck flask equipped for lithiation[5] and is cooled to $-100\,^{\circ}$C. Butyllithium (50 mmol) is added at such a rate that the temperature does not exceed $-100\,^{\circ}$C. After 1 h at $-100\,^{\circ}$C, a stream of carbon dioxide gas is bubbled through the reaction mixture for 1.5 h at $-100\,^{\circ}$C to $-85\,^{\circ}$C. The cooling bath is removed and the temperature allowed to rise to 25 °C (1.5 h) after which a stream of dry nitrogen is bubbled through the mixture for 1.5 h. The solution is agained cooled to $-100\,^{\circ}$C and butyllithium (30 mmol, 20% excess) added at a rate such that the temperature does not exceed $-99\,^{\circ}$C. The mixture is stirred for 30 min at $-100\,^{\circ}$C, then allowed to warm to 25 °C, and to remain at that temperature for 6 h. The mixture is poured into an excess of 5% hydrochloric acid. The organic layer is separated and the aqueous layer extracted with ether (3 × 150 ml). The combined organic solutions are washed with 5% sodium hydroxide solution and then dried and concentrated to a yellow oil; yield: 5.20 g which is analyzed by G.L.C./M.S. The major fraction is **6a**; yield: 56%.

M. S.: *m/e* (relative intensity) = 208 ($M^{+\cdot}$, 100%), 207 (34), 180 (66), 179 (68), 178 (56), 165 (41), 89 (45), 76 (28).

^{1}H-N.M.R. (CDCl$_3$): $\delta = 3.12$ (s, 4H, CH$_2$CH$_2$); 7.05–8.10 ppm (m, 8H$_{arom}$).

2,8-Dimethoxydibenzosuberone (6b):

2-Bromo-5-methoxylbenzyl bromide[6] (**1b**; 14 g, 50 mmol) is subjected to the sequence of lithiation, carbonation, lithiation and cyclization as described in the preparation of dibenzosuberone (**6a**). The crude product, an orange solid, is recrystallized from dichloromethane/methanol (1/1) to afford long, slightly yellow needles; yield: 3.20 g (48%); m. p. 119–121 °C. A second crop (0.50 g) has m. p. 118–119.5 °C; while the analytical sample has m. p. 121–122.5 °C and is colorless.

$C_{17}H_{16}O_3$	calc.	C 76.10	H 6.01
(268.3)	found	76.31	5.94

^{1}H-N.M.R. (CDCl$_3$): $\delta = 3.12$ (s, 4H, CH$_2$CH$_2$); 3.85 (s, 6H, OCH$_3$); 6.60–8.20 ppm (AMX multiplet, 6H$_{arom}$).

2,3,7,8-Bis[methylenedioxy]dibenzosuberone (6c):

Following the procedure used for the congener (**6b**) but starting with 2-bromo-4,5-methylenedioxybenzyl bromide[7] (**1c**; 14.7 g, 50 mmol), tan needles of **6c** are obtained; total yield: 3.87 g (30%); m. p. 162.5–165 °C. The analytical sample, m. p. 163.5–164.5 °C; is colorless.

$C_{17}H_{12}O_5$	calc.	C 68.92	H 4.08
(296.3)	found	68.98	4.21

I. R. (CHCl$_3$): $\nu_{C=O} = 1620$ cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 3.14$ (s, 4H, CH$_2$CH$_2$); 6.08 (s, 4H, OCH$_2$O); 6.72 (s, 2H, H-1 and H-9); 7.67 ppm (s, 2H, H-4, H-6).

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