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INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS OF SUBSTITUTED FURFURYL E-2-(PHENYLSULFONYL)ACRYLATES

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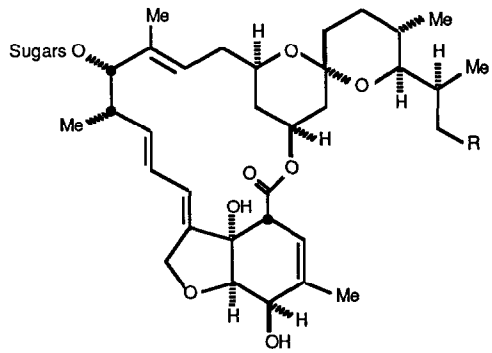
Abstract: Several substituted furfuryl E-2-(phenylsulfonyl)acrylates have been prepared by direct routes and cyclized in good yield under very mild conditions to give highly oxidized systems of potential use in natural products synthesis.

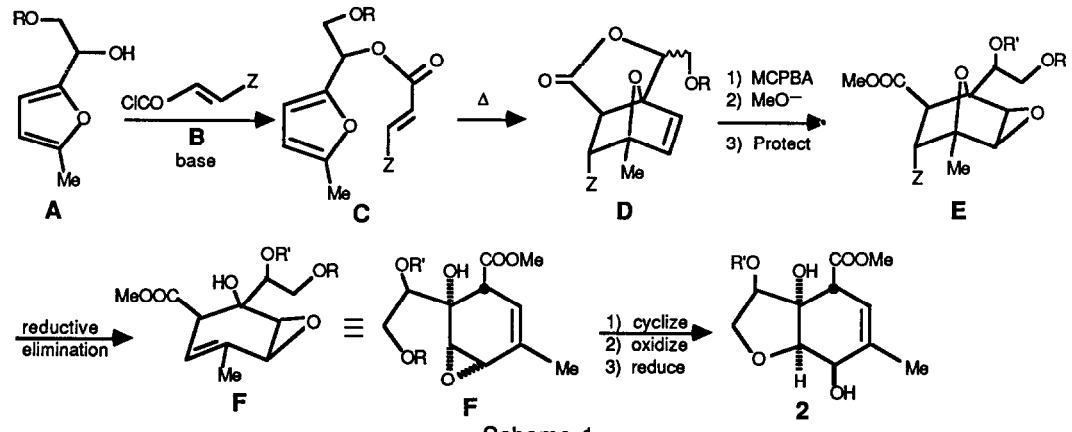
Recently there has been great interest in synthetic approaches to the avermectins and milbemycins[2] due to the complexity of their structures and their potent biological activity, e.g., the derivative ivermectin **1** is a commercial anthelmintic agent with high potential for agriculture[3] and use in human ophthalmic medicine.[4] Numerous groups have published work aimed at the total synthesis of these molecules and their substructures, the bicyclic acetal "top" portion and the hexahydro benzofuran "bottom" segment.[5] We have been interested in a route to a highly functionalized synthon for the bottom half of these molecules based on an intramolecular Diels-Alder cycloaddition of an N-furfuryl acrylamide followed by a subsequent ring opening via reductive elimination.[6] Due to difficulties associated with hydrolysis of tri- and tetracyclic lactams in this series, we decided to investigate an analogous route utilizing furfuryl acrylates since the resulting lactones would be much more easily hydrolyzed. We report herein the successful preparation and cyclization of several substituted furfuryl acrylates and their further chemistry.



1 R = H, Me

This synthetic approach to the bottom half synthon **2** (Scheme 1) involved as the two key steps: 1) the intramolecular Diels-Alder reaction of the furfuryl acrylate **C**, prepared from the furfuryl alcohol **A** and the activated acryloyl chloride **B**, to give the tricyclic lactone **D**; and 2) the reductive elimination of the epoxy ester **E** (or some derivative) to give the homoallylic alcohol **F**. It was our plan to cyclize **F** (by removal of the R protecting group) and correct the C5 stereochemistry by an oxidation-reduction scheme to finally produce **2**. In order to assess the feasibility

of this approach, we had to develop a good route to **A** and a procedure for the successful cyclization of **C** to give **D**. This was done as shown in Scheme 2.



Scheme 1

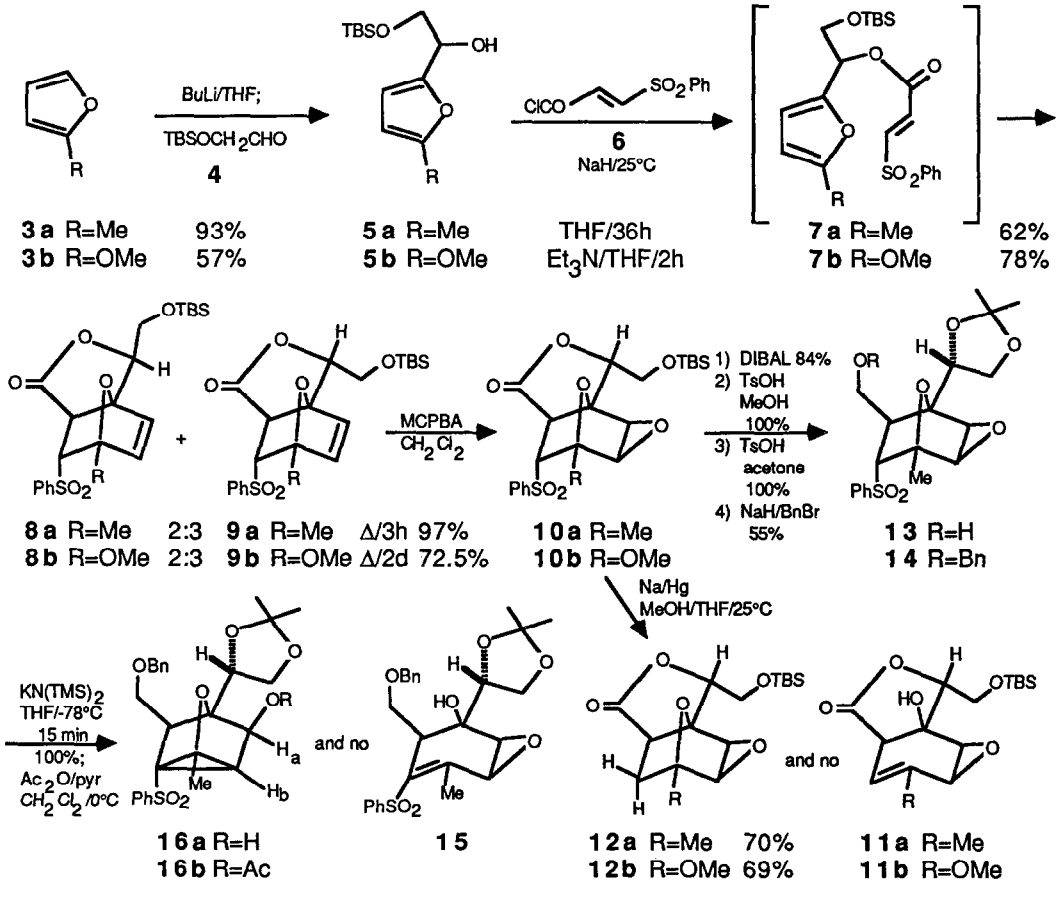
Treatment of 2-methylfuran **3a** with butyllithium in THF followed by trapping with the α-silyloxy aldehyde **4**[7,8] afforded the furfuryl alcohol **5a** in 93% yield. Reaction of this alcohol (and its benzyloxy analogue) with E-2-chloro- and E-2-(carbomethoxy)acryloyl chloride produced the corresponding acrylates, but we were unable to effect intramolecular cyclization of these compounds under normal conditions.[9] However, acylation of the anion of **5a** with the more highly activated E-2-(phenylsulfonyl)acryloyl chloride **6**[10] at 25°C for 36h produced in 62% yield, presumably via the acrylate **7a**, the desired cycloadducts **8a** and **9a** as a 2:3 mixture of stereoisomers at the silyloxymethyl group. Thus the strong electron-withdrawing ability of the phenylsulfonyl group lowers the high activation energy for cyclization of normal furfuryl acrylates so that cyclization can occur, even at room temperature. Generally simple furfuryl acrylates give no intramolecular Diels-Alder cycloadducts,[11a] although those substituted with a carboxy group in the ß-position can be cyclized.[11bc] However furfuryl acrylates substituted at the 5-position with a methyl[11b] or an acetoxymethyl group[11c] do not undergo intramolecular cyclization even with Z-2-(carboxy)acrylates. Thus the facile cyclization of **7a**, even though the furyl ring has a 5-methyl substituent, indicates that the E-2-(phenylsulfonyl) acrylate system is a much more powerful dienophilic system and should find use in other cycloadditions.

The two isomers **8a** and **9a** were easily separated by crystallization and their structures assigned by virtue of an x-ray crystallographic study of the major isomer **9a**.[12] We proceeded on with the major isomer **9a**, subjecting it to epoxidation to give the corresponding exo epoxide **10a** in 97% yield. Unfortunately direct reductive elimination of **10a** by the standard method (methanolic sodium amalgam)[13] failed to produce the desired olefin **11** giving instead the product of simple reductive desulfonation **12a** in good yield. Presumably protonation of the anion formed on reduction of the sulfone by the methanol solvent is faster than ß-elimination to give the very strained trans-fused lactone **11a**.[14]

This failure to open the bridged ring system by reductive cleavage of the strained C–O bond caused us to investigate two other routes to compounds similar to **2**. In the first we planned to prepare the corresponding cyclic acetal **10b** and convert it to either the enol ether **11b** or the derived ketone, and thence into the required methyl-substituted olefin. The second alternative was to open the lactone ring and protect the various functional groups prior to either reductive elimination or simple base-catalyzed elimination. The first of these alternatives was easily tested. Alkylation of the anion of 2-methoxyfuran **3b** with the aldehyde **4** gave in 57% yield the alcohol **5b**. This was transformed into a 2:3 mixture of **8b** and **9b** in 78% yield by reaction with **6** in the presence of NaH at 25°C for only 2h. In this case the high dienophilicity of the ß-phenylsulfonyl acrylate combined with the increased reactivity of the methoxy-substituted furan allows the reaction to be quite fast at room temperature.[15] The major isomer **9b**, obtained by simple chromatography, was epoxidized to give the desired acetal **10b** in 72% yield. However, again attempts at reductive elimination produced only the simple desulfonated product **12b** rather than the desired enol ether **11b**. Also

simple acidic (1N HCl) hydrolysis of **10b** did not afford the corresponding 4-hydroxycyclohexanone, nor did treatment with TMSI.[16] Also treatment of both **9b** and **12b** under similar conditions (1N HCl or TMSI) did not produce the expected hydroxy ketones. We have no good rationalization for the failure of these cyclic ketals to open in acid.

The second alternative required opening of the lactone and protection of the resultant functionality. Reduction of **10a** with DIBAL afforded the corresponding diol in 84% yield which was converted to the hydroxy acetonide **13** in quantitative yield. The primary alcohol of **13** was then benzylated (55% yield) to give the required substrate **14** for the base-catalyzed elimination to give **15**. However treatment of **14** with potassium hexamethyldisilazide in THF at -78°C for 15 min. did not produce the expected ß-elimination product **15** but rather a quantitative yield of the very strained cyclopropane **16a**, the structure of which was assigned by virtue of its NMR spectra, including a 2D COSY, and that of the corresponding acetate **16b**. In particular the chemical shifts of H_a and H_b in **16a** (acetone-d_6: δ H_a 3.94, H_b 2.33) and **16b** (acetone-d_6: δ H_a 5.00, H_b 2.37) were conclusive in assigning the structures since in **15** one would expect them to appear at much different positions and neither to shift dramatically on acetylation. It is quite surprising that no ß-elimination is seen in this reaction since analogous base treatment of a simpler oxanorbornane epoxide with an ester in place of the sulfone was reported to give 50% of the ß-elimination product (γ,δ-epoxy-α,ß-enoate) along with 50% of the cyclopropyl system.[17] We have no rationalization for this difference in behavior.



3a R=Me 93% **3b** R=OMe 57%

5a R=Me **5b** R=OMe

7a R=Me 62% **7b** R=OMe 78%

8a R=Me 2:3 **8b** R=OMe 2:3

9a R=Me Δ/3h 97% **9b** R=OMe Δ/2d 72.5%

10a R=Me **10b** R=OMe

13 R=H **14** R=Bn

16a R=H **16b** R=Ac

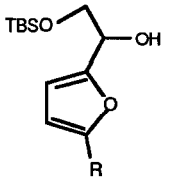
15

12a R=Me 70% **12b** R=OMe 69%

11a R=Me **11b** R=OMe

Scheme 2

Finally several other 5-substituted furfuryl alcohols **17a-d** were prepared by analogous routes using **4** to trap the 2-lithiofurans. However, all attempts at acylation-cyclization of **17** to give the cycloadducts analogous to **8** and **9** were unsuccessful due in great part to the instability of the starting alcohols **17** and their acylated derivatives.



17a R=CH_2Cl
17b CH_2OTHP
17c CH_2OBn
17d CH_2OTBS
17e OTBS

The failure of these compounds (e.g. **10, 12, 14**) to produce the desired hydroxy cyclohexene systems (e.g., **11** or **15**) has caused us to seek alternative routes to the ivermectin bottom half synthon **2**. However, we have discovered that the high dienophilicity of E-2-(phenylsulfonyl) acrylate permits intramolecular cycloadditions of furfuryl systems under very mild conditions.

Acknowledgement. We thank the National Institutes of Health (GM-31349) for their generous financial support.

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2. For an excellent review, see: a) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87. b) Fisher, M. H.; Mrozik, H. in *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: 1984; pp 553-606.
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7. Prepared in 82% overall yield from allyl alcohol by silylation ($TBSCl/Et_3N/DMAP/CH_2Cl_2$/25°C/2h) and oxidative cleavage (cat $OsO_4/NaIO_4/H_2O/Et_2O$/25°C/10h).
8. All new compounds exhibited spectral data (500 MHz ^1H NMR, IR, MS, and/or elemental analysis) in full accord with their assigned structures.
9. The benzyloxy 2-(carbomethoxy)acrylate gave a 15% yield of the desired cycloadduct when stirred for 53d at 25°C.
10. Prepared in 3 steps and 61% overall yield from E-2-chloroacrylic acid by addition of thiophenol in base, oxidation with peracetic acid to give the corresponding acid,[10b] and final acid chloride formation with thionyl chloride. b) Montanari, F.; Negrini, A. *Gazzetta* **1957**, *87*, 1073.
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12. We thank Drs. Chuck Strouse and Saeed Khan for their assistance in obtaining the x-ray structure, the details of which will be reported elsewhere.
13. a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4933. b) Kocienski, P. J. *Phosphorus Sulfur* **1985**, *25*, 477; *Chem. Ind.* **1981**, 548. c) Kocienski, P.; Todd, M. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1777.
14. MM2 calculations on the parent systems indicate that trans-fused lactones of this type are quite strained, e.g., there is a strain energy difference of ~3.9 kcal/mole favoring the cis-fused olefinic lactone over the trans-fused isomer.
15. A comparable rate for complete cyclization (25°C/2h) has been reported for only two other furfuryl acrylates, both of which are greatly accelerated by the *gem*-dimethyl effect. See: Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429.
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17. Rodrigo[17a] reports a 1:1 mixture of epoxyenoate and cyclopropane while Campbell[17b] reports only the cyclopropane product. a) Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826. b) Campbell, M.; Sainsbury, M.; West, R. *Tetrahedron Lett.* **1987**, *28*, 3865.

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