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Diastereoselective Spiroannulation of Phenolic Substrates: Synthesis of (±)-2-*tert*-Butyl-6-methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one.

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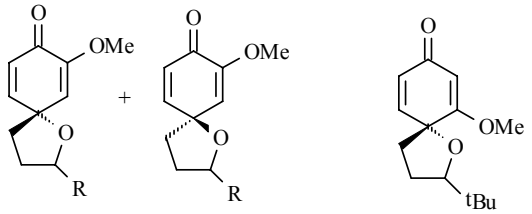
Abstract: The synthesis of a new spiroether is described. The title compound is obtained as a diastereomeric mixture in 45% yield.

Keywords: Spiroannulation, oxidation, phenol, diastereoslective, lead tetraacetate.

Introduction

We recently published our results related to the diastereoselective spiroannulation of phenolic substrates producing spiroethers **1-3**, as shown in Figure 1 [1,2].

Figure 1



1 R= methyl (dr 64/36)
2 R=isopropyl (dr 71/29)
3 R= tert-butyl (dr 81/19)

4

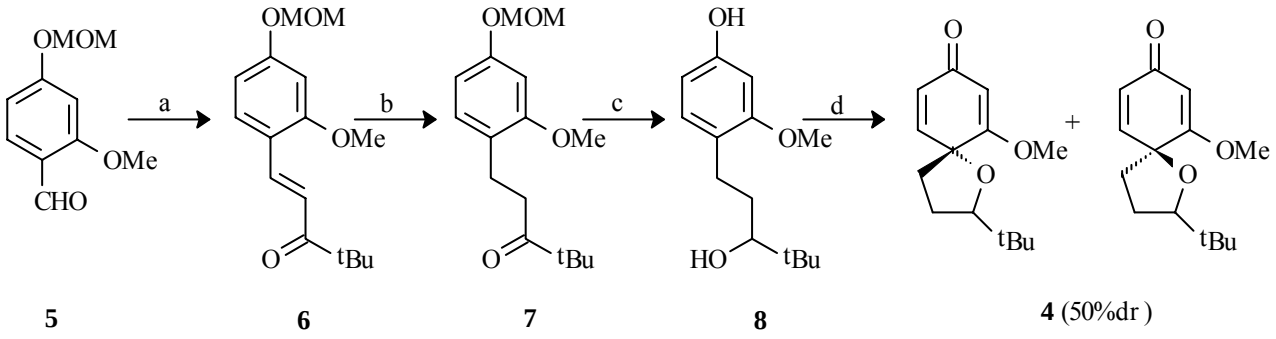
We had observed that increasing the size of the alkyl group on the side chain of the phenol increased the diastereoselectivity from 64/36, when the alkyl group was a methyl, to 81/19 for a tertiary butyl group. Furthermore, the oxidant used to carry out these transformations also played a role in the outcome of the reactions. For instance, oxidation with lead tetraacetate (LTA) gave higher

chemical yields as well as higher diastereoselectivity than either [bis(trifluoroacetoxy)iodo]benzene (PIFA) or (Diacetoxyiodo)benzene (PIDA). We speculated that the nature and the location of the substituent on the aromatic ring of the phenol had a strong influence on the reaction outcomes. We now wish to report the synthesis of the isomeric spiroether **4** and show that indeed, the position of the methoxy substituent does affect the results of this reaction.

Results and Discussion

The synthesis of phenol **8** was performed as described in Scheme 1. We have previously reported the synthesis of aldehyde **5,** which we prepared from the corresponding catechol aldehyde in 78% yield [3]. Following its synthesis, aldehyde **5** was condensed with pinacolone to afford the α,β-unsaturated ketone **6** in 65% yield after purification by chromatography. Hydrogenation of **6** was carried out under a slight positive pressure of hydrogen to afford **7** as an oil in 98% yield. Reduction of the ketone carbonyl, followed by acid workup, provided the necessary deprotected phenol **8** as a racemate in 82% yield (Scheme 1).

Scheme 1



5 **6** **7** **8** **4** (50%dr)

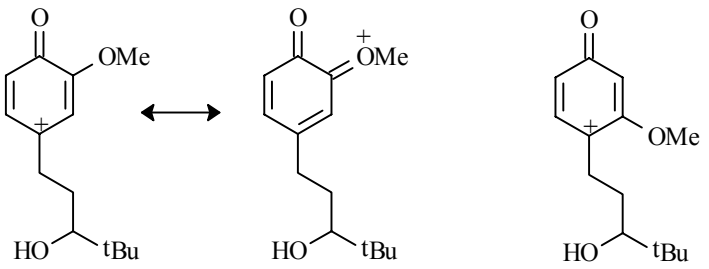
(a) 50% THF/EtOH, pinacolone, NaOH, reflux (65%); (b) EtOAc, H_2, Pd/C (98%);
(c) [1] EtOH, $NaBH_4$; [2] 10% HCl (82%); (d) Acetone, $Pb(OAc)_4$ (45%) (50%dr from ^{1}H-NMR)

We treated phenol **8** under reaction conditions seemingly identical to those previously described in the synthesis of **1-3** (Figure 1) [1,2], and we obtained racemic **4** in 45% yield with a 50/50 diastereomeric ratio. This ratio was determined by analysis of the ^{1}H-NMR spectrum of the crude reaction mixture. The signals for H_{10} located at 6.55 and 6.63 ppm for each of these diastereomers were used to determine the diastereomeric ratio, while signals for H_7 (5.44 and 5.46) and H_9 (6.01 and 6.05) as well as the signals for the methoxy group (3.74 and 3.77) were used as a confirmation of the stereoselectivity observed. Contrary to compounds **1-3**, which were partially separable by column chromatography [1,2], the diastereomers of **4** were not separable and characterization of the products was carried out from the diastereomeric mixture. In this case, only one spot was observed by thin layer chromatography. We did not attempt the spiroannulation with either PIFA and PIDA since results with these oxidants did not previously show any diastereoselectivity [1,2].

While the lower yield of **4** (45%) compared to **3** (69%) can be partially attributed to the greater steric factors near the reactive site in **8** [1,2], the diastereoselectivity observed does suggest that the position of the methoxy group has an influence on the approach of the nucleophile in this spiroannulation reaction, since it is the only difference between the two starting phenols. It has been

shown that oxidation of phenolic substrates produces a phenoxonium ion (**9a**) such as the one shown in Figure 2 [4].

Figure 2



9a **9b** **10**

When the methoxy group is located at the 3-position on the phenol, as in the case previously studied for **1-3** [1,2], the phenoxonium ion can be stabilized by resonance giving rise to structure **9b** as shown in Figure 2. On the other hand, when the methoxy group is located at the 2-position on the phenol, as seen in **8,** the second resonance structure (equivalent to **9b**) for the phenoxonium ion **10** cannot be formed and the intermediate is hence less stable and most likely less reactive as well. This lower reactivity may also partially explain the poor yield obtained. Furthermore, assuming that **10** is the reacting intermediate, one would not expect any stereoselectivity in the formation of the spirocenter since the steric factors influencing the approach of the nucleophilic hydroxyl would be identical from either side of the cyclic carbocation.

Conclusions

We have reported the synthesis of a new spiroether **4** and have shown that the location of the methoxy group on the phenol influences the diastereoselectivity of this spiroannulation reaction, most likely via the resonance stabilization of the reactive intermediate. It is expected that other electron donating groups located at the 3-position on the phenol will have a similar effect in terms of stereoselectivity. We are presently investigating this possibility, as well as the influence the size of the 3-subtituent may have on the diastereoselectivity of this reaction.

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. ^{1}H-NMR spectra were recorded on a Bruker AMX300 spectrometer at 300MHz and chemical shifts are expressed in

ppm using TMS as internal standard. ^{13}C-NMR spectra were recorded on a Bruker AMX300 spectrometer at 75.4MHz and chemical shifts are expressed in ppm using chloroform 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.

1-(2-Methoxy-4-O-methoxymethylphenyl)-4,4-dimethyl-1-penten-3-one (**6**).

To a solution of 2-methoxy-4-O-methoxymethylbenzaldehyde (**5**, 848 mg, 4.3 mmol) in 50% ethanol/tetrahydrofuran (80 mL) was added pinacolone (964 mg, 9.6 mmol) and sodium hydroxide (376 mg, 9.4 mmol). The resulting mixture was refluxed for 24 hours. Water (50 mL) was added, the solution was concentrated *in vacuo* to about 50% of its original volume and the aqueous residue was extracted with dichloromethane (3 x 40 mL). The organic fractions were combined, washed with brine (30 mL), dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a yellow oil. Chromatography on silica gel (15% EtOAc/hexanes) afforded an oil (860 mg, 72%). IR (neat): 1681 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, t-butyl), 3.50 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.25 (s, 2H, OCH_2O), 6.60 (d, 1H, J=2.2Hz, Ar-H_3), 6.65 (dd, 1H, J=2.2, 8.6Hz, Ar-H_5), 7.13 (d, 1H, J=15.7Hz, H_1), 7.49 (d, 1H, J=8.6Hz, Ar-H_6), 7.93 (d, 1H, J=15.7Hz, H_2); ^{13}C-NMR ($CDCl_3$) δ: 26.7 (C_5), 43.3 (C_4), 55.7 (OCH_3), 56.4 (OCH_3), 94.5 (OCH_2O), 100.2 (Ar-C_3), 107.9 (Ar-C_5), 118.2 (C_2), 119.7 (Ar-C_1), 130.5 (Ar-C_6), 138.3 (C_1), 160.3 (Ar-C_2 and Ar-C_4), 205.0 (C_3); MS m/e (relative %):278 [M^+] (2), 221 (100), 191 (16), 189 (16), 176 (6); Anal. Calc'd for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found C 69.14, H 7.91.

1-(2-Methoxy-4-O-methoxymethylphenyl)-4,4-dimethyl-3-pentanone (**7**)

To a solution of ketone **6** (860 mg, 3.1 mmol) in ethyl acetate (75 mL) was added Pd/C (279 mg) and the resulting mixture was stirred under a positive pressure of hydrogen for 6 hours. The suspension was filtered through Celite® and the solvent was evaporated *in vacuo* to give a yellowish oil. Chromatography on silica gel (20% EtOAc/hexanes) afforded a colorless oil (812 mg, 94%); IR (neat) cm^{-1}: 1702 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 9H, t-butyl), 2.76 (m, 4H, H_1 and H_2), 3.48 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.16 (s, 2H, OCH_2O), 6.56 (m, 2H, Ar-H_3 and Ar-H_5), 7.03 (d, 1H, J=9.1, Ar-H_6); ^{13}C-NMR ($CDCl_3$) δ: 25.1 (C_1), 25.5 (C_5), 37.1 (C_2), 44.3 (C_4), 55.5 (OCH_3), 56.2 (OCH_3), 94.9 (OCH_2O), 100.3 (Ar-C_3), 107.2 (Ar-C_5), 123.6 (Ar-C_1), 130.5 (Ar-C_6), 158.5 (Ar-C_2 and Ar-C_4), 216.0 (C_3); MS m/e (relative %): 280 [M^+] (51), 223 (20), 182 (12), 181 (100), 151 (52); Anal. Calc'd for $C_{16}H_{24}O_4$: C 68.55, H 8.63; found C 68.43, H 8.54.

o1-(4-hydroxy-2-methoxyphenyl)-4,4-dimethyl-3-pentanol (**8**)

To a cold (0^{o}C) solution of ketone **7** (810 mg, 2.9 mmol) in ethanol (50 mL) was added sodium borohydride (139 mg, 3.7 mmol). The resulting mixture was stirred at 0^{o}C for 30 minutes then at room temperature for 2 hours. HCl (10%, 50 mL) was added and the solution was stirred at room temperature for 20 hours. The solution was concentrated *in vacuo* to about half its original volume and the residue was extracted with dichloromethane (3 x 40 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellowish oil. Chromatography on silica gel (25% EtOAc/hexanes) afforded a clear oil

(564 mg, 82%). IR (neat) cm^{-1}: 3382 (OH); ^{1}H-NMR ($CDCl_3$) δ: 0.87 (s, 9H, t-butyl), 1.62 (m, 2H, H_2), 2.69 (m, 2H, H_1), 3.78 (s, 3H, OCH_3), 6.35 (dd, 1H, J=2.4, 8.0Hz, Ar-H_5), 6.41 (d, 1H, J=2.4Hz, Ar-H_3), 6.99 (d, 1H, J=8.0Hz, Ar-H_6); ^{13}C-NMR ($CDCl_3$) δ: 26.0 (C_5), 26.6 (C_2), 32.2 (C_1), 34.9 (C_4), 55.5 (OCH_3), 79.6 (C_3), 99.3 (Ar-C_3), 107.3 (Ar-C_5), 121.9 (Ar-C_1), 130.6 (Ar-C_6), 155.7 (Ar-C_4), 158.3 (Ar-C_2); MS m/e (relative %): 238 [M^+] (8), 236 (29), 179 (12), 137 (100), 107 (12), 77 (9); Anal. Calc'd for $C_{14}H_{22}O_3$: C 70.56, H 9.30; found C 70.43, H 9.19.

(±)-*2-tert-Butyl-6-methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one* (**4**)

To a cold (0°C) solution of phenol **8** (156 mg, 0.7 mmol) in acetone (20 mL) was added lead tetraacetate (954 mg, 2.2 mmol). The solution was stirred at 0°C for 2 hours, the mixture was filtered through Celite® and ethylene glycol (10 drops) was added. The solution was stirred at room temperature for 20 hours, filtered through Celite® and the solvent was evaporated *in vacuo* to give a pale yellow oil. ^{1}H-NMR of the crude reaction mixture indicated that two diastereomers were produced in a 50/50 ratio. Chromatography on silica gel (25% EtOAc/hexanes) afforded a pale yellow oil (70 mg, 45%) as a mixture of diastereomers (only one spot by thin layer chromatography). Characterization was performed on the mixture. Whenever distinguishable, values given are for one isomer with those of the second one listed in square brackets. IR (neat) cm^{-1}: 1680 (CO); ^{1}H-NMR ($CDCl_3$) δ: 0.93 [0.95] (s, 9H, t-butyl); 2.10 (m, 5H, H_2, H_3 and H_4), 3.74 [3.77] (s, 3H, OCH_3), 5.44 (d, 1H, J=1.7Hz, H_7) [5.46 (J=1.7 Hz)], 6.01 (dd, 1H, J=1.7, 9.7Hz, H_9) [6.05 (J=1.7, 9.7Hz)], 6.55 (d, 1H, J=9.7, H_{10}) [6.63 (J=9.7Hz)]; ^{13}C-NMR ($CDCl_3$) δ: 26.0 [26.2] (t-butyl CH_3), 27.6 [28.1] (C_3), 29.8 [33.7] (t-butyl C), 36.8 [37.1] (C_4), 55.7 [55.9] (OCH_3), 78.2 (C_5), 89.5 [91.3] (C_2), 101.1 (C_7), 126.0 (C_9), 147.1 (C_{10}), 175.7 [176.8] (C_6), 187.7 (C_8); MS m/e (relative %): 236 [M^+] (100), 180 (24), 179 (32), 178 (19), 151 (22), 137 (44), 91 (19); Anal. Calc'd for $C_{10}H_{10}O_4$: C 61.81, H 5.19; found C 61.52, H 5.40.

References

1. Plourde G.L. *Tetrahedron Lett.* **2002**, *43*, 3597.
2. Plourde G.L. *Molbank* **2003** M315-M322.
3. Plourde G.L.; Fisher B.B. *Molecules* **2003,** *8*, 315.
4. Quideau S.; Metthew A.L.; Pouységu L. *Org. Lett.*, **1999,** *1*, 1651.

Sample availability: Available from the authors.