Diastereoselective Spiroannulation of Phenolic Derivatives: Effect of the o-Alkoxy Substituent on the Diastereoselectivity

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Abstract

This study was aimed at determining the effect, if any, that steric factors may have on the diastereoselectivity in the spiroannulation of simple phenols. A series of phenols bearing different size substituents *ortho* to the phenolic hydroxyl were synthesized and spiroannulated to the corresponding spiroethers in good to excellent yields (76-94%). However, the diastereoselectivity of the reaction remain mostly unchanged suggesting that stereoelectronic rather than steric factors influence the diastereoselectivity in this reaction.

Keywords: Spironannulation, Diastereoselectivity, Asymmetric, Phenols, Oxidation, Lead tetraacetate

1. Introduction

The spiroannulation (or spirocyclization) of simple 4-substituted phenols has been known for more than 50 years, (Cha *et al*, 2009; Frie *et al*, 2009; Moriarty *et al*., 2001; Pierce *et al*, 2008) yet the asymmetric version of the reaction in which the stereochemistry of the newly formed spirocarbon is controlled lack in examples. For the past 10 years our focus has been to develop methods to accomplish the asymmetric spiroannulation of simple phenols in order to use these methods in 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). We have previously shown that the synthesis of spirocompounds from simple phenols can be accomplished diastereoselectively, albeit with only moderate diastereoselectivity (4:1 ratio of diastereomers for **1**) (Plourde, G.L. 2002a; Plourde, G.L. 2003a; Plourde, G.L. 2003b; Plourde, G.L. 2003c). Other studies have also shown the importance of the presence of electron donating groups (EDG) such as methoxy or amide *ortho* to the phenolic hydroxyl as shown in compounds **1-3** in Figure 1 (Plourde *et al*., 2005; Plourde *et al*., 2007; Plourde *et al*., 2008). Such groups not only increase the overall chemical yield of the spiroannulation reaction, but also appear to favour a higher diastereoselectivity as well. Furthermore, it was also shown that when the EDG is located *meta* to the phenolic hydroxyl as shown in **4**, the spiroannulation reaction is no longer diastereoselective (product **5** is produced in 45% yield with a 1:1 ratio of diastereomers from **4**) suggesting that an electronic effect may be the cause of the enhanced diastereoselectivity in the case of the *ortho* substituted phenols (Plourde *et al*., 2005). We speculated that this may be the result of the stabilization of a phenoxenium ion by the EDG in the transition state. A similar effect has also been observed in the oxidative carbon-based nucleophilic substitution of phenols (Quideau *et al*., 1999). We have recently studied the effect that the size of the *ortho*-alkoxy substituent may have on the diastereoselectivity of this reaction and our results are summarized below.

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. ^{1}H-NMR spectra were recorded on a Bruker AMX300 spectrometer at 300 MHz and chemical shifts are expressed in ppm using TMS as internal standard. ^{13}C-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 were recorded on a Varian CP-3800 GC system with a Saturn 2200 MS station.

*2.2 Synthesis of phenols **9a-d***

2.2.1 (1E)-1-[4-(benzyloxy)-3-hydroxyphenyl]-4,4-dimethyl-1-en-3-one (**7**)

To a solution of mono-protected benzaldehyde **6** (1.61g, 7.1mmol) in 1:1 mixture of tetrahydrofuran/ethanol (150mL) was added sodium hydroxide (0.86g, 21.6mmol) and pinacolone (3.1g, 31.2mmol). The mixture was refluxed for 24 hours at which point thin layer chromatography showed an incomplete reaction. Additional quantities of sodium hydroxide (0.75g, 2.7mmol) and pinacolone (3.1g, 30.9mmol) were added and the mixture was refluxed for an additional 24 hours. The resulting dark red mixture was cooled to room temperature, acidified with 10% HCl (150mL), concentrated *in vacuo* and extracted with dichloromethane (4 x 50mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent was evaportated *in vacuo* to give an amber oil that solidified upon standing. Chromatography on silica gel using 15% ethyl acetate/hexanes as eluent afforded a light yellow solid (1.72g, 79%). mp: 92-93^oC. IR (KBr) cm^{-1}: 3406, 1673. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, ^{t}Bu), 5.15 (s, 2H, OCH_2), 5.71 (s, 1H exchangeable with D_2O, OH), 6.99 (d, 1H, J=15.5Hz, H_2), 7.24 (m, 8H, aromatic Hs), 7.59 (d, 1H, J=15.5Hz, H_1). ^{13}C-NMR ($CDCl_3$) δ: 26.8, 43.6, 71.5, 112.3, 113.4, 119.6, 122.8, 128.3, 129.0, 129.2, 137.0, 143.0, 146.4, 148.0, 204.7. MS (rel %) for $C_{20}H_{22}O_3$: 310 [M^+] (17), 251 (100), 219 (51), 162 (22), 91 (36), 57 (58).

2.2.2 1-(4-benzyloxy-3-ethoxyphenyl)-4,4-dimethylpent-1-ene-3-one (**8a**)

To a solution of **7** (0.45g, 1.5mmol) in acetonitrile (30mL) was added iodoethane (0.80g, 5.1mmol) and potassium carbonate (0.69g, 5mmol). The mixture was reflux for 24 hours, cooled to room temperature, washed with distilled water (30mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 30mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude reaction product was purified by chromatography on silica gel using 10% ethyl acetate/hexanes as eluent to afford a light yellow solid (0.46g, 95%). mp: 88-90^oC. IR (KBr) cm^{-1}: 1678. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, ^{t}Bu), 1.49 (t, 3H, J=7.1Hz, ethyl CH_3), 4.18 (q, 2H, J=7.1Hz, ethyl CH_2), 5.19 (s, 2H, OCH_2), 7.04 (d, 1H, J=15.6Hz, H_1), 7.24 (m, 9H, aromatic Hs), 7.59 (d, 1H, J=15.6Hz, H_2). ^{13}C-NMR ($CDCl_3$) δ: 15.1, 26.6, 65.1, 71.1, 113.2, 114.4, 118.9, 122.6, 127.3, 128.1, 128.8, 137.0, 143.1, 149.4, 150.8, 204.4. MS (rel %) for $C_{22}H_{26}O_3$: 338 (M^+) (100), 281 (56), 191 (18), 91 (8).

2.2.3 1-(4-benzyloxy-3-isopropoxyphenyl)-4,4-dimethylpent-1-ene-3-one (**8b**)

To a solution of **7** (0.44g, 1.4mmol) in acetonitrile (30mL) was added 2-bromopropane (0.64g, 5.2mmol) and potassium carbonate (0.71g, 5.1mmol). The mixture was reflux for 24 hours, cooled to room temperature, washed with distilled water (30mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 30mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude reaction product was purified by chromatography on silica gel using 10% ethyl acetate/hexanes as eluent to afford a white solid (0.49g, 98%). mp: 59-60^oC. IR (KBr) cm^{-1}: 1678. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, ^{t}Bu), 1.37 (d, 6H, J=6.2Hz, isopropyl CH_3), 4.57 (m, 1H, isopropyl CH), 5.17 (s, 2H, OCH_2), 6.97 (d, 1H, J=15.5Hz, H_1), 7.30 (m, 8H, aromatic Hs), 7.60 (d, 1H, J=15.5Hz, H_2). ^{13}C-NMR ($CDCl_3$) δ: 22.4, 26.6, 43.4, 71.1, 72.7, 114.8, 117.6, 119.0, 123.1, 127.3, 128.1, 128.8, 137.1, 143.0, 148.2, 152.2, 204.1.

2.2.4 1-(4-benzyloxy-3-isopropoxyphenyl)-4,4-dimethylpent-1-ene-3-one (**8c**)

To a solution of **7** (0.28g, 0.9mmol) in acetonitrile (30mL) was added bromomethylcyclohexane (0.49g, 2.8mmol) and potassium carbonate (0.69g, 5.0mmol). The mixture was reflux for 24 hours, cooled to room temperature, washed with distilled water (30mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 30mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude reaction product was purified by chromatography on silica gel using 10% ethyl acetate/hexanes as eluent to afford a light yellow solid (0.25g, 70%). mp: 103-105^oC. IR (KBr) cm^{-1}: 1678. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, ^{t}Bu), 1.25 (m, 6H cyclohexyl Hs), 1.83 (m, 5H, cyclohexyl Hs), 3.86 (d, 2H, J=6.0Hz, cyclohexyl OCH_2), 5.15 (s, 2H, OCH_2), 6.97 (d, 1H, J=15.5Hz, H_1), 7.30 (m, 8H, aromatic Hs), 7.61 (d, 1H, J=15.5Hz, H_2). ^{13}C-NMR ($CDCl_3$) δ: 26.1, 26.7, 30.1, 37.9, 43.3, 71.2, 75.0, 113.3, 114.7, 118.9, 122.5, 127.3, 128.1, 128.7, 137.2, 143.3, 149.9, 150.9, 204.4. MS (rel %) for $C_{29}H_{34}O_3$: 406 (83), 349 (100), 318 923), 253 (28), 220 (33), 91 (10), 57 (8).

2.2.5 1-(4-benzyloxy-3-(2,6-dichlorobenzyloxy)phenyl)-4,4-dimethylpent-1-ene-3-one (**8d**)

To a solution of **7** (0.45g, 1.5mmol) in acetonitrile (30mL) was added 2,6-dichlorobenzylbromide (0.73g, 3.1mmol) and potassium carbonate (0.83g, 6.0mmol). The mixture was reflux for 24 hours, cooled to room temperature, washed with distilled water (30mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 30mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude reaction product was purified by chromatography on silica gel using 10% ethyl acetate/hexanes as eluent to afford a light yellow oil

(0.57g, 84%). IR (neat) cm^{-1}: 1679. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, 9H, ^{t}Bu), 5.17 (s, 2H, OCH_2), 5.42 (s, 2H, OCH_2), 6.98 (d, 1H, J=15.6Hz, H_1), 7.30 (m, 11H, aromatic Hs), 7.60 (d, 1H, J=15.6Hz, H_2). ^{13}C-NMR ($CDCl_3$) δ: 26.6, 43.4, 67.3, 71.3, 114.9, 115.9, 119.2, 124.2, 127.5, 128.1, 128.7, 130.0, 130.6, 132.5, 136.9, 137.3, 142.8, 149.1, 151.8, 204.4.

2.2.6 (±)-1-(3-ethoxy-4-hydroxyphenyl)-4,4-dimethylpentan-3-ol (**9a**)

To a solution of **8a** (0.41g, 1.2mmol) in ethyl acetate (30mL) was added 5% Pd/C (0.24g) and the mixture was shaken at room temperature in an hydrogenator with a H_2 pressure maintained at 30-35 psi. The mixture was filtered through Celite®, dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude reaction mixture was dissolved in ethanol (30mL) and sodium borohydride (0.14g, 3.8mmol) was added. The mixture was stirred at room temperature for 3 hours. The solution was acidified (10% HCl) and allowed to stir overnight. The solution was washed with water (10mL), extracted with dichloromethane (3 x 25mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (0.27g, 90%). IR (neat) cm^{-1}: 3422. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, ^{t}Bu), 1.44 (t, 3H, J=6.8Hz, ethyl CH_3), 1.54 (m, 1H, H_{2a}), 1.61 (broad s, 1H exchangeable with D_2O, OH), 1.80 (m, 1H, H_{2b}), 2.54 (m, 1H, H_{1a}), 2.85 (m, 1H, H_{1b}), 3.22 (broad d, 1H, J=10.5Hz, H_3), 4.10 (q, 2H, J=6.8Hz, ethyl CH_2), 5.54 (s, 1H exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=8.6Hz, ArH_5). ^{13}C-NMR ($CDCl_3$) δ: 15.1, 25.9, 33.3, 33.9, 35.1, 79.6, 112.2, 114.4, 121.0, 134.5, 144.0, 145.8. MS (rel %) for $C_{15}H_{24}O_3$: 252 [M^+] (100), 165 (19), 151 (37).

2.2.7 (±)-1-(4-hydroxy-3-isopropoxyphenyl)-4,4-dimethylpentan-3-ol (**9b**)

To a solution of **8b** (0.42g, 1.2mmol) in ethyl acetate (30mL) was added 5% Pd/C (0.27g) and the mixture was shaken at room temperature in an hydrogenator with a H_2 pressure maintained at 30-35 psi. The mixture was filtered through Celite®, dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude reaction mixture was dissolved in ethanol (30mL) and sodium borohydride (0.12g, 3.1mmol) was added. The mixture was stirred at room temperature for 3 hours. The solution was acidified (10% HCl) and allowed to stir overnight. The solution was washed with water (10mL), extracted with dichloromethane (3 x 25mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (0.26g, 81%). IR (neat) cm^{-1}: 3420. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, ^{t}Bu), 1.36 (d, 6H, J=6.2Hz, isopropyl CH_3), 1.54 (m, 1H, H_{2a}), 1.67 (broad s, 1H exchangeable with D_2O, OH), 1.80 (m, 1H, H_{2b}), 2.53 (m, 1H, H_{1a}), 2.83 (m, 1H, H_{1b}), 3.21 (broad d, 1H, J=10.8Hz, H_3), 4.58 (m, 1H, J=6.2Hz, isopropyl CH), 5.60 (s, 1H exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=8.0Hz, ArH_5). ^{13}C-NMR ($CDCl_3$) δ: 22.5, 25.9, 33.2, 33.9, 35.1, 71.8, 79.5, 113.9, 114.5, 121.2, 134.4, 144.0. MS (rel %) for $C_{16}H_{26}O_3$: 266 [M^+] (100), 249 (35), 205 (8), 165 (33), 123 (44).

2.2.8 (±)-1-(4-hydroxy-3-methylcyclohexyloxyphenyl)-4,4-dimethylpentan-3-ol (**9c**)

To a solution of **8c** (0.22g, 0.5mmol) in ethyl acetate (30mL) was added 5% Pd/C (0.20g) and the mixture was shaken at room temperature in an hydrogenator with a H_2 pressure maintained at 30-35 psi. The mixture was filtered through Celite®, dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude reaction mixture was dissolved in ethanol (30mL) and sodium borohydride (0.12g, 3.1mmol) was added. The mixture was stirred at room temperature for 3 hours. The solution was acidified (10% HCl) and allowed to stir overnight. The solution was washed with water (10mL), extracted with dichloromethane (3 x 25mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (0.08g, 43%). IR (neat) cm^{-1}: 3419. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, ^{t}Bu), 1.0-1.8 (m, 13H, cyclohexyl Hs, H_{2a} and H_{2b}), 2.54 (m, 1H, H_{1a}), 2.83 (m, 1H, H_{1b}), 3.22 (broad d, 1H, J=10.5Hz, H_3), 3.82 (d, 2H, J=7.1Hz, OCH_2), 5.53 (s, 1H exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=8.5Hz, ArH_5). ^{13}C-NMR ($CDCl_3$) δ: 25.9, 26.0, 26.7, 30.1, 33.3, 33.9, 35.1, 37.9, 74.4, 79.6, 112.1, 114.3, 120.9, 134.5, 144.0, 146.1. MS (rel %) for $C_{20}H_{32}O_3$: 319 (100), 218 (21), 123 (16).

2.2.9 (±)-1-(3-(2,6-dichlorobenzyloxy)-4-hydroxyphenyl)-4,4-dimethylpentan-3-ol (**9d**)

To a solution of **8d** (0.53g, 1.1mmol) in ethyl acetate (30mL) was added 5% Pd/C (0.37g) and the mixture was shaken at room temperature in an hydrogenator with a H_2 pressure maintained at 30-35 psi. The mixture was filtered through Celite®, dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude reaction mixture was dissolved in ethanol (30mL) and sodium borohydride (0.19g, 4.9mmol) was added. The mixture was stirred at room temperature for 3 hours. The solution was acidified (10% HCl) and allowed to stir overnight. The solution was washed with water (10mL), extracted with dichloromethane (3 x 25mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using 25% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (0.20g, 46%). IR (neat) cm^{-1}: 3497. ^{1}H-NMR ($CDCl_3$) δ:

0.92 (s, 9H, ^{t}Bu), 1.57 (m, 1H, H_{2a}), 1.85 (m, 1H, H_{2b}), 2.61 (m, 1H, H_{1a}), 2.85 (m, 1H, H_{1b}), 3.25 (broad d, 1H, J=10.4Hz, H_3), 5.35 (s, 2H, OCH_2), 5.69 (s, 1H exchangeable with D_2O, OH), 6.85 (m, 3H, aromatic Hs), 7.35 (m, 3H, aromatic Hs). ^{13}C-NMR ($CDCl_3$) δ: 25.9, 33.2, 33.9, 35.1, 66.6, 79.6, 113.8, 114.9, 122.3, 128.8, 130.9, 132.0, 134.6, 137.1, 144.6, 145.5. MS (rel %) for $C_{20}H_{24}Cl_2O_3$: 382 (63), 365 (100), 282 (17), 219 (7).

*2.3 Synthesis of spiroethers **10a-d***

2.3.1 (±)-2-tert-butyl-7-ethoxy-1-oxospiro[4.5]deca-6,9-diene-8-one (**10a**)

To a cold (0^{o}C) solution of alcohol **9a** (59mg, 0.23mmol) in acetone (35mL) was added lead (IV) acetate (264mg, 0.58 mmol). The resulting mixture was stirred at 0^{o}C for 2.5 hours, filtered through Celite® and ethylene glycol (4 drops) was added. The resulting mixture was stirred at room temperature overnight, filtered through Celite® and the solvent was evaporated *in vacuo*. ^{1}H-NMR data was obtained at this stage in order to determine the diastereomeric ratio of the mixture by using the signals for H_6 of the major and minor isomers. The diastereomeric ratio was determined to be 76/24. The crude product was then purified by chromatography on silica gel using 25% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (49mg, 92%). Whenever distinguishable, data for both isomers are given. In this case the data for the minor isomer of the mixture is listed in [square brackets]. IR (neat) cm^{-1}: 1677. ^{1}H-NMR ($CDCl_3$) δ: 0.94 [0.95] (s, 9H, ^{t}Bu), 1.42 (t, 3H, J=7.1Hz, ethyl CH_3), 1.95-2.07 (m, 4H, H_3 and H_4), 3.91 (m, 3H, ethyl CH_2 and H_2), 5.66 (d, 1H, J=2.7Hz, H_6) [5.76, d, J=2.7Hz, H_6], 6.12 (d, 1H, J=9.9Hz, H_9) [6.14, d, J=9.9Hz, H_9], 6.78 (dd, 1H, J=2.7, 9.9Hz, H_{10}) [6.87, dd, J=2.7, 9.9Hz, H_{10}]. ^{13}C-NMR ($CDCl_3$) δ: 14.5, 26.1, 27.7, 33.8, 38.4, 63.4, 79.7, 88.9, 118.0, 126.4, 149.1, 150.7, 181.4. MS (rel %) for $C_{15}H_{22}O_3$: 250 [M^+] (75), 167 (100), 165 (29), 139 (33), 91 (7).

2.3.2 (±)-2-tert-butyl-7-isopropoxy-1-oxospiro[4.5]deca-6,9-diene-8-one (**10b**)

To a cold (0^{o}C) solution of alcohol **9b** (55mg, 0.21mmol) in acetone (35mL) was added lead (IV) acetate (240mg, 0.54 mmol). The resulting mixture was stirred at 0^{o}C for 2.5 hours, filtered through Celite® and ethylene glycol (4 drops) was added. The resulting mixture was stirred at room temperature overnight, filtered through Celite® and the solvent was evaporated *in vacuo*. ^{1}H-NMR data was obtained at this stage in order to determine the diastereomeric ratio of the mixture by using the signals for H_6 of the major and minor isomers. The diastereomeric ratio was determined to be 71/29. The crude product was then purified by chromatography on silica gel using 25% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (41mg, 76%). Whenever distinguishable, data for both isomers are given. In this case the data for the minor isomer of the mixture is listed in [square brackets]. IR (neat) cm^{-1}: 1676. ^{1}H-NMR ($CDCl_3$) δ: 0.94 [0.95] (s, 9H, ^{t}Bu), 1.31[1.34] (d, 6H, J=6.5Hz, isopropyl CH_3), 2.06 (m, 4H, H_3 and H_4), 3.92 [4.35] (m, 2H, isopropyl CH and H_2), 5.67 (d, 1H, J=2.8Hz, H_6) [5.77, d, J=2.7Hz, H_6], 6.11 (d, 1H, J=10.0Hz, H_9) [6.13 (d, J=10.0Hz, H_9], 6.76 (dd, 1H, J=2.7, 10.0Hz, H_{10}) [6.84 (dd, H=2.7, 10.0Hz, H_{10}]. ^{13}C-NMR ($CDCl_3$) δ: 21.9, 26.3, 34.0, 38.6, 79.9, 89.1, 119.8, 126.7, 147.9, 150.6, 182.2. MS (rel %) for $C_{16}H_{24}O_3$: 264 [M^+](100), 205 (11), 165 (58), 123 (51).

2.3.3 (±)-2-tert-butyl-7-methylcyclohexyloxy-1-oxospiro[4.5]deca-6,9-diene-8-one (**10c**)

To a cold (0^{o}C) solution of alcohol **9c** (37mg, 0.12mmol) in acetone (35mL) was added lead (IV) acetate (138mg, 0.30 mmol). The resulting mixture was stirred at 0^{o}C for 2.5 hours, filtered through Celite® and ethylene glycol (4 drops) was added. The resulting mixture was stirred at room temperature overnight, filtered through Celite® and the solvent was evaporated *in vacuo*. ^{1}H-NMR data was obtained at this stage in order to determine the diastereomeric ratio of the mixture by using the signals for H_6 of the major and minor isomers. The diastereomeric ratio was determined to be 65/35. The crude product was then purified by chromatography on silica gel using 25% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (14mg, 38%). Whenever distinguishable, data for both isomers are given. In this case the data for the minor isomer of the mixture is listed in [square brackets]. IR (neat) cm^{-1}: 1678. ^{1}H-NMR ($CDCl_3$) δ: 0.95 [0.96] (s, 9H, ^{t}Bu), 1.26 (m, 4H, cyclohexyl Hs), 1.84-2.06 (m, 11H, cyclohexyl Hs, H_3 and H_4), 3.53 (m, 2H, OCH_2), 3.93 (m, 1H, H_2), 5.62 (d, 1H, J=2.7Hz, H_6) [5.74, d, J=2.7Hz, H_6], 6.12 (d, 1H, J=9.9Hz, H_9) [6.14, d, J=9.9Hz, H_9], 6.77 (dd, 1H, J=2.7, 9.9Hz, H_{10}) [6.87, dd, H=2.7, 9.9Hz, H_{10}]. ^{13}C-NMR ($CDCl_3$) δ: 26.1, 26.7, 27.5, 30.2, 33.8, 37.2, 38.1, 73.3, 79.7, 88.7, 117.8, 126.5, 149.5, 150.4, 181.3. MS (rel %) for $C_{20}H_{30}O_3$: 316 (100), 204 (12), 123 (7).

2.3.4 (±)-2-tert-butyl-7-(2,6-dichlorobenzyloxy)-1-oxospiro[4.5]deca-6,9-diene-8-one (**10d**)

To a cold (0^{o}C) solution of alcohol **9d** (51mg, 0.13mmol) in acetone (35mL) was added lead (IV) acetate (151mg, 0.33 mmol). The resulting mixture was stirred at 0^{o}C for 2.5 hours, filtered through Celite® and ethylene glycol (4 drops) was added. The resulting mixture was stirred at room temperature overnight, filtered through Celite® and the solvent was evaporated *in vacuo*. ^{1}H-NMR data was obtained at this stage in order to determine the diastereomeric ratio of the mixture by using the signals for H_6 of the major and minor isomers. The diastereomeric ratio was

determined to be 51/49. The crude product was then purified by chromatography on silica gel using 20% ethyl acetate/hexanes as eluent to afford a slightly yellow oil (47mg, 94%). Whenever distinguishable, data for both isomers are given. In this case the data for the minor isomer of the mixture is listed in [square brackets]. IR (neat) cm^{-1}: 1677. ^{1}H-NMR ($CDCl_3$) δ: 0.96 [0.97] (s, 9H, ^{t}Bu), 2.05 (m, 4H, H_3 and H_4), 3.97 (m, 1H, H_2), 5.08 (s, 2H, OCH_2), 5.88 (d, 1H, J=2.7Hz, H_6) [5.98, d, J=2.7Hz, H_6], 6.13 (d, 1H, J=10.0Hz, H_9) [6.14, d, J=10.0Hz, H_9], 6.79 (dd, 1H, J=2.7, 10.0Hz, H_{10}) [6.87, dd, H=2.7, 10.0Hz, H_{10}], 7.3 (m, 3H, aromatic Hs). ^{13}C-NMR ($CDCl_3$) δ: 26.1, 27.6, 33.8, 38.1, 65.0, 79.6, 88.9, 119.5, 126.5, 128.6, 130.8, 131.4, 137.4, 149.1, 150.4, 180.7. MS (rel %) for $C_{20}H_{22}Cl_2O_3$: 381 [M^+] (100), 205 (66).

3. Results and Discussion

In order to study the influence that the size of the alkoxy group may have on the diastereoselectivity of the reaction we synthesized a series of four phenols **9a-d** bearing alkoxy functions *ortho* to the phenolic hydroxyl as shown in Scheme 1. These compounds were synthesized in three steps following a procedure similar to one that we have already published starting from the mono-protected benzaldehyde **6** (Plourde, G.L., 2002a; Plourde *et al*., 2002b; Plourde *et al*., 2005). Yields were comparable to those previously obtained in similar syntheses and are shown in Scheme 1.

The spiroannulation reaction of these phenols was carried out using the same method as previously described in order to allow for comparison of results as shown in Scheme 2 (Plourde, G.L. 2002a; Plourde, G.L. 2003a; Plourde, G.L. 2003b; Plourde, G.L. 2003c). Yields ranging from 38 to 94% were obtained for these spiroethers. It should be noted that we have not attempted to optimize these yields, especially for **10c** which was the lowest at 38%. Furthermore, in order to maintain consistency with our previous work, we used the integration of the ^{1}H-NMR signal for H-6 to calculate the diastereomeric ratios obtained in these reactions. These ratios were calculated from the crude reaction mixture prior to any purification of the material recovered and are shown in Scheme 2. As can be seen from the results in Scheme 2 as well as the partial ^{1}H-NMR spectra for **10a-d** shown in Figure 2, the diastereomeric ratio does not appear to be affected in a positive manner by the change of the alkyl function located on the ether oxygen in **9**. Instead, a slight decrease in the diastereomeric ratio is observed as the alkoxy group increases in size. This is clearly observed from the diagram shown in Figure 2. For comparison, the optimized diastereomeric ratio originally obtained with a methoxy group as substituent was 81/19 (Plourde, G.L., 2002a). The diastereoselectivity of the reaction even disappeared completely when the 2,6-dichlorobenzyl substituent was used (**10d**). While there may be a steric effect associated with this change, it is most likely due to the electron withdrawing character of this group which may be destabilizing the transition state. The possibility that a combination of both steric and electronic factors may influence the diastereomeric ratio in **10d** also exists. The effect appears somewhat similar to that of halogen substituents in electrophilic aromatic substitution, *i.e.* the halogen deactivates the ring by induction yet favours ortho/para substitution due to resonance stabilization. We are presently in the process of making the necessary phenols bearing halogens *ortho* to the phenolic hydroxyl to support this hypothesis.

4. Conclusions

We have prepared a series of four spiroethers bearing increasingly larger substituents in order to ascertain whether the reaction would be affected by the steric factors associated with those substituents. While we were hoping for an increase in diastereoselectivity, we observed the opposite trend *i.e.* the diastereoselectivity appears to decrease (although only slightly) with an increase in size of the substituents used. Furthermore, the results obtained with the 2,6-dichlorobenzyl group *ortho* to the phenolic hydroxyl in **9d** suggest that electronic factors are more important for the diastereoselectivity of this reaction and while weakly electron withdrawing groups still allow for the spiroannulation reaction to take place, this reaction is no longer diastereoselective. We are presently attempting to confirm this hypothesis. This finding appears to support our previously published work suggesting a stabilization effect by electron donating groups *ortho* to the phenolic hydroxyl (Plourde and English, 2005).

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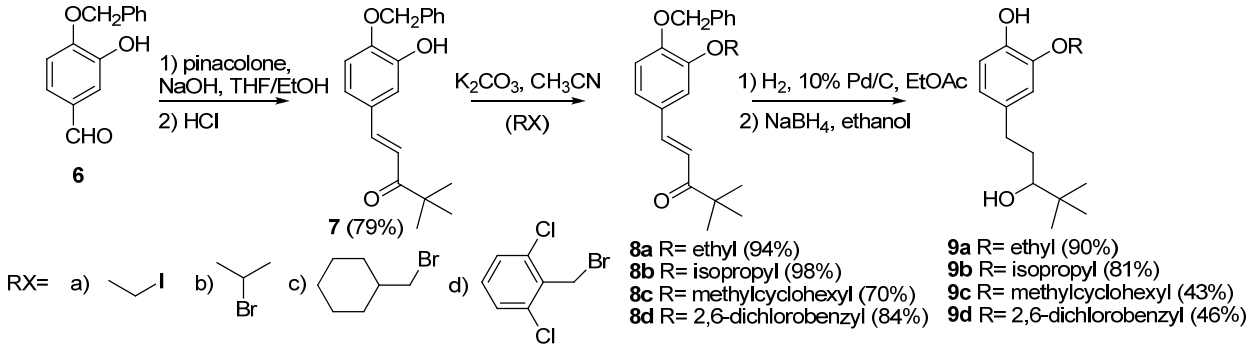
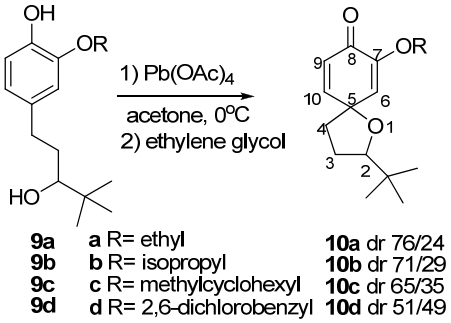


Scheme 1. Synthesis of phenols **9a-d**



Scheme 2. Spiroannulation of **9a-d**

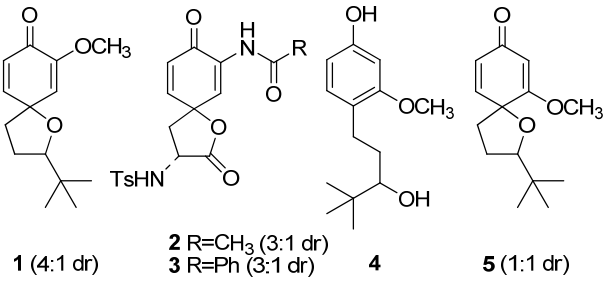


Figure 1. Diastereomeric ratios of spirocompounds

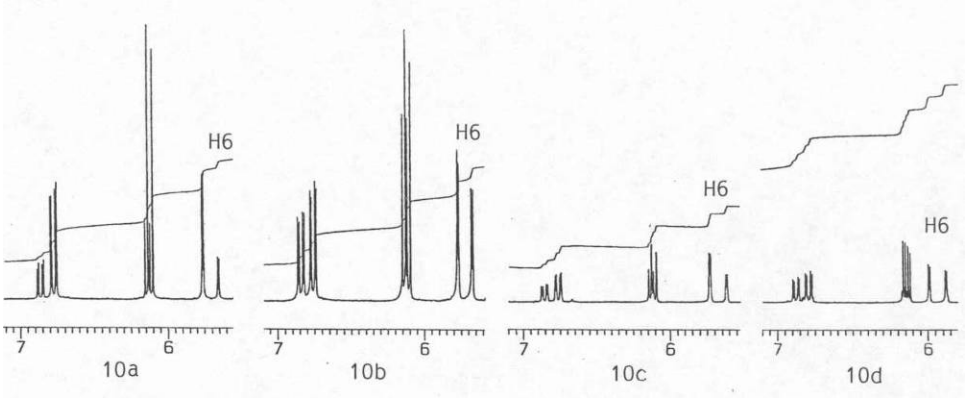


Figure 2. Partial ^{1}H-NMR spectra for **10a-d** showing the diastereomeric ratios