An Improved Synthesis of α,α,α′,α′-Tetramethyldicarboxylic Acids

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The synthesis of α,α,α′,α′-tetramethyldicarboxylic acids (**1**), *via* the classical method of Haller and Bauer[2] from isobutyrophenone (**2**) through intermediates **3** and **4**, has been described by Adams and Anderson[3] as well as others[4]. This synthetic procedure has numerous major disadvantages:

- three time consuming separate steps,
- an extremely difficult hydrolysis of diamide **4**, resulting in easily contaminated diacid **1**,
- decomposition of the initial diketone **3** upon attempted purification,
- moderately expensive starting material **2**, or, if unavailable, an additional step from 2-methylpropanoic acid (**5**).

We have found that these tetrasubstituted dicarboxylic acids can be conveniently prepared in a single flask by alkylation of the α-anion of 2-methylpropanoic acid (**6**)[5], which is formed by the reaction of lithium diisopropylamide and **5** in the tetrahydrofuran. Hexamethylphosphoric triamide is used as a cosolvent; however, comparable yields can be realized without hexamethylphosphoric triamide. The yield data of the purified diacids are given in the Table and reflect a *minimum* value.

It was previously observed[3] that the melting points of unsubstituted dicarboxylic acids approach each other with increasing carbon chains. This phenomenon was not observed in the series of substituted diacids[3]; however, this original observation was based upon impure diacid products.

When pure diacids are used, there seems to be an approachment in melting point data but approximately 30° lower than that reported[3] for the corresponding unsubstituted diacids.

Table. Preparation of α,α,α′,α′-Tetramethyldicarboxylic Acids (**1**)

n	Yield (%)[a, b]	M.p.[b]
3	42, 52[c] (26, Lit.[4] 46)	168–170°[d] (168–169°)
4	39 (47, Lit.[4] 41)	185–187°[d] (179–181°) (Lit.[4] 185.8–186.1°)
5	62 (50)	140–141°[d] (139.5–141°)
6	46, 40[c] (46)	118–121°[d] (117–118°)
7	53 (28)	76–77°[e] (75–77°)
8	48 (22)	92–93°[e] (86–88°)
9	68 (11)	73–74°[f] (57–59°)
10	52 (47)	87.5–89°[f] (84–86°)

[a] Isolated, recrystallized products; reaction yields were not optimized.

[b] Value in brackets is that reported in reference 3.

[c] Without hexamethylphosphoric triamide cosolvent.

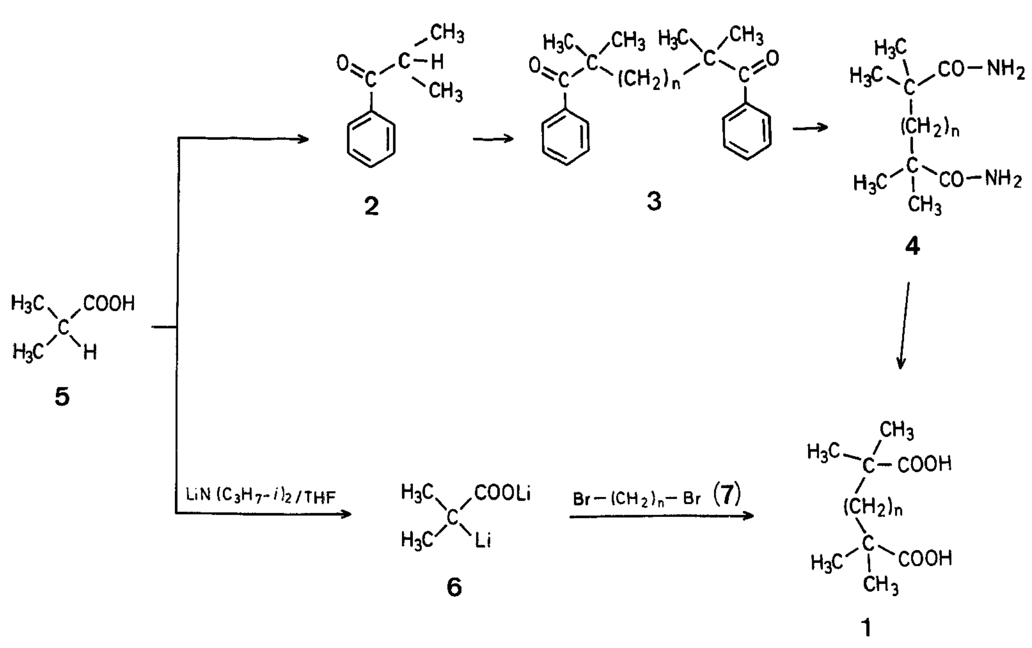
[d] Recrystallized from ethyl acetate.

[e] Recrystallized from petroleum ether (b.p. 60–80°).

[f] Recrystallized from petroleum ether (b.p. 40–60°).

Preparation of α,α,α′,α′-Tetramethylheptanedioic Acid (1; n = 3): General Procedure:

To a mixture of tetrahydrofuran (130 ml) and redistilled diisopropylamine (19.6 g, 0.196 mol) cooled to −20° was added *via* a hypodermic syringe 2.1 *M* *n*-butyllithium (11.0 g, 0.196 mol) in hexane while maintaining the temperature below 0° under nitrogen. After 30 minutes, 2-methylpropanoic acid (7.75 g, 0.088



mol) was added dropwise still maintaining the temperature at −20°, then hexamethylphosphoric triamide (17.9 g, 0.10 mol) was added. The mixture was allowed to warm slowly to 50° and this temperature was maintained for 2 hours. The pale yellow solution was cooled to −20°, and 1,5-dibromopentane (10.12 g, 0.044 mol) was added at a rate to keep the temperature below 0°. The reaction mixture was heated to 40° for 1 hour, then hydrolyzed by ice-cold 10% hydrochloric acid (300 ml). The resultant solution (with possible suspension) was extracted with dichloromethane (3 × 100 ml). The combined organic layers were washed with 10% hydrochloric acid (4 × 10 ml), then water (2 × 100 ml), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford a pale yellow oil, from which white crystals precipitated. Recrystallization of the crude product from petroleum ether (b.p. 60–80°) gave $\alpha,\alpha,\alpha',\alpha'$-tetramethylheptanedioic acid; yield: 13.3 g (62%); m.p. 140–141°; lit.[3] m.p. 139.5–141°.

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Erratum:

G. R. Newkome et al., *Synthesis* **1975**, 517–518;

The heading for the experimental procedure (page 517) should be:

Preparation of α,α,α′,α″-Tetramethylazelaic Acid (1; n = 5):

The last two lines of this procedure (page 518) should be:

(b.p. 60–80°) gave α,α,α′,α′-tetramethylazelaic acid; yield: 13.3 g (62%); m.p. 140–141°; lit.[3] m.p. 139.5–141°.