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Synthesis of 3,4,7,8-Tetrahydronaphthalene-1,5(2*H*,6*H*)-dione

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Abstract: A short and high yielding route for the preparation of the title compound, starting from commercially available 1,5-dihydroxynaphthalene, is described. The key step in the sequence is the air oxidation of a bis(trimethylsilyloxy)diene precursor.

Keywords: 1,5-Dihydroxynaphthalene, bis(trimethylsilyloxy)diene, air oxidation.

Introduction

In the context of the development of structural analogs of calcitriol, the hormonally active metabolite of vitamin D_3 [1], we required an efficient synthesis of enedione **4** (Scheme 1). We herein describe a four-step synthesis involving naphthalene-1,5-diol as starting material.

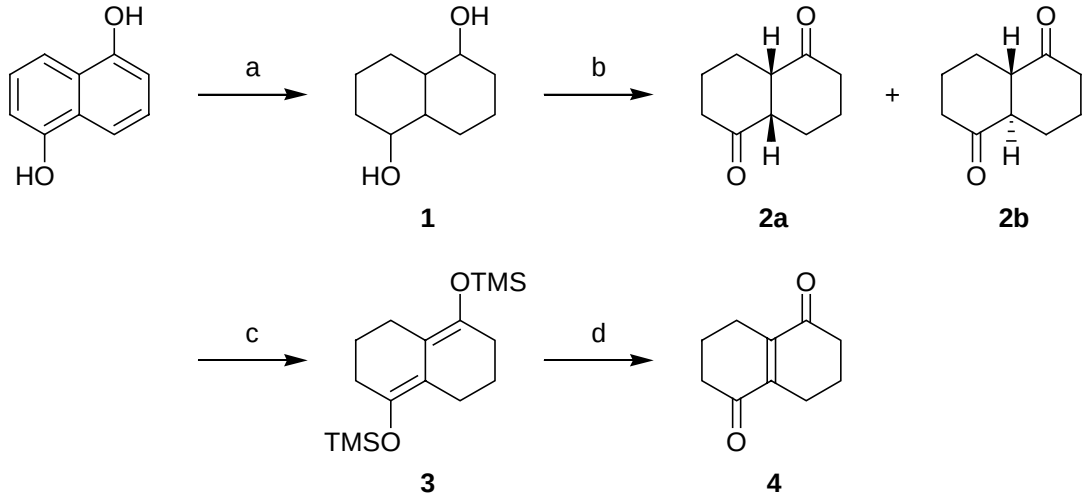
Results and Discussion

Most reported syntheses of enedione **4** involve the dehydrogenation of decalin-1,5-dione **2** via halogenation–dehydrohalogenation in yields varying from 36 to 69% [2,3,4,5]. One report describes the direct oxidation of **2** with oxygen in an acid medium (54% yield) [6]. An efficient method also involves the direct oxidation in 50% yield of decalindiol **1** with IBX (*o*-iodylbenzoic acid) [7]. Finally, and further underlying the need for the development of novel efficient procedures, a high yield (27%) but rather long seven-step sequence involving nitromethane, acrolein and 2-cyclohexenone as starting materials was very recently disclosed [8].

Our sequence rests on the conversion of bis(trimethylsilyloxy)diene **3**, obtained from decalindione **2** via treatment with trimethylsilyl iodide and hexamethyldisilazane, into enedione **4** upon standing at the

air [9]. When the procedure is applied to purified (column chromatography) diene **3**, a quantitative conversion was observed.

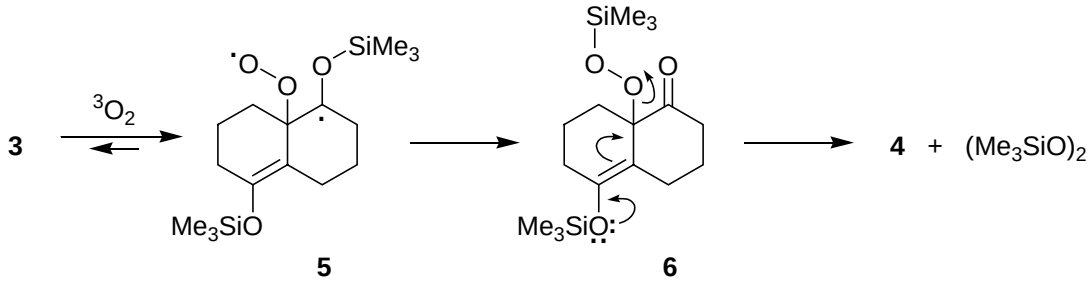
Scheme 1. Synthetic pathway to 3,4,7,8-tetrahydronaphthalene-1,5(2*H*,6*H*)-dione **4**.



(a) H_2, Raney Ni W-7, EtOH, 110 bar, 100 °C, 4 h (67%); (b) TPAP, *N*-methylmorpholine *N*-oxide, molecular sieves (powder), CH_3CN, rt, 90 min (88%); (c) $(Me_3Si)_2NH$, Me_3SiI, CH_2Cl_2, –30 °C → rt (83%); (d) air, 96 h (100%).

The present procedure was considered as a possible extension of the described oxidation of **2** with oxygen in acid medium, which presumably proceeds via the enol form(s) of the diketone. A few examples of the reaction of an enol silyl ether with singlet oxygen ($^1O_2$) have been reported [10]. In one case, this resulted in the corresponding α,β-unsaturated enone [10a]. More recently, Nishiguchi *et al*. described the quantitative formation of 1,6-diketo-2,4-dienes upon acid treatment of 1,6-bis(trimethylsilyloxy)-1,3,5-trienes under an air atmosphere [11]. The mechanism of the oxidative hydrolysis remains, however, unclear.

Scheme 2. Tentative mechanism of the air oxidation of bis(enolsilylether) **3**.



Presumably, the reaction with aerial oxygen ($^3O_2$) involves a radical pathway (Scheme 2). After addition of triplet oxygen to the enol double bond, homolytic cleavage of the (Si–O)-bond in **5** is accompanied by transfer of the trimethylsilyl radical to afford derivative **6**. Subsequent elimination eventually yields **4**.

With the aim of obtaining **4** in an efficient way our preferred pathway to decalin-1,5-dione **2** involves the perhydrogenation of commercially available naphthalene-1,5-diol in ethanol with Raney

nickel W-7 catalyst (110 bar, 100 °C, 4 h, 67% yield), followed by the oxidation of the stereoisomeric mixture of decalindiol **1** [12]. We found TPAP (tetra-*n*-propylammonium perruthenate) to be a superior reagent for that purpose [13]. Under these conditions dione **2** is obtained as a 4:1 mixture of *cis*- and *trans*-derivative, respectively (88% yield) [14]. If necessary both isomers **2a** and **2b** can be separated by repeated crystallisation.

Conclusions

An efficient four-step sequence to hexahydronaphthalene-1,5-dione **4** in 49% overall yield, suitable for multigram preparation, starting from naphthalene-1,5-diol is developed.

Experimental

General

Dichloromethane was distilled from CaH_2. Extra-dry acetonitrile (<10 ppm H_2O) was purchased from Acros Organics and used as such. TLC were run on glass plates precoated with silica gel (Merck, 60F-254). Column chromatography was performed on silica gel (Merck, 230-400 mesh) or Florisil®, 100–200 mesh. IR spectra were recorded on a Perkin–Elmer series 1600 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-500 spectrometer. Mass spectra (EI) were recorded on a Hewlett–Packard 5898A spectrometer at 70 eV.

(4aS,8aS)-Octahydronaphthalene-1,5-dione (**2a**) *and (4aR,8aS)-octahydronaphthalene-1,5-dione* (**2b**)

To a stirred suspension of *N*-methylmorpholine *N*-oxide (2.07 g, 17.7 mmol, 3 eq) and diol **1** (2.0 g, 11.8 mmol) in dry acetonitrile (30 mL) was added powdered 4Å-molecular sieves (3 g). After 15 min the mixture was cooled to 0 °C and tetra-*n*-propylammonium perruthenate (TPAP; 0.211 g, 0.6 mmol, 0.1 eq) was added portionwise. Stirring was continued at rt for 1.5 h and the solvent was evaporated under reduced pressure. The residue was taken up in EtOAc and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure to give a 4:1 mixture of diones **2a** and **2b**, respectively (1.73 g, 88%), which was further separated by repeated crystallisation from petroleum ether. Data of **2a**: mp 85 °C; R_f (CH_2Cl_2/EtOAc, 9:1) 0.62; IR (KBr film) ν 2943 (s), 2908 (m), 2880 (m), 2857 (m), 1702 (s), 1459 (w), 1445 (w), 1427 (w), 1349 (m), 1320 (w), 1294 (w), 1261 (m), 1229 (w), 1201 (w), 1167 (w), 1106 (w), 1064 (w), 1028 (w), 982 (w), 917 (w), 880 (w), 840 (w), 808 (w), 800 (w), 700 (w), 675 (w), 564 (m), 488 (m) cm^{-1}; ^{1}H-NMR/COSY (500 MHz, C_6D_6) δ 2.23–2.19 (2 H, m), 2.09–2.05 (4 H, m), 1.78–1.72 (4 H, m), 1.41–1.37 (2 H, m),1.00–0.93 (2H, m) ppm; ^{13}C-NMR/APT (75 MHz, $CDCl_3$) δ 210.59 (C), 51.50 (CH), 40.76 (CH_2), 24.22 (CH_2), 23.58 (CH_2) ppm; MS *m/z* (%) 166 (M^+, 80), 110 (28), 98 (23), 97 (100), 96 (10), 95 (24), 84 (83), 83 (90), 82 (31), 81 (20), 79 (27), 77 (10), 70 (10), 69 (13), 68 (38), 67 (55), 66 (10), 65 (10), 55 (74), 54 (43), 53 (25), 43 (13), 42 (23), 41 (62). Data of **2b**: mp 167–168 °C; R_f (CH_2Cl_2/EtOAc, 9:1) 0.62; IR (KBr film) ν 2943 (s), 2908 (m), 2880 (m), 2857 (m), 1702 (s), 1459 (w), 1445 (w), 1427 (w), 1349 (m), 1320 (w), 1294 (w), 1261 (m), 1229 (w), 1201 (w), 1167 (w), 1106 (w), 1064 (w), 1028 (w), 982 (w), 917 (w), 880 (w), 840 (w), 808 (w), 800 (w), 700 (w), 675 (w), 564 (m), 488 (m) cm^{-1}; ^{1}H-NMR/COSY (500 MHz, C_6D_6) δ 2.10 (2 H, dddd, *J* = 13.6, 4.2, 2.1, 2.1 Hz), 1.83 (2 H, m, *J* = 13.8 Hz), 1.65 (2 H, td, *J* = 13.7,

6.2 Hz), 1.59–1.57 (2 H, m), 1.55–1.49 (2 H, m), 1.41–1.32 (2 H, m), 1.07 (2 H, qt, *J* = 13.5, 4.1 Hz) ppm; ^{13}C-NMR/APT (75 MHz, $CDCl_3$) δ 209.77 (C), 55.43 (CH), 41.13 (CH_2), 24.92 (CH_2), 24.36 (CH_2) ppm; MS *m/z* (%) 166 (M^+, 49), 138 (14), 123 (24), 111 (10), 110 (38), 109 (10), 98 (25), 97 (52), 96 (11), 95 (39), 94 (11), 84 (100), 83 (97), 82 (39), 81 (24), 79 (29), 69 (13), 68 (43), 67 (70), 66 (11), 65 (11), 55 (80), 54 (57), 53 (31), 51 (11), 50 (4), 43 (13), 42 (32), 41 (71).

1,2,3,5,6,7-Hexahydro-4,8-di(trimethylsilyloxy)naphthalene (**3**)

A solution of dione **2** (4:1 mixture of isomers; 1.0 g, 6.2 mmol) in dry CH_2Cl_2 (50 mL) was placed under Ar, protected from light and cooled to –30 °C. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS; 3.05 mL, 14.5 mmol, 2.4 eq) and trimethylsilyl iodide (1.89 mL, 13.3 mmol, 2.2 eq) were slowly added dropwise. The mixture was stirred at –30 °C for 20 min, allowed to warm, stirred at rt for 30 min and then cooled again to –60 °C. The reaction mixture was washed with a saturated $NaHCO_3$ solution, the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual yellow oil was purified by column chromatography on Florisil (petroleum ether/CH_2Cl_2, 7:3) to afford bis(trialkylsilyl)enol ether **3** (1.6 g, 83%): R_f (CH_2Cl_2) 0.75; IR (KBr film) ν 2956 (w), 2836 (w), 1628 (m), 1442 (w), 1353 (m), 1251 (s), 1213 (s), 1199 (s), 1119 (w), 1053 (w), 977 (s), 910 (w), 887 (w), 866 (s), 840 (s), 751 (w) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.22 (4 H, t, *J* = 6.1 Hz), 2.13 (4 H, t, *J* = 6.2 Hz), 1.66 (4 H, quintet, *J* = 6.2 Hz), 0.17 (18 H, s) ppm.

3,4,7,8-Tetrahydronaphthalene-1,5(2H,6H)-dione (**4**)

After concentration *in vacuo* the residual oil **3** was s left in a round bottom flask open at the air (O_2) at rt for 96 h. From time to time the content of the flask is gently swirled so as to obtain a thin film at the surface of the flask. During that period the oil slowly crystallises into a yellow solid. The latter was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 99:1) to give enedione **4** (0.495 g, 50% from **2**). However, purified **3** left standing exposed to the air for 96 h afforded after purification **4** in 100% yield. Data of **4**: mp 108 °C; R_f (CH_2Cl_2/EtOAc, 9:1) 0.37; UV (CH_3OH) λ_{max} 260 nm; IR (KBr film) ν 2944 (m), 2873 (w), 1671 (s), 1461 (w), 1418 (w), 1321 (w), 1255 (w), 1227 (w), 1143 (m), 1120 (m), 1036 (m), 939 (w), 864 (w), 821 (w), 730 (w), 680 (w), 568 (w), 499 (w), 461 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48–2.46 (8 H, m), 1.97 (4 H, quintet, *J* = 6.3 Hz) ppm; ^{13}C NMR/APT (75 MHz, $CDCl_3$) δ 201.5 (C), 145.9 (C), 38.2 (CH_2), 22.3 (CH_2), 21.8 (CH_2) ppm; MS *m/z* (%) 164 (M^+, 99), 136 (100), 135 (24), 121 (31), 94 (6), 93 (14), 92 (10), 91 (14), 80 (40), 79 (97), 78 (10), 77 (29), 66 (12), 65 (17), 55 (33), 53 (21), 52 (38), 51 (27), 50 (11), 41 (17).

Acknowledgements

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Sample Availability: No samples available.