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Studies towards the diastereoselective spiroannulation of phenolic derivatives

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Abstract—The oxidative spiroannulation of simple phenols bearing a chiral center was carried out. Good yields (61–83%) of spirocompounds were obtained. An increase in diastereomeric ratios from 55/45 to 81/19 was observed as the steric factor surrounding the chiral carbon increased.

As part of our ongoing research focusing on oxaspirocompounds such as **1** and **2** (Fig. 1),[1,2] we wanted to use these simple molecules as starting materials in the asymmetric synthesis of natural products from the manumycin family.[3] To accomplish this task we required optically pure spirocompounds as starting materials. Unfortunately, to our knowledge the asymmetric synthesis of this type of spirocompounds does not exist. Hence, our first goal was to find a synthetic route to carry out the asymmetric spiroannulation of phenolic derivatives. We now wish to report our preliminary findings towards the asymmetric synthesis of simple oxaspirocompounds.

As a first approach, we decided to study the effect of having a stereocontrol element located on the propyl side chain of the starting phenols. More accurately, we decided to investigate the effect of having a chiral center next to the nucleophile during the spiroannulation reaction. It was also decided that spiroethers rather than spirolactones would be synthesized since we had previously observed that spirolactones are sometimes unstable to purification by column chromatography.[2] We expected that the spiroether counterparts would eliminate this problem since the ether moiety should be less susceptible to acid hydrolysis.

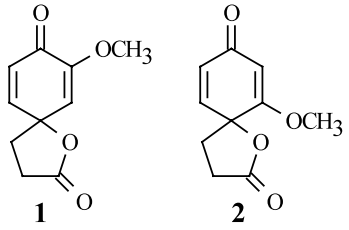

Figure 1.

We prepared the necessary phenolic derivatives **6a–c** in racemic forms according to Scheme 1. The synthesis of the starting materials **6a** was straightforward and first involved the condensation of vanillin **3** with acetone [3 M NaOH, rt], followed by hydrogenation [H_2, Pd/C, EtOAc] to afford the ketone **5a** in 68% yield as a white solid (33–34°C). In the case of **5b** and **5c**, all attempts to synthesize these compounds using a similar method failed [**3**, isopropylmethylketone or pinacolone, 3 M NaOH, THF or EtOH or THF/EtOH], presumably due to the lack of solubility of the phenoxide salts in these solvents. This problem was quickly eliminated by protecting the phenolic hydroxyl of **3** as a benzyl ether [K_2CO_3, CH_3CN, $PhCH_2Cl$, NaI], giving **4** as a white solid (60–61°C) in 99% yield according to known literature procedure.[4] Condensation of **4** with pinacolone [NaOH, THF/EtOH, reflux] afforded **5c** in 54% yield as a white solid (65–66°C) after hydrogenation [H_2, Pd/C, EtOAc]. The synthesis of **5b** according to this procedure was more difficult and provided a mixture of many products as observed by thin-layer chromatography (at least seven spots) and the crude ^1H NMR spectrum. Eventually, we were able to isolate **5b** in 22% yield as a colorless oil using LDA as the base at low temperature (–94°C). Reduction of ketones **5a–c** [$NaBH_4$, EtOH] proceeded uneventfully and provided good yields of alcohols **6a–c** (**6a** 91%, **6b** 90%, **6c** 96%) as colorless oils.

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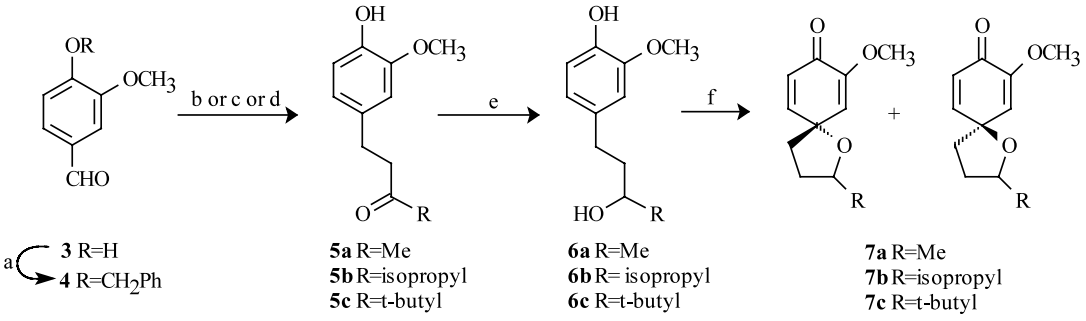

Scheme 1. (a) $PhCH_2Cl$, NaI, CH_3CN, K_2CO_3, reflux (99%); (b) 1. acetone, 3 M NaOH, rt; 2. H_2, Pd/C, EtOAc (68% **5a**); (c) 1. **4**, isopropyl methyl ketone, LDA, THF, –94°C; 2. H_3O^+; 3. H_2, Pd/C, EtOAc (22% **5b**); (d) 1. **4**, pinacolone, THF/EtOH, NaOH, reflux; 2. H_2, Pd/C, EtOAc (54% **5c**); (e) EtOH, $NaBH_4$ (91% **6a**, 90% **6b**, 96% **6c**); (f) oxidant, acetone, 2.5 h, see Table 1 for details.

The oxidative spiroannulation of these racemic alcohols was first attempted on **6a** in order to optimize the conditions. The results and reaction conditions for these spiroannulations are summarized in Table 1. All spiroannulation reactions were performed in acetone for 2.5 h using three different oxidants.[†] Entry 1 shows that at room temperature the spiroannulation proceeded nicely with lead tetraacetate as the oxidant giving **7a** as a colorless oil in 64% yield. The diastereomeric ratio was estimated to be 56/44 using the signals for H_6 (5.75 δ major, 5.70 δ minor) from the ^1H NMR spectrum of the crude reaction mixture. This diastereomeric ratio, as well as all others found in Table 1, was also confirmed by GC analysis. Unfortunately, these diastereomers were not separable and characterization of the products was carried out using the diastereomeric mixture which was first purified by column chromatography. This reaction was also performed at lower temperatures (entries 2–4). In these cases, the yields stayed constant at around 60%, but the diastereomeric ratio slightly increased to 65/35 (entry 4) when performed at −45°C. This increase in diastereoselectivity suggests that the preference for the formation of one diastereomer over the other is kinetically controlled, although we cannot exclude other causes such as selective product decomposition. We also used two

Table 1. Spiroannulation of **6** to **7**.

Entry	R	T (°C)	Oxidant	Product	% Yield[a,b]	Diastereomeric ratio[c]
1	Methyl	22	$Pb(OAc)_4$	**7a**	64	56/44
2	Methyl	0	$Pb(OAc)_4$	**7a**	62	62/38
3	Methyl	−15	$Pb(OAc)_4$	**7a**	61	64/36
4	Methyl	−45	$Pb(OAc)_4$	**7a**	61	65/35
5	Methyl	0	PIDA	**7a**	30	53/47
6	Methyl	0	PIFA	**7a**	32	54/46
7	Isopropyl	0	$Pb(OAc)_4$	**7b**[e]	83	71/29[d]
8	*t*-Butyl	0	$Pb(OAc)_4$	**7c**[f]	69	81/19[d]
9	*t*-Butyl	0	PIDA	**6c**	100	n/a
10	*t*-Butyl	22	PIDA	**7c**	30	55/45
11	*t*-Butyl	0	PIFA	**6c**	100	n/a
12	*t*-Butyl	22	PIFA	**7c**	31	57/43

[a] Yields are based on total isolated products.

[b] All reactions were performed in acetone for 2.5 h.

[c] Diastereomeric ratios were measured from the ^1H NMR spectrum of the crude reaction mixture using the signals for H_6 of both diastereomers.

[d] Major and minor isomers were partially separable by column chromatography and were fully characterized.

[e] ^1H NMR ($CDCl_3$) δ: major **7b**: 0.94 (d, 3H, $J=6.8$ Hz, CH_3), 1.01 (d, 3H, $J=6.6$ Hz, CH_3), 1.70–1.88 (m, 2H, H_3), 2.10–2.20 (m, 3H, H_4 and isopropyl CH), 3.69 (s, 3H, OCH_3), 3.96 (m, 1H, H_2), 5.76 (d, 1H, $J=2.7$ Hz, H_6), 6.12 (d, 1H, $J=10.0$ Hz, H_9), 6.79 (dd, 1H, $J=2.7$, 10.0 Hz, H_{10}); minor **7b**: 0.94 (d, 1H, $J=6.8$ Hz, CH_3), 1.00 (d, 1H, $J=6.7$ Hz, CH_3), 1.73–1.88 (m, 2H, H_3), 2.06–2.23 (m, 3H, H_4 and isopropyl CH), 3.72 (s, 3H, OCH_3), 3.90 (m, 1H, H_2), 5.67 (d, 1H, $J=2.6$ Hz, H_6), 6.13 (d, 1H, $J=9.9$ Hz, H_9), 6.87 (dd, 1H, $J=2.6$, 9.9 Hz, H_{10}).

[f] ^1H NMR ($CDCl_3$) δ: major **7c**: 0.95 (s, 9H, CH_3), 1.91–2.13 (m, 4H, H_3 and H_4), 3.69 (s, 3H, OCH_3), 3.95 (dd, 1H, $J=5.8$, 9.0 Hz, H_2), 5.77 (d, 1H, $J=2.7$, H_6), 6.13 (d, 1H, $J=10.0$ Hz, H_9), 6.80 (dd, 1H, $J=2.7$, 10.0 Hz, H_{10}); minor **7c**: 0.92 (s, 9H, CH_3), 1.90–2.10 (m, 4H, H_3 and H_4), 3.67 (s, 3H, OCH_3), 3.89 (dd, 1H, $J=5.9$, 8.7 Hz, H_2), 5.67 (d, 1H, $J=2.7$ Hz, H_6), 6.14 (d, 1H, $J=9.9$ Hz, H_9), 6.89 (dd, 1H, $J=2.7$, 9.9 Hz, H_{10}).

[†] Typical procedure for $Pb(OAc)_4$ oxidation: A solution of phenol **6a–c** (~200 mg) was dissolved in acetone (10 mL) and cooled to the appropriate temperature. The oxidant (2.5 equiv.) was added in one portion and the solution was stirred for 2.5 h. The precipitate was filtered through Celite, ethylene glycol (10 drops) was added and the solution was stirred for 24 h. The precipitate was filtered through Celite and the solvent was evaporated in vacuo. The resulting product was purified by chromatography on silica gel using a mixture of ethyl acetate and hexanes as eluant.

other oxidants for the spiroannulation of **6a**, iodobenzene diacetate (PIDA) and [bis(trifluoroacetoxy)iodo]-benzene (PIFA). These two oxidants have been used before in similar spiroannulation reactions.[2,5–9] Contrary to what was expected, when the reaction was performed at 0°C with either PIDA or PIFA, the isolated yields decreased to about 30% (entries 5–6). This was surprising since in the synthesis of **2** (Fig. 1), we obtained higher yields of spiroannulated products with either PIDA or PIFA (46%), when compared with lead tetraacetate (10%).[2] However, more important is the fact that the diastereomeric ratio decreased to 54/46 (entries 5–6), suggesting that a change in oxidant results in different transition states being involved in the formation of these spiroethers. We are presently investigating this hypothesis.

Having found good conditions [acetone, 0°C, $Pb(OAc)_4$] for the transformation of **6a** to **7a**, the size of the alkyl moiety adjacent to the hydroxyl group was increased to isopropyl **6b** and *t*-butyl **6c**. Spiroannulation of **6b** [acetone, 0°C, $Pb(OAc)_4$, 2.5 h] afforded **7b** in 83% yield, with an estimated diastereomeric ratio of 71/29 (5.76 δ H_6-major, 5.67 δ H_6-minor). In this case we were able to partially separate the racemic diastereomers and obtained the major product (5.76 δ) as a white solid (77–78°C) and the minor product as a colorless oil. Changing the alkyl moiety to *t*-butyl **6c** also improved on the diastereoselectivity of the reaction and we obtained **7c** in 69% yield with an estimated diastereomeric ratio of 81/19 (5.77 δ H_6-major, 5.62 δ H_6-minor). These diastereomers were also partially separated by column chromatography and we isolated the major product (5.77 δ) as a white solid (60–61°C) and the minor product (5.62 δ) as a colorless oil. In both of these cases, the major and minor isomers of **7b** and **7c** were fully characterized. All attempts to carry out this reaction with PIDA or PIFA at 0°C (entries 9 and 11) failed and only the alcohol **6c** was recovered. Only when the reactions were performed at room temperature did we obtain spiroannulation products (entries 10 and 12). However, as previously observed with **6a**, only 30% yield was obtained while the diastereoselectivity (55/45) significantly decreased when compared to the lead tetraacetate reaction (81/19) (entry 8).

We have shown that in the spiroannulation of phenolic derivatives bearing a chiral carbon on the alkyl side chain a preference exists for the selective formation of one of the two possible diastereomers. To our knowledge, the syntheses of **7a–c** represent the first examples of diastereoselective spiroannulation of simple phenolic derivatives. We believe that the electron-donating character of the methoxy group is directly affecting the diastereoselectivity when $Pb(OAc)_4$ is used as the oxidant, and we are presently attempting to proof this hypothesis by changing the nature and location of this group. We are also working on the asymmetric synthesis of **7c**, in order to unambiguously assign the structure of the major isomer.

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