Access to Orthogonal Protected Phenols – Synthesis of a Silylated Quinol

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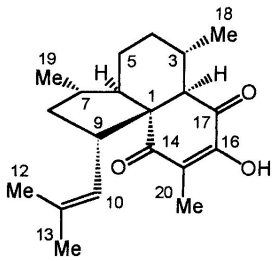
Herein we describe the synthesis of *t*-butyldimethylsilyl protected quinol (**9**), using an oxidation/reduction sequence to create the desired orthogonality. The title compound acts as a synthetic equivalent for a quinone, required in the total synthesis of Elisabethin A. It contains a masked quinone and therefore is a suitable precursor for the quinone moiety of this diterpenoid.

Key words: Orthogonal Protected Phenols, Quinol, Total Synthesis, Elisabethin A

Introduction

In the course of studies towards the total synthesis of Elisabethin **A** (**1**), it was necessary to elaborate a synthetic strategy for a quinol which is protected orthogonally to a methylether. Elisabethin A is a natural product which was isolated from the Caribbean gorgonian *Pseudopterogorgia elisabethae* (Octocorallia) [1]. Marine natural products are among the most promising sources of new biologically active molecules. Certain diterpenoid secondary metabolites possess a broad spectrum of biological activities. Elisabethin type natural products were found to have antitumor and antituberculosis activity [2]. Keeping in mind the biologically scope of Elisabethin A (**1**), we intended to synthesise this molecule. The retrosynthetic disconnection implies an intramolecular Diels-Alder reaction of an (*E*,*Z*)-diene to a *p*-benzoquinone. A possible precursor (compound **9**) for this quinone moiety is described in this report. It contains a masked quinone and a highly reactive aldehyde function.



Elisabethin **A** (**1**)

Results and Discussion

The synthesis of masked quinol **9** started from the commercially available 2,6-dimethoxy toluene (**2**) which was acetylated using acetyl chloride and titanium chloride as Lewis acid to give a quantitative yield of acetophenone **3** [3]. Bayer-Villiger oxidation of **3** with MCPBA gave the desired ester **4** [4] which was hydrolysed with aq. KOH to furnish phenol **5** in 83% yield. The oxidation to the benzoquinone **6** [5] was achieved in 94% yield by treating phenol **5** with CAN in acetonitrile. Quinone **6** was reduced by sodium dithionite to produce hydroquinone **7** [5] in 85% yield. After several unsuccessful attempts the twice *o*,*p*-activated position was regio selectively formylated by refluxing compound **7** with hexamethylene-tetra amine and acetic acid to yield **8** [6] in 40% crude yield. The free hydroxyl groups were protected as silylethers to furnish the desired aldehyde **9** in 45% yield (Scheme 1).

Experimental Section

All moisture sensitive reactions were carried out under Argon. Anhydrous solvents were obtained as follows: Et_2O distilled from $LiAlH_4$; acetone, CH_2Cl_2 and DMF distilled from P_2O_5. All other solvents were HPLC grade. Column chromatography was performed with Merck silica gel (240 – 400 mesh). TLC was carried out with E. Merck silica gel 60-F254 plates. NMR spectra were recorded on either Bruker Avance DPX 250 MHz or Bruker Avance DRX 400 MHz. All NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^{1}H, δ = 7.26; ^{13}C, δ = 77.0). Mass spectra were measured on a Micro Mass, Trio 200 Fisions Instrument. HRMS were taken with a Finnigan MAT 8230 with a resolution of 10000.

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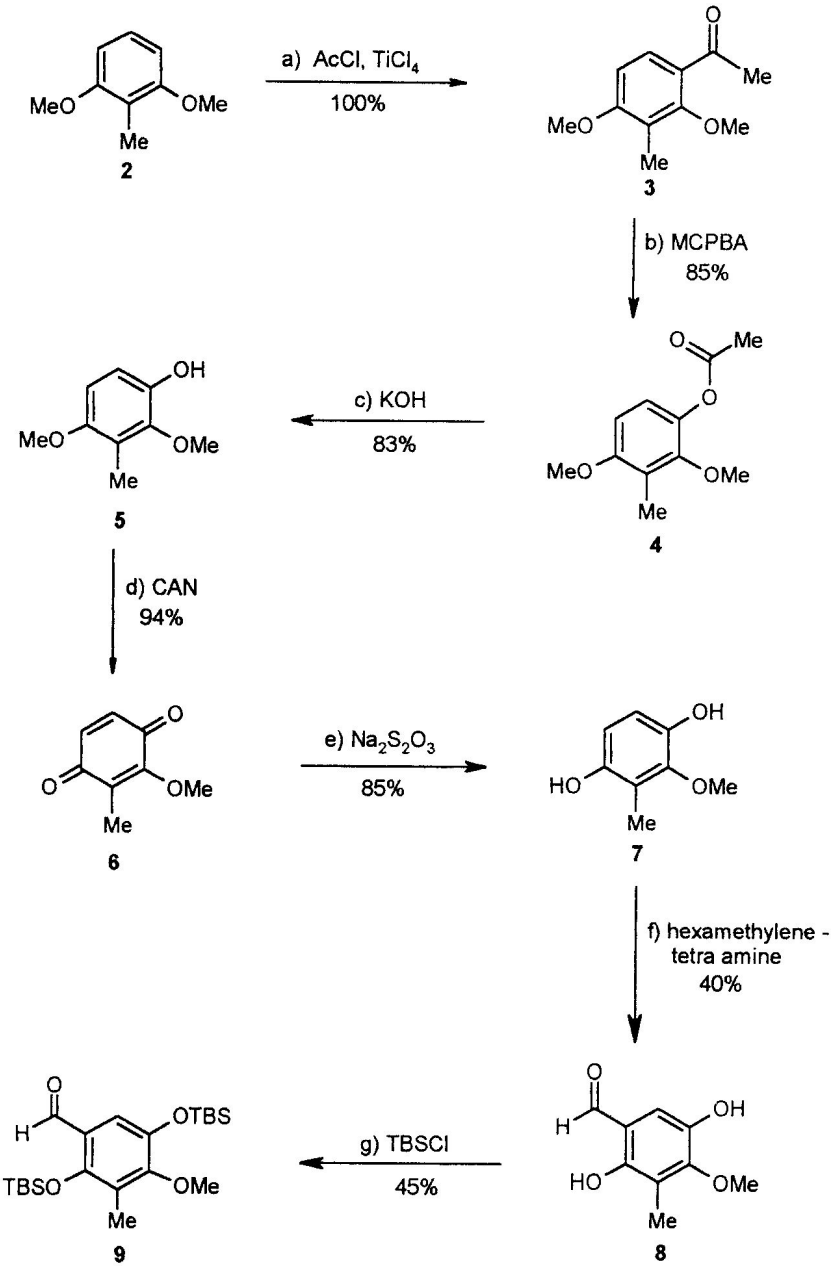

Scheme 1. *Reagents and conditions*: a) $TiCl_4$ (2.0 equiv), AcCl (2.0 equiv), C_6H_6, 0 °C, 30 min, 100%; b) MCPBA (2.0 equiv), TsOH-H_2O (0.03 equiv), CH_2Cl_2, 16 h, rt, 85%; c) KOH (2.0 equiv), MeOH/H_2O, 3 h, 100 °C, 83%; d) CAN (2.5 equiv), CH_3CN, H_2O, 45 min, rt, 94%; e) $Na_2S_2O_3$ (3.85 equiv), Et_2O, H_2O, 30 min, rt, 85%; f) hexamethylene-tetra amine (10.0 equiv), AcOH, 80 °C, 30 min, 40%; g) TBSCl (6.0 equiv), imidazole (6.0 equiv), DMF, rt, 16 h, 45%. MCPBA = *m*-chloroperbenzoic acid, TsOH-H_2O = *p*-toluenesulphonic acid hydrate, CAN = cerium ammonium nitrate.

1-(2,4-Dimetoxy-3-methyl-phenyl)-ethanone (**3**)

Titanium chloride (57.3 g, 302 mmol) and acetyl chloride (23.7 g, 302 mmol) was placed in a three necked flask equipped with reflux condensor, mechanical stirrer and a dropping funnel and cooled to 0 °C. After 15 min this solution solidified and the colour changed from yellow to orange. A solution of 2,6-dimethoxy- toluene **2** (23.0 g, 151 mmol) in benzene (100 ml) was transferred dropwise into the flask under argon over a period of 15 min. Stirring was continued for half an hour. The solution was quenched by the cautious addition of aq. HCl (5%). Phases were separated and the H_2O layer was extracted with ether (5 × 100 ml), dried over $MgSO_4$ and solvent was removed under reduced pressure. After purification by column chromatography (hexane / EtOAc 8:2),

the product **3** was isolated in 100% (29.4 g) yield as a brown oil.

R_f 0.53 (SiO_2, hexane/EtOAc 6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.7 Hz, 1 H, ArH), 6.59 (d, J = 8.7 Hz, 1 H, ArH), 3.79 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 2.54 (s, 3 H, COMe), 2.09 (s, 3 H, ArMe). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 198.4, 161.9, 159.1, 128.7, 119.9, 105.6, 61.5, 55.4, 29.9, 8.6. MS (EI, 70 eV): m/z = 194 (22) $[M]^+$, 178 (100) $[M\text{-}CH_3]^+$, 136 (12) $[M\text{-}CH_3\text{-}COCH_3]^+$, 91 (12). HRMS (20 °C, 70eV): m/z = calcd for $C_{11}H_{14}O_3$, 194.0943; found, 194.0937.

Acetic acid 2,4-dimethoxy-3-methyl-phenyl ester (**4**)

Acetophenone **3** (29.7 g, 153 mmol) was dissolved in CH_2Cl_2 (100 ml) together with *p*-toluensulfonic acid hydrate (1.50 g) at 0 °C. *m*-Chloro-per-benzoic acid (68.6 g, 306 mmol) was added carefully under vigorous stirring over a period of about 1 h at 0 °C. The colour of the solution changed from yellow to orange. This mixture was stirred for 16 h at r.t., diluted with sat. $NaHCO_3$ solution (100 ml) and extracted with CH_2Cl_2 (4 × 100 ml). Solvents were evaporated *in vacuo* from the organic layers and the solid residue was shaken with sat. aq $NaHCO_3$ solution (6 × 100 ml) to remove the benzoic acid. After decanting, the residue was dissolved in Et_2O, passed through a plug of $MgSO_4$, solvents were evaporated and the crude product was further purified by column chromatography (hexane/EtOAc 8:2) to give 27.4 g (85%) of the desired ester **4**.

R_f 0.53 (SiO_2, hexane/EtOAc 6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.86 (d, J = 8.9 Hz, 1 H, ArH), 6.59 (d, J = 8.9 Hz, 1 H, ArH), 3.80, 3.75 (2s, each 3 H, OMe), 2.32 (s, 3 H, COMe), 2.17 (s, 3 H, ArMe). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.5, 156.3, 150.4, 137.5, 121.0, 119.6, 105.5, 61.7, 55.6, 20.6, 9.0. MS (EI, 70 eV): m/z = 210 (12) $[M]^+$, 168 (100) $[M\text{-}C_2H_2O]^+$, 153 (60), 125 (16). HRMS (20 °C, 70 eV): m/z = calcd for $C_{11}H_{14}O_4$, 210.0892; found, 210.0889.

2,4-Dimethoxy-3-methyl phenol (**5**)

To a solution of ester **4** (27.3 g, 130 mmol) in MeOH (100 ml) was added KOH (14.9 g, 260 mmol), dissolved in a mixture of MeOH/ H_2O at r.t. The solution was stirred at r.t. for 30 min, heated at 50 °C for 1 h and then refluxed for 3 h. After the addition of H_2O (200 ml), the solution was acidified with aq HCl (15%), washed with brine (150 ml), extracted with Et_2O (7 × 150 ml), dried over $MgSO_4$ and liberated from solvents *in vacuo* to give a brown crude oil. Purification by column chromatography (hexane/EtOAc 19:1) furnished the desired phenol **5** as a yellow oil in 83 % (18.2 g) yield.

R_f 0.55 (SiO_2, hexane/EtOAc 8:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.53 (d, J = 8.9 Hz, 1 H, ArH), 6.76 (d, J = 8.9 Hz, 1 H, ArH), 5.63 (br s, 1 H, OH), 3.78 (s, 6 H, OMe), 2.19 (s, 3 H, ArMe). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 151.8, 145.9, 142.8, 119.9, 111.7, 106.7, 60.7, 55.9, 9.2. MS (EI, 70 eV): m/z = 168 (100) $[M]^+$, 153 (83) $[M\text{-}CH_3]^+$, 125 (45), 65 (40), 53 (36). HRMS (20 °C, 70 eV): m/z = calcd for $C_9H_{12}O_3$, 168.0786; found, 168.0791.

2-Methoxy-3-methyl-1,4-benzoquinon (**6**)

To a solution of phenol **5** (20.0 g, 119 mmol) in CH_3CN (250 ml) was added under rapid stirring cerium ammonium nitrate (163.3 g, 298 mmol) in H_2O (325 ml) at r.t. over a period of 10 min. Stirring was continued for 45 min then the mixture was extracted with CH_2Cl_2 (5 × 250 ml). The combined organic extracts were washed with H_2O (250 ml), 10% $NaHCO_3$ (2 × 250 ml), H_2O (250 ml) and then brine (250 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Quinone **6** was isolated as a yellow oil (17.0 g, 94%).

R_f 0.64 (SiO_2, hexane/EtOAc 1:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.65 (d, J = 10.0 Hz, 1 H, ArH), 6.56 (d, J = 10.0 Hz, 1 H, ArH), 4.01 (s, 3 H, OMe), 1.94 (s, 3 H, ArMe). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.7, 182.7, 155.2, 135.8, 134.3, 128.4, 60.3, 8.1. MS (EI, 70 eV): m/z = 152 (100) $[M]^+$, 137 (7) $[M\text{-}CH_3]^+$, 122 (41), 109 (21), 84 (93), 66 (32). HRMS (50 °C, 70 eV): m/z = calcd for $C_8H_8O_3$, 152.0473; found 152.0477.

2-Methoxy-3-methyl-benzene-1,4-diol (**7**)

To quinone **6** (17.0 g, 112 mmol) in Et_2O (400 ml) was added an aq solution of sodium dithionite (74.9 g, 430 mmol) in H_2O (350 ml) under rapid stirring in two portions. After 30 min of stirring the two layers were separated and the organic phase was dried over $MgSO_4$. After evaporation of solvents the desired hydroquinone **7** was obtained in 85% (14.7 g) yield.

R_f 0.38 (SiO_2, hexane/ EtOAc 3:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.66 (d, J = 8.7 Hz, 1 H, ArH), 6.64 (d, J = 8.7 Hz, 1 H, ArH), 5.24 (s, 1 H, OH), 4.50 (s, 1 H, OH), 3.77 (s, 3 H, OMe), 2.19 (s, 3 H, ArMe). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 147.6, 145.8, 142.7, 112.4, 112.4, 110.9, 60.8, 9.2. MS (EI, 70 eV): m/z = 154 (100) $[M]^+$, 139 (83) $[M\text{-}CH_3]^+$, 111 (53), 57 (47). HRMS (50 °C, 70 eV): m/z = calcd for $C_8H_{10}O_3$, 154.0630; found, 154.0624.

2,5-Dihydroxy-4-methoxy-3-methyl-benzaldehyde (**8**)

A solution of hydroquinone **7** (14.5 g, 94.1 mmol) and hexamethylene- tetra amine (132 g, 940 mmol) in acetic acid (600 ml) was heated at 80 °Cfor 30 min. The reaction mixture was diluted with H_2O (500 ml) and extracted with CH_3Cl (4 × 300 ml). The combined extracts were washed with sat. $NaHCO_3$ (400 ml). The organic phase was dried over $MgSO_4$

and solvents were evaporated *in vacuo* to give desired aldehyde **8** in 40% (6.85 g) crude yield.

R_f 0.32 (SiO_2, hexane/ EtOAc 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.70 (s, 1 H, CHO), 6.94 (s, 1 H, ArH), 5.79 (s, 1 H, OH), 3.86 (s, 3 H, OMe), 2.19 (s, 3 H, ArMe). MS (EI, 70 eV): *m*/*z* = 182 (100) $[M]^+$, 167 (19) $[M\text{-}CH_3]^+$, 153 (7), 83 (53). HRMS (50 °C, 70 eV): *m*/*z* = calcd for $C_8H_{10}O_4$, 182.0579; found, 182.0577.

2,5-Bis-(tert-butyl-dimethyl-silanyloxy)-4-methoxy-3-methyl- benzaldehyde (**9**)

To a solution of crude aldehyde **8** (3.00 g, 16.0 mmol) in dry DMF (20.0 ml) was added imidazole (7.00 g, 96.0 mmol) under constant stirring at r.t.. Then TBSCl (14.5 g, 96.0 mmol) was added to the reaction mixture at 0 °C. The ice bath was removed and stirring was continued for 16 h at r.t.. The reaction mixture was diluted with cold H_2O (50 ml) and extracted with toluene (6 × 25 ml). The combined toluene layers were washed with H_2O (3 × 20 ml). Further purification by column chromatography (hexane/EtOAc 19:1) over silica gel furnished the title compound **9** in 45% (3.0 g) yield.

R_f 0.82 (SiO_2, hexane/ EtOAc 8:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.18 (s, 1 H, CHO), 7.15 (s, 1 H, ArH), 3.82 (s, 3 H, OMe), 2.13 (s, 3 H, ArMe), 1.00, 1.05 (2s, each 9 H, $SiCMe_3$), 0.19, 0.14 (2s, each 6 H, $SiMe_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 188.2, 155.9, 151.9, 143.5, 124.3, 123.5, 115.5, 59.3, 25.4, 18.3, 10.1, −4.2, −4.0. MS (EI, 70 eV): *m*/*z* = 395 (3) $[M\text{-}CH_3]^+$, 353 (100) $[C_{17}H_{29}O_4Si_2]^+$, 281 (16), 224 (9). HRMS (80 °C, 70 eV): *m*/*z* = calcd for $C_{21}H_{38}O_4Si_2$ —CH_3, 395.2074; found, 395.2081.

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