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Synthesis of 6-Methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one

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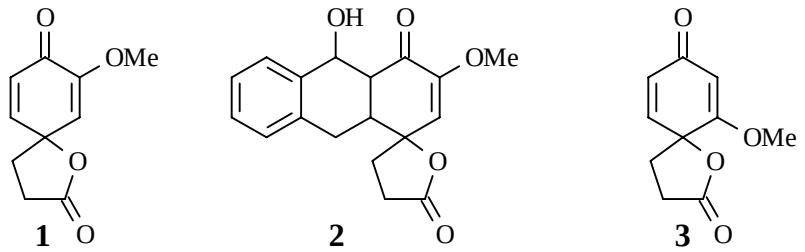
Abstract: The synthesis of a new spirolactone is described. The title compound is obtained as a white solid in 46% yield from 3-(4-hydroxy-2-methoxyphenyl)propanoic acid using [Bis(trifluoroacetoxy)iodo]benzene (PIFA) as the oxidant.

Keywords: Spiroannulation, oxidation, phenol, spirolactone, PIFA.

Introduction

For the past few years our research program has been focused on both the synthesis and the synthetic usefulness of simple oxaspiro compounds such as **1** (Figure 1). We recently published the synthesis of **2**, a product resulting from the Diels-Alder reaction between spirolactone **1** and a α-hydroxy-o-quinodimethane [1]. We subsequently found that **2** possesses cytotoxic activity towards 60 different human cancer cell lines [2,3]. In continuation with this project, we required the spirolactone **3** as one of the starting materials necessary to prepare derivatives of **2**. We now report the synthesis of **3** from 2,4-dihydroxybenzaldehyde.

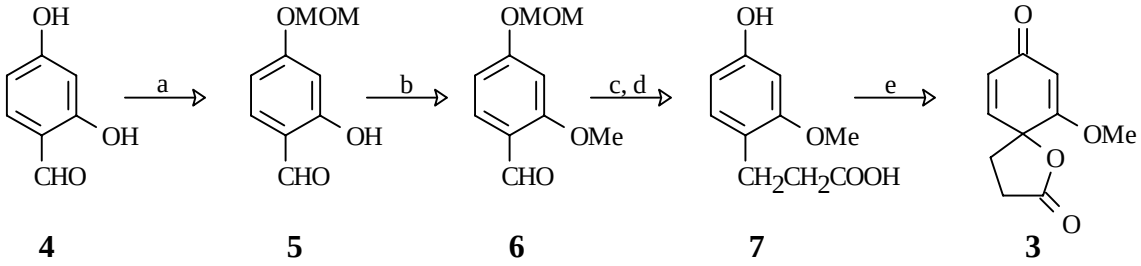
Figure 1



Results and Discussion

Since we had previously prepared spirolactone **1**, we envisioned that our target compound **3** could be obtained via a similar route from 2,4-dihydroxybenzaldehyde (**4**) (Scheme 1). For the first step in the planned synthesis we needed to selectively protect the 4-hydroxyl group in aldehyde **4**. A survey of the literature suggested two methods for the regioselective protection of the 4-hydroxyl position of **4** [4,5]. We could not duplicate the results obtained by Mendelson and coworkers with the benzyl protecting group [4], but we were more successful with the TBDMS group using the procedure reported by Liu *et al*. [5]. Unfortunately, this protecting group was cleaved while introducing the methyl group on the 2-hydroxyl [2M NaOH, THF, MeI, $(Bu)_4NHSO_4$]. Others have reported the easy base catalyzed cleavage of phenolic TBDMS ethers [6].

Scheme 1



(a) K_2CO_3, acetone, MOMCl, (84%); (b) 2M NaOH, THF, $(Bu)_4NHSO_4$, CH_3I, (93%); (c) pyridine, piperidine, malonic acid, 55^{o}C, then 10% HCl; (d) H_2, Pd/C, EtOH, (81%); (e) acetone, PIFA, 0^{o}C, (46%).

We eventually found that it was possible to selectively protect the 4-hydroxyl of **4** as the methoxymethyl ether in 84% yield. Treatment of **5** with methyl iodide under basic conditions [2M NaOH, THF, $(Bu)_4NHSO_4$] proceeded in 93% yield after stirring at room temperature for 3 days. We found that without the ammonium salt the reaction was very sluggish and did not reach completion. In these cases we typically obtained a yield ranging between 50-60% for **6**. Knoevenagel condensation of **6** [pyridine, piperidine, $CH_2(COOH)_2$, 55^{o}C, 20 h], followed by hydrolysis of the MOM protecting group [10% HCl, THF] and hydrogenation [10% Pd/C, H_2] afforded the propanoic acid **7** in 81% yield. Oxidative spiroannulation of **7** using lead tetraacetate [$Pb(OAc)_4$, acetone, rt] produced only 10% of

isolated spirolactone **3**. This was disappointing since typically we can generate **1** in 85% yield using this oxidant. We finally were able to generate **3** in 46% yield from the propanoic acid **7** using PIFA [PIFA, acetone, 0^{o}C] as the oxidant. The lower yield obtained in this reaction could be explain by the fact that the compound appears to be sensitive to the chromatographic conditions used. To test this hypothesis, 18 mg of **3** were dissolved in ethyl acetate containing 300 mg of silica gel. After stirring the mixture for 2 hours and filtering, only 8 mg (42%) of **3** were recovered after filtration. All attempts to recover more material failed, even after washing the silica gel with 15% methanol in chloroform. For the lead tetraacetate oxidation, the lower yield might have resulted from a combination of effects, instability of the product towards chromatography as well as the strength of the oxidant used in this case.

Conclusions

We have described the synthesis of the new spirolactone **3** using PIFA as the oxidant. We are now in the process of preparing other spirocompounds such as **3**, and we are also investigating the asymmetric synthesis of these spirocompounds.

Acknowledgements

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Experimental

General

Melting points were determined on a hot stage instrument and are uncorrected. Infrared spectra were recorded either as KBr pellets or neat on a Perkin Elmer System 2000 FTIR. NMR spectra were recorded on a Bruker AMX300 spectrometer and chemical shifts are expressed in ppm using TMS as internal standard. Mass spectra were recorded on a Hewlett Packard 5898B spectrometer. Elemental analysis was performed at the Central Equipment Laboratory of the University of Northern British Columbia.

2-Hydroxy-4-O-methoxymethylbenzaldehyde (**5**) [7].

To a solution of 2,4-dihydroxybenzaldehyde (**4**) (107 mg, 0.78 mmol) in acetone (5 mL) was added potassium carbonate (161 mg, 1.17 mmol) and chloromethyl methyl ether (149 mg, 1.86 mmol). The resulting mixture was stirred at room temperature for 24 h. 10% Aqueous HCl (5 mL) was added and the solution was extracted with ethyl acetate (3 x 10 mL). The organic fractions were combined, washed with brine (10 mL), dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a white solid. Chromatography on silica gel (25% EtOAc/hexanes) afforded a white solid (118 mg,

84%); Mp: 50-51°C; IR (KBr): 3158 (OH), 1670 (CO); ^{1}H-NMR ($CDCl_3$) δ: 3.49 (s, 3H, OCH_3), 5.23 (s, 2H, OCH_2O), 6.61 (d, 1H, J=2.2Hz, Ar-H_3), 6.66 (dd, 1H, J=2.2, 8.7Hz, Ar-H_5), 7.43 (d, 1H, J=8.7Hz, Ar-H_6), 9.75 (s, 1H CHO); ^{13}C-NMR ($CDCl_3$) δ: 56.7 (OCH_3), 94.2 (OCH_2O), 103.6 (C_3), 109.3 (C_5), 116.0 (C_1), 135.6 (C_6), 164.3 (C_2), 164.5 (C_4), 194.8 (CHO); MS m/e (relative %): 182 [M^+] (100), 153 (8), 151 (16), 137 (4), 121 (5), 81 (3), 65 (8); Anal. Calc'd for $C_9H_{10}O_4$: C 59.32, H 5.54; found C 59.24, H 5.65.

2-Methoxy-4-O-methoxymethylbenzaldehyde (**6**).

To a solution of **5** (1.69 g, 9.3 mmol) in THF (50 mL) was added 2M NaOH (20 mL, 40 mmol) and tetrabutylammonium hydrogensulfate (1.57 g, 4.6 mmol). The mixture was stirred at room temperature for 10 min. and methyl iodide (8.7 g, 61.3 mmol) was added. The resulting mixture was stirred at room temperature for 3 days, then it was concentrated *in vacuo*, and the residue extracted with EtOAc (3 x 70 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give a yellowish solid. Chromatography on silica gel (25% EtOAc/hexanes) afforded a white solid (1.69 g, 93%); Mp: 73-74°C; IR (neat) cm^{-1}: 1682 (CO); ^{1}H-NMR ($CDCl_3$) δ: 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.24 (s, 2H, OCH_2), 6.61 (d, 1H, J=2.1Hz, Ar-H_3), 6.69 (dd, 1H, J=2.1, 8.6Hz, Ar-H_5), 7.80 (d, 1H, J=8.6Hz, Ar-H_6), 10.31 (s, 1H, CHO); ^{13}C-NMR ($CDCl_3$) δ: 55.9 (OCH_3), 56.6 (OCH_3), 94.3 (OCH_2O), 99.7 (Ar-C_3), 108.3 (Ar-C_5), 119.8 (Ar-C_1), 130.8 (Ar-C_6), 163.8 (Ar-C_2), 164.0 (Ar-C_4), 188.7 (CO); MS m/e (relative %): 196 [M^+] (48), 165 (5), 135 (7), 134 (7), 45 (100); Anal. Calc'd for $C_{10}H_{12}O_4$: C 61.20, H 6.17; found C 61.00, H 6.10.

3-(4-hydroxy-2-methoxyphenyl)-propanoic acid (**7**).

To a solution of aldehyde **6** (500 mg, 2.6 mmol) in pyridine (15 mL) was added piperidine (1 mL) and malonic acid (775 mg, 7.4 mol). The resulting solution was stirred at 55°C for 20 h., cooled and poured into 10% HCl (125 mL). The solution was extracted with ethyl acetate (3 x 30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in THF (25 mL), 10% HCl (10 mL) was added and the solution stirred at room temperature for 18 h. The solution was extracted with ethyl acetate (3 x 30 mL), dried ($MgSO_4$) and concentrated to half its volume (~ 40 mL). To this solution was added 10% Pd/C (52 mg) and the mixture was stirred under an atmosphere of H_2 for 2 h. The solution was filtered through Celite and the solvent was evaporated *in vacuo* to give a yellow oil. Chromatography on silica gel (5% MeOH in 50% EtOAc/hexanes) afforded a white solid (405 mg, 81%); Mp: 105-106°C; IR (neat) cm^{-1}: 3386 (OH), 1709 (CO); ^{1}H-NMR (methanol-d_4) δ: 2.43 (t, 2H, J=8.0Hz, H_2), 2.73 (t, 2H, J=8.0Hz, H_3), 3.73 (s, 3H, OCH_3), 6.23 (dd, 1H, J=2.2, 8.0Hz, Ar-H_5), 6.34 (d, 1H, J=2.2Hz, Ar-H_3), 6.87 (d, 1H, J=8.0Hz, Ar-H_6); ^{13}C-NMR (methanol-d_4) δ: 26.8 (C_4), 35.7 (C_3), 55.7 (OCH_3), 99.8 (Ar-C_3), 107.7 (Ar-C_5), 121.0 (Ar-C_1), 131.3 (Ar-C_6), 158.5 (Ar-C_2), 159.9 (Ar-C_4), 177.6 (CO); MS m/e (relative %): 196 [M^+] (34), 138 (9), 137 (100), 107 (24), 77 (9); Anal. Calc'd for $C_{10}H_{12}O_4$: C 61.20, H 6.17; found C 61.00, H 6.20.

6-Methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**3**).

To a solution of phenol **7** (165 mg, 0.84 mmol) in acetone (10 mL) was added at 0^{o}C PIFA (386 mg, 0.87 mmol). The solution was stirred at 0^{o}C for 0.5 h. and the solvent was evaporated *in vacuo* to give a pale yellow solid. Chromatography on silica gel (75% EtOAc/hexanes) afforded a white solid (46 mg, 46%); Mp: 108-109^{o}C; IR (neat) cm^{-1}: 1788 (CO ester), 1670 (CO enone); ^{1}H-NMR ($CDCl_3$) δ: 2.34 (m, 1H, H_{4a}), 2.50 (m, 1H, H_{4b}), 2.71 (m, 1H, H_{3a}), 2.93 (m, 1H, H_{3b}), 3.82 (s, 3H, OCH_3), 5.54 (d, 1H, J=1.6Hz, H_7), 6.19 (dd, 1H, J=1.2, 9.9Hz, H_9), 6.63 (d, 1H, J=9.9, H_{10}); ^{13}C-NMR ($CDCl_3$) δ: 28.3 (C_4), 31.6 (C_3), 56.4 (OCH_3), 78.4 (C_5), 101.5 (C_7), 128.7 (C_9), 142.6 (C_{10}), 171.9 (C_6), 176.3 (CO enone), 186.1 (CO ester); MS m/e (relative %): 194 [M^+] (100), 162 (49), 152 (23), 140 (88), 134 (42), 108 (18); Anal. Calc'd for $C_{10}H_{10}O_4$: C 61.81, H 5.19; found C 61.52, H 5.40.

References and Notes

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Sample Availability: samples of all compounds are available from MDPI.