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Synthesis of a tetrasubstituted arylphosphonate via the anionic phospho-Fries rearrangement

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Abstract—The anionic phospho-Fries rearrangement of phosphoric acid (3,5-di-isopropoxy)phenyl ester diethyl ester (**11**) gave rise to (2-hydroxy-4,6-di-isopropoxy-phenyl)phosphonic acid diethyl ester (**12**) in excellent yield. The phenol functionality of **12** was converted to the corresponding triflate which was coupled with vinyltributylstannane, under Stille conditions, to give a styrene. This molecule is intended to serve as the aromatic fragment in the synthesis of a phosphorus-based transition-state analogue for the hydrolysis of the *S*-(−)-zearalenone lactone.

S-(−)-Zearalenone (**1**, Fig. 1) is a macrolactone of the resorcylic acid family;[1] it is an estrogenic mycotoxin that has a negative impact on the fertility of livestock. In efforts directed toward the generation of antibodies that might catalyze the degradation of *S*-(−)-zearalenone, we sought to prepare a transition-state analogue for the hydrolysis of the lactone, viz. **2**. Synthesis of **2** could draw heavily upon existing syntheses of zearalenone (**1**),[2] vis-à-vis construction of the aliphatic part of the molecule. However, the aryl phosphonate presented two significant challenges: formation of the Ar–P bond and formation of the macrolactone. Herein, we describe our efforts toward the assembly of the aromatic subunit in compound **2**.

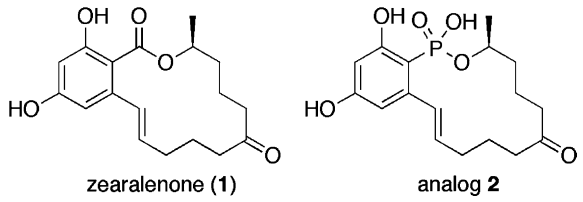
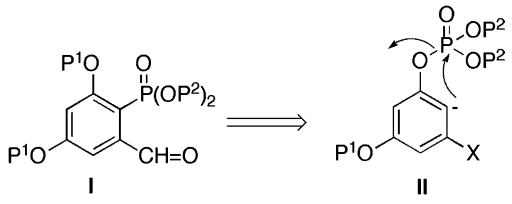


Figure 1.

Wittig chemistry was selected intially for the macrocyclization step in our synthesis of **2**, thus an aldehyde of the type **I** (Scheme 1) was our immediate target. It was envisioned that a precursor **II** would undergo regioselective deprotonation *ortho* to an electron-withdrawing group X, which would subsequently rearrange to give the tetrasubstituted aromatic ring. While many simple examples of this anionic phospho-Fries rearrangement[3] have been reported previously, such a highly substituted example was unprecedented.



Scheme 1.

In a forward sense, resorcylic acid (**3**) was converted to its ethyl ester (Scheme 2). Protection as the mono-*p*-methoxybenzyl ether was difficult to achieve in good yield. However, phosphorylation of the remaining phenol under Atherton–Todd conditions[4] gave **4**. Treatment of **4** with LDA gave a single product, in good yield, which we hoped was **5a**.

One-dimensional NMR spectra of the isolated material was consistent with both **5a** and **5b**. Confirmation of the formation of the *ortho*-hydroxyaryl phosphonate functionality was afforded by a doublet in the

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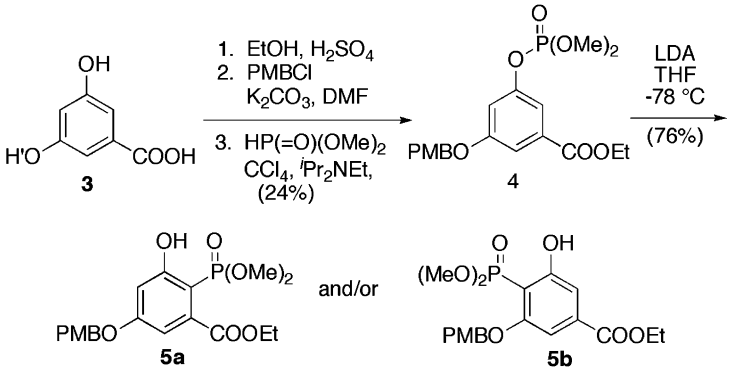


Scheme 2.

^{13}C NMR at δ 100.3 ppm ($^{2}J_{CP}$ = 177 Hz). A sharp signal was observed for the phenolic proton (δ 11.32 ppm) which is strongly hydrogen bonded to the adjacent phosphoryl oxygen. It was the two-dimensional HMBC spectrum which verified that the isolated material was in fact regioisomer **5b**, the undesired compound. The ^{13}C signal of the ester carbonyl at δ 165 ppm showed a correlation to both H2 and H6 (Fig. 2), indicating that there was no substituent *ortho* to the COOEt group. Conversely, C5, bearing the OPMB substituent (δ 159 ppm) showed long range coupling to only H6. Thus, it was concluded that the product was **5b** and that the OPMB group is superior to the COOEt substituent at directing metallation to the *ortho*-position.

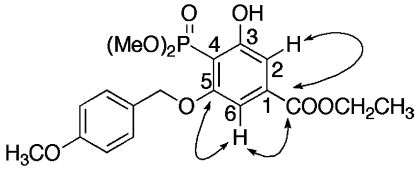
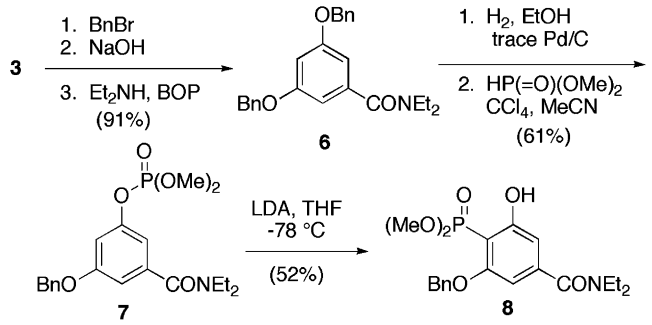


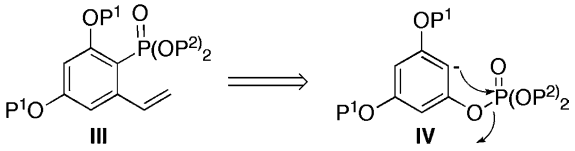
Figure 2. HMBC correlations in compound **5b**.

We were optimistic that replacing the ethyl ester with a diethyl amide, according to Meyers and Avila,[5] would reverse the regioselectivity. Tribenzylation of resorcylic acid (**3**), followed by hydrolysis of the ester gave an acid which was converted to diethylamide **6** in good overall yield (Scheme 3). It was possible to cleave one of the benzyl ethers in **6**[6] and convert the resulting phenol to phosphate **7**. Unfortunately, rearrangement gave compound **8**, again the undesired regioisomer.



Scheme 3.

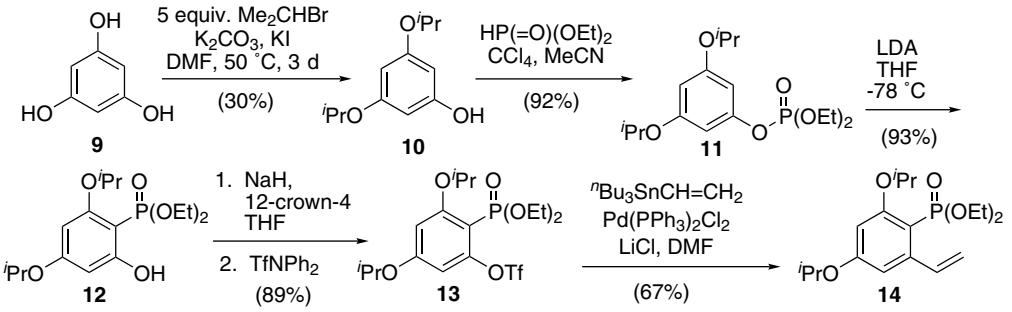
It seemed we were unlikely to overcome the strong directing effect of the two *meta*-related ether substituents. Rearrangement of a symmetrical substrate **IV**[7] (Scheme 4) could only give one product. The resulting phenol might be elaborated to a styrene **III** which would be useful in a RCM approach[8] to target **2**.



Scheme 4.

The realization of this approach is illustrated in Scheme 5. Formation of di-isopropyl ether **10** from phloroglucinol (**9**) was difficult,[9] although the mono-protected derivative could be isolated and resubjected to the reaction conditions. Phosphorylation gave **11** which rearranged cleanly to give **12**. We experienced inordinate difficulty in converting phenol **12** to triflate **13** (vide supra). Ultimately, anion formation in the presence of a crown ether, followed by reaction with diphenyltriflamide afforded triflate **13**. This was converted uneventfully to styrene **14** under Stille conditions.

The difficulties encountered in the formation of triflate **13** seem to be related to the acidity and/or hydrogen bonding capacity of its phenol. Some relevant compounds and their estimated pK_a values[10] are given in Figure 3. Fürstner et al. reported the conversion of **15** to the corresponding triflate using triflic anhydride and pyridine in dichloromethane.[8] These conditions could be used to convert compound **16** to its triflate ester, but in poor yield. We found that *N*-phenyltrifluoromethanesulfonamide was more effective than triflic anhydride but the yield was still only 65%. These, and many other reaction conditions, failed to deliver triflate **13**. The relative acidity of **17**,[7a] **18**[7b] (and **12**) implies that their conjugate bases are weaker and inter alia maybe poorer nucleophiles.



Scheme 5.

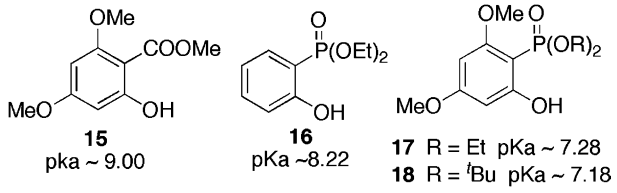


Figure 3.

In summary, we have uncovered some unexpected regiochemical outcomes in the anionic phospho-Fries rearrangement. For the purposes of our ultimate synthetic goal, the problem was circumvented by rearrangement of a symmetrical substrate **11**. Elaboration of the resulting phenol gave styrene **14** which is being utilized in the synthesis of compound **2**, a transition-state analogue for the hydrolysis of the lactone in *S*-(−)-zearalenone. This will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.104.

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10. These values were obtained from SciFinder Scholar, which states that they were calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67, error: ±0.2 units.