

Synthesis of a New Spirolactone: 7,10-Dimethoxy-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione

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Abstract

The title compound was synthesized in 36 % yield by oxidative spiroannulation of the corresponding 2,4,5-trisubstituted phenol. Interestingly, this phenol was prepared in 57 % yield from another spirocompound, namely 7-methoxy-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione. We have speculated that the formation of the phenol was due to a series of reactions involving a conjugate addition of methanol to the original spiro lactone followed by aromatization and lactone hydrolysis.

Keywords: Spiroannulation, Aromatization, Phenols, Oxidation, Lead tetraacetate

1. Introduction

As part of our continuing efforts towards the synthesis of natural products from simple spirocompounds such as **1** (Figure 1), our focus for the past few years has been towards the asymmetric synthesis of natural products such as the Aranorosins (Mukhopadhyay et al., 1997; Roy et al., 1992; Watanabe et al., 2003), Gymnastatins (Amagata et al., 1998a; Amagata et al., 1998b; Numata et al., 1997; Phoon et al., 2004) and Manumycins (Hu et al., 2001; Sattler et al., 1998). A representative example from each natural product family is shown in Figure 1, Aranorosin **2**, Gymnastatin E **3** and Nisamycin **4**. As can be seen in Figure 1, all of the natural products have a similar feature, *i.e.* they all possess at least one epoxide functional group in their structure with a carbon skeleton very similar to that of simple spirocompound such as **1**. The first step in our study was to demonstrate the feasibility of preparing optically pure spirocompounds for the purpose of synthesizing these natural products in an asymmetric fashion. We have recently reported the asymmetric synthesis of compounds (+)-**5** and (+)-**6** shown in Figure 1. The synthesis was accomplished in 4 steps yielding pure (+)-**5** and (+)-**6** in around 40 % yield, the key step in these reactions being the diastereoselective oxidative spiroannulation of the appropriately substituted phenols (Plourde et al., 2007; Plourde et al., 2008). As a second step towards the synthesis of these natural products, we recently studied the epoxidation reaction of simple spirocompounds in order to produce structures more closely associated with the natural products found in Figure 1. However, instead of using the optically pure lactones (+)-**5** and/or (+)-**6**, we decided to use **1** since we believed it to be a good model to optimize the reaction conditions necessary to control the epoxidation. Spirolactone **1** [previously synthesized in

our laboratory] is easily synthesized in high yield and it bears an electron donating group (OCH₃) at C-7 which would mimic the electronic nature of the amide functional group found at C-7 in either (+)-**5** or (+)-**6** (Plourde, 1985). However, while studying the epoxidation reaction of **1**, we obtained unexpected results which we are reporting herein.

2. Experimental

2.1 General

Melting points were determined on a hot stage instrument and are uncorrected. Infrared spectra were obtained on a Perkin Elmer System 2000 FTIR. ¹H-NMR spectra were recorded on a Bruker AMX300 spectrometer at 300 MHz and chemical shifts are expressed in ppm using TMS as internal standard. ¹³C-NMR spectra were recorded on a Bruker AMX300 spectrometer at 75.4 MHz and chemical shifts are expressed in ppm using residual solvent signal as internal standard. Mass spectra (EI) were recorded on a Varian CP-3800 GC system with a Saturn 2200 MS station.

2.2 Experimental procedures for the synthesis of the title compound

2.2.1 3-(4-Hydroxy-2,5-dimethoxyphenyl)propionic acid (**10**)

To a solution of spiro lactone **1** (177 mg, 0.91 mmol) in toluene (4 mL) was added benzyltrimethylammonium hydroxide (40 % in methanol) (0.8 mL, 1.91 mmol, 2.1 equiv.). After the appearance of a black precipitate, the mixture was stirred vigorously at room temperature for 1.25 hours. The reaction was quenched by the addition of 10 % aqueous HCl (10 mL) and extracted with ethyl acetate (6 x 5 mL). The organic fractions were combined, dried (MgSO₄) and the solvent evaporated *in vacuo* to afford an orange oil. The crude product was purified by chromatography on silica gel using 25 % hexanes/ethyl acetate as eluent affording a white solid. This product was recrystallized from a 1/1 mixture of ethanol/toluene to afford white flakes (117 mg, 57 %). mp: 109-111 °C. IR (KBr) cm⁻¹: 3479, 1715. ¹H-NMR (CDCl₃) δ: 2.63 (t, 2H, *J* = 7.6Hz, H₂), 2.86 (t, 2H, *J* = 7.6Hz, H₃), 3.75 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 6.54 (s, 1H, Ar-H₃), 6.71 (s, 1H, Ar-H₆). ¹³C-NMR (CDCl₃) δ: 26.0 (C₃), 34.7 (C₂), 56.2 (OCH₃), 57.2 (OCH₃), 99.5 (Ar-C₃), 113.9 (Ar-C₆), 119.5 (Ar-C₁), 140.3 (Ar-C₄), 145.2 (Ar-C₅), 152.5 (Ar-C₂), 179.5 (C=O). MS (rel %) for C₁₁H₁₄O₅: 226 (100) [M⁺], 224 (5), 168 (8), 167(32), 165 (4) 164 (2).

2.2.2 7,10-Dimethoxy-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione (**11**)

To a solution of propionic acid **10** (92.0 mg, 0.41 mmol) in acetone (5 mL) was added at room temperature lead tetraacetate (723.0 mg, 1.63 mmol, 4 equiv.). The yellow solution was stirred at room temperature for 2 days, filtered through celite© and ethylene glycol (5 drops) was added. The solution was stirred at room temperature overnight, filtered through celite© and evaporated *in vacuo* to give a yellow solid. The crude product was recrystallized from benzene to afford a yellow solid (33.0 mg, 36 %). mp: 139-142 °C. IR (KBr) cm⁻¹: 1728, 1682. ¹H-NMR (CDCl₃) δ: 2.35 (m, 1H, H_{3a}), 2.55 (m, 1H, H_{3b}), 2.71 (m, 1H, H_{4a}), 2.74 (m, 1H, H_{4b}), 3.73 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 5.46 (s, 1H, H₆), 5.55 (s, 1H, H₉). ¹³C-NMR (CDCl₃) δ: 29.2 (C₃), 33.4 (C₄), 55.9 (OCH₃), 57.1 (OCH₃), 81.0 (C₅), 101.1 (C₉), 110.1 (C₆), 151.0 (C₇), 172.7 (C₁₀), 176.6 (C₈), 181.4 (C₂). MS (rel %) for C₁₁H₁₂O₅: 224(90) [M⁺], 209(8), 168 (10), 167 (100), 137 (13).

3. Results and Discussion

As can be seen in Figure 1, spiro compound **1** possesses two alkene double bonds differing only by the substitution pattern on the vinylic carbons. The first double bond (double bond bearing the OCH₃ group) can be considered to be an electron rich double bond (ERDB) due to the presence of the vinylic OCH₃ functional group, while the second one (double bond bearing only hydrogen atoms) would be more deficient in electrons and as such considered an electron poor double bond (EPDB) and therefore would be more susceptible to attack by nucleophiles. Hence, by choosing the correct reaction conditions it should be possible to differentiate between these double bonds and carry out the epoxidation reaction only on one of them. Epoxidation involving the use of nucleophilic species would be appropriate to carry out the epoxidation of the disubstituted double bond (EPDB) in **1**. Literature precedents suggested that this epoxidation could be done using the hydrogen peroxide anion (HOO⁻) in the presence of a phase transfer catalyst as previously described for similar systems (Alcaraz et al., 1998; Enhnen et al., 1990; Moore, 1967; Payne, 1959; Salladie et al., 1987). However, all our attempts to carry out this transformation following this type of procedure failed to give the desired product. Instead, we observed in all cases one major product that we eventually identified as the propionic acid **10** based on the ¹H- and ¹³C-NMR spectral data. ¹³C-NMR data suggested that the new product possessed only one carbonyl group (179.5 ppm) and a second methoxy group could be observed in both the ¹³C-NMR (55.9 and 57.1 ppm) and ¹H-NMR (3.75 and 3.82 ppm). The ¹H-NMR spectrum also showed the presence of only 2 protons in the 6.5-7.0 ppm region suggesting that the 6-membered ring had potentially rearomatized. Furthermore, the fact that only 2

protons could be found in this region of the spectrum suggested that one of the vinylic proton in **1** was substituted during the reaction, most likely by the OCH₃ group that we had already identified in the ¹H-NMR spectrum of this product. We speculated that the formation of **10** probably took place as shown in Figure 2. This probable mechanism shows that the initial conjugate addition took place with methanol (from the 40 % solution of phase transfer catalyst) instead of the peroxide anion, producing the enolate anion **8**. Deprotonation of **8** as shown in Figure 2 would result in the rearomatization of the molecule as well as the lactone ring opening to produce the dianion **9**. Acidification of **9** to produce **10** was accomplished during the acidic workup. While the lactone ring opening in structure **8** is unusual, there is literature precedent suggesting that such ester hydrolysis is possible, yet rare (Barclay et al., 1962). In the case of the transformation suggested in Figure 1 for **8** to **9**, the driving force may simply be the rearomatization of the 6-membered ring which would force the unusual lactone opening to take place. We later found out that the formation of **10** from **1** can be accomplished simply in the presence of the phase transfer catalyst (40 % benzyltrimethyl ammonium hydroxide in methanol) and no other reagents are necessary. Hence, we were able to prepare **10** from **1** in 57 % yield using this process as shown in Scheme 1. We are now attempting to prepare other derivatives by introducing other small alcohols in the reaction mixture and possibly other weak nucleophiles to ascertain the scope of this transformation. We also carried out the spiroannulation reaction of **10** to produce the new spiro lactone **11** in 36 % yield using a previously reported procedure (Plourde, 2002; Plourde, 2003a-c; Plourde et al., 2005).

4. Conclusion

We have successfully prepared a new spiro lactone **11** from phenol **10** which was produced via the conjugate addition to a simple spiro lactone **1** followed by rearomatization of the molecule and lactone ring opening. While this reaction is simple in nature, it may provide a new method for the synthesis of other 7,10-disubstituted spiro compounds which are uncommon. We are presently working on the optimization of this process as well as studying this methodology to establish its potential as a general method for forming 7,10-disubstituted spiro compounds.

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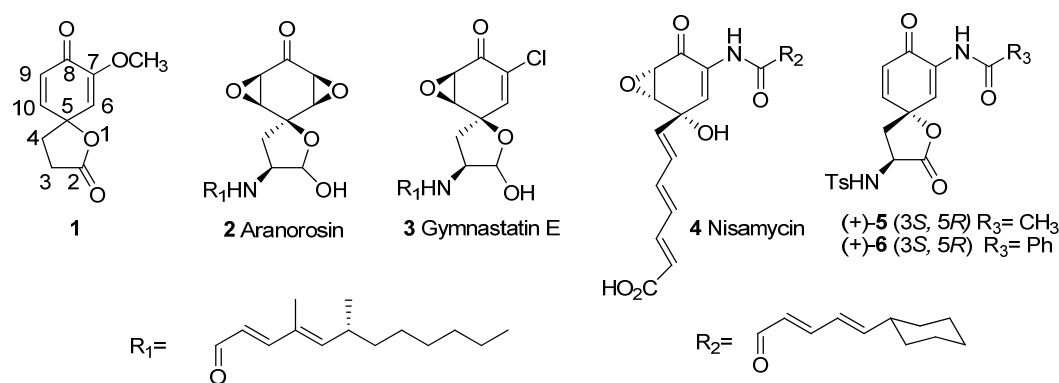


Figure 1. Structure of Spirolactones and Natural Products

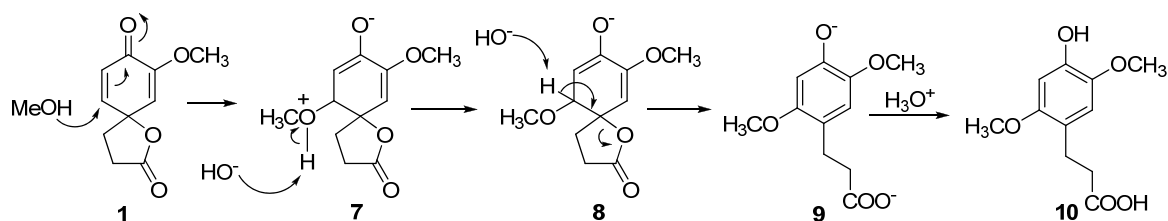
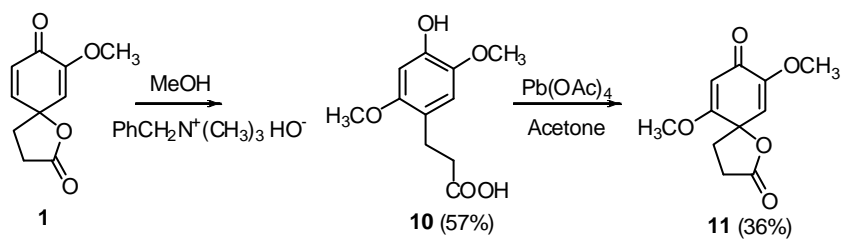


Figure 2. Possible mechanism for the formation of phenol 10

Scheme 1. Synthesis of spiro lactone **11**