Modified Preparation of (2*R*)-2-*tert*-Butyl-6-methyl-4*H*-1,3-dioxin-4-one; a Chiral Acetylacetic Acid Derivative for the Synthesis of Enantiopure Compounds

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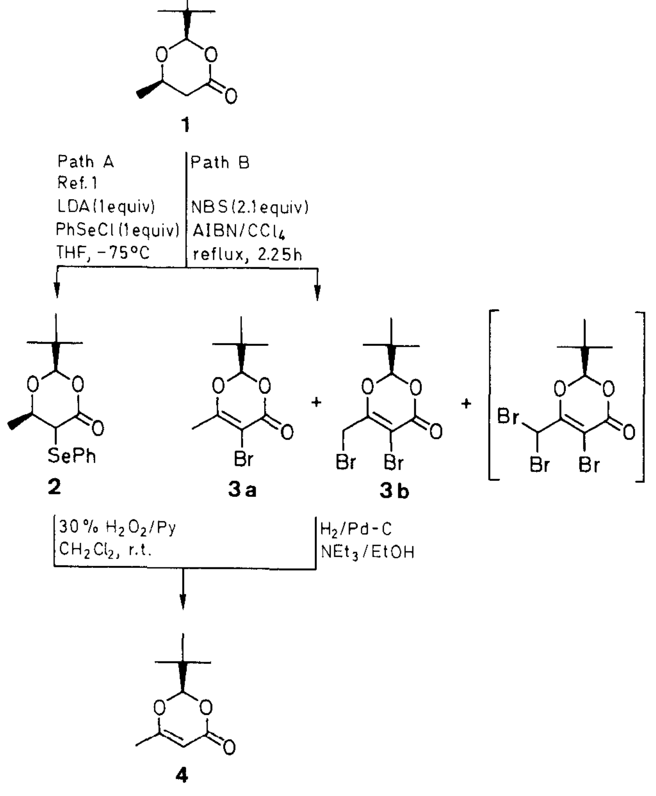
An improved synthesis of the title compound in ca. 45% yield on up to a 174 mmol scale is reported. Bromination of (2*R*,6*R*)-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one gives a mixture of mono- and dibromides which must be purified by chromatography to remove impurities which may poision the palladium catalyst in the following dehalogenation step.

Several years ago we described two methods for the preparation of (2*R*)-2-*tert*-butyl-6-methyl-4*H*-1,3-dioxin-4-one (**4**) from (2*R*,6*R*)-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one (**1**). One pathway proceeded via an α-selenium compound **2**,[1] which gave the dioxinone **4** in ca. 80% overall yield after an oxidative elimination (path A). Another route to dioxinone **3** proceeded via an *N*-bromosuccinimide (NBS) bromination. The resulting crude mixture of bromides **3a** and **3b** was catalytically dehalogenated to give **4** in an overall yield of 60%.[2] The resulting acetylacetic acid derivative **4** was shown to be a useful building block in the synthesis of enantiopure compounds (EPC).[3-7] Upon running the reaction shown in path B on scales larger than the originally described 30 mmol unexpected difficulties were occasionally encountered which lowered the overall yield. This led us to investigate the reactions of the bromide path B in greater detail.



Within a short period of time it was clear that the difficulties occurred during the catalytic dehalogenation, whereas the NBS bromination proceeded flawlessly. The ratio of monobromide **3a** to dibromide **3b** varied from 2:1 to 3.5:1 when 2.1 equivalents of NBS were used. We had shown earlier that the product ratio of mono-, di-, and tribromides was dependent on the reaction time and the amount of NBS employed.[8] It turned out that the trace amounts of halides which were present in the oily crude product (**3a**, **3b**) "poisoned" the Pd-C catalyst used in the hydrogenation, preventing complete reaction. If the mixture of mono- and dibromide was purified over basic alumina before dehalogenation then complete conversion to the product was observed. In addition, the amount of catalyst could be reduced from 3.2 to 0.8 mol % with respect to **1**. In order to prevent possible over hydrogenation, leading to starting material **1**, we estimated the theoretical amount of hydrogen required from the ratio of **3a** to **3b** via ^{1}H NMR spectroscopy and monitored the hydrogen uptake volumetrically (Figure).

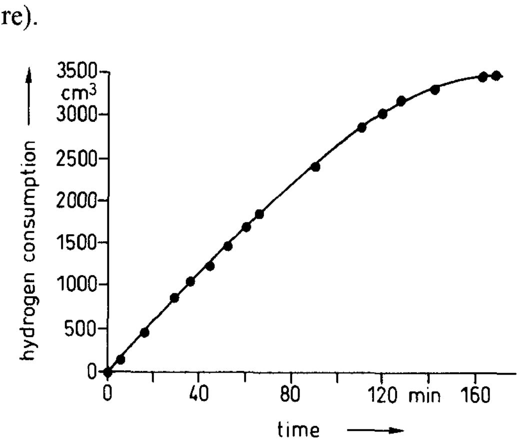


Figure. Hydrogen consumption during catalytic dehalogenation

Following the above mentioned procedure we were able to reproducibly obtain 45% yields of dioxinone **4** on a 174 mmol scale (ca. 13 g).

(2*R*)-2-*tert*-Butyl-6-methyl-4*H*-1,3-dioxin-4-one (4):
Dibromides 3a, 3b:
(2*R*,6*R*)-2-*tert*-Butyl-6-methyl-1,3-dioxan-4-one (**1**),[9] (30.0 g, 174 mmol), NBS (65.4 g, 366 mmol) and AIBN (0.6 g) in CCl_4 (600 mL) were heated at reflux for 2.25 h (bath temperature 85–90 °C). After cooling the mixture to 0 °C and rapid filtration (fritted glass filter), the pale yellow solution was concentrated on a rotary evaporator and the resulting yellow oil dried for a short period of time under high vacuum. Filtration through alumina (basic activity I, ca. 280 g, 5 cm diameter column, 0.2 bar pressure, ca. 1.2 L Et_2O) gave a partially crystalline oil which was dried for 2.5 h while rotating at r.t. under high vacuum.

(2R)-2-tert-Butyl-6-methyl-4H-1,3-dioxin-4-one (**4**):

The oil (33.8 g, **3a**/**3b** = ca. 2:1, ^{1}H NMR (90 MHz, $CDCl_3$): **3a**: $\delta = 5.1$ [H–C(2)]; **3b**: $\delta = 5.15$ [H–C(2)], stored overnight at −78 °C) and NEt_3 (47 mL, 366 mmol) were dissolved in EtOH (600 mL) and hydrogenated with 10 % Pd-C (1.5 g) and H_2 at r.t. and atmospheric pressure (low pressure hydrogenation system Roche, H_2 uptake: 3.45 L, theoretical 3.5 L; see Figure). After filtration through Celite the yellow ethanol solution was concentrated to dryness. The residue was taken up in Et_2O (900 mL) and water (300 mL), the water layer separated and the organic phase washed with 250 mL each of 1 N HCl, sat. $NaHCO_3$, and sat. NaCl. After drying over $MgSO_4$ and filtration the organic phase was concentrated to give light yellow crystals (20.6 g, 70 %) which were dissolved upon light warming in Et_2O (6 mL) and pentane (25 mL). Diluting with additional pentane (75 mL) and addition of a seed crystal at −20 °C induced crystallization to give the product **4** as pale yellow crystals (12.8 g, 43 % overall); mp 59.8–60.2 °C[10]; $[\alpha]_D^{r.t.}$ −215.1° (c = 1.04, $CHCl_3$). Crystallization of the concentrated mother liquor in Et_2O (2 mL) and pentane (50 mL) gave enriched **4** (3.8 g, 13 %) as a light yellow, sticky, solid; $[\alpha]_D^{r.t.}$ −109.8° (c = 1.08, $CHCl_3$). Spectral data have been reported in the literature.[2]

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(10) Unfortunately, an incorrect value for the mp of **4** (48.5 °C) is given in *both* of our previous papers.[1,2] The mp 60–62 °C from J. Zimmermann's thesis (Dissertation No. 8518, ETH Zürich, 1988) was confirmed in the course of the present work.