SYNTHETIC APPROACH TO THE IVERMECTIN BOTTOM HALF USING INTERNAL CYCLOADDUCTS OF N-FURFURYL ACRYLAMIDES: FUNCTIONALITY AND OPTICAL ACTIVITY[1]

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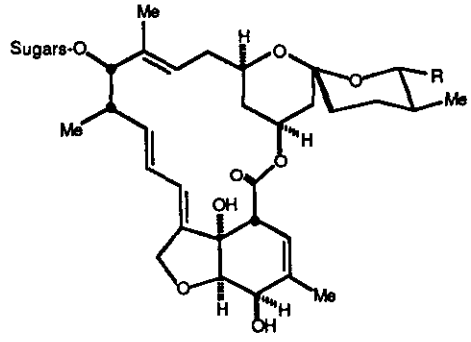
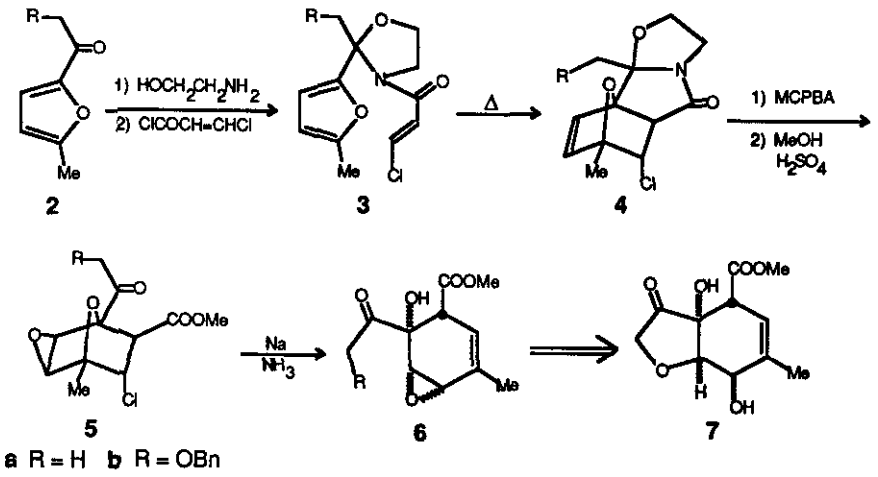
Abstract — The 2-(α-benzyloxyacetyl) furan **2b** is converted into the aminal **3b** which undergoes internal cycloaddition to give a highly oxidized intermediate **5b** in a potential route to ivermectin **1**, while the use of (S)-valinol in this sequence permits the ready preparation-separation of both enantiomers of **5a**.

Recently[3] we reported the development of a synthetic approach to the bottom half of the strongly antiparasitic and anthelmintic compound ivermectin **1**.[4,5] In this route, the acetylfuran **2a** was converted into the N-(E-ß-chloroacryloyl) aminal **3a** which underwent smooth intramolecular cycloaddition to give the tetracyclic adduct **4a**. After epoxidation and

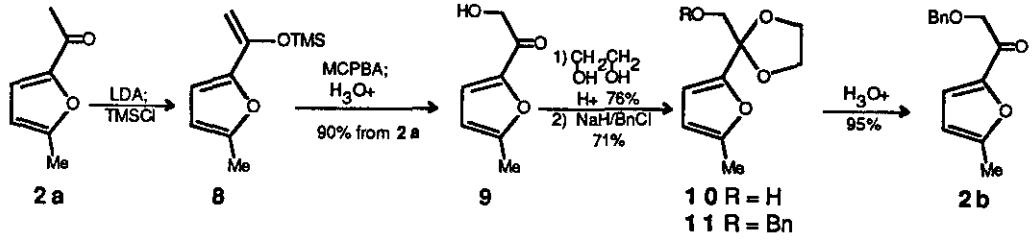


1 Ivermectin R = s-Bu, i-Pr

hydrolysis, the resultant chloro epoxide **5a** was reductively eliminated to give the cyclohexenol **6a**. What is now required in this approach is the α-oxidation of the ketone of **6a** to give the corresponding α-hydroxyketone which might be induced to cyclize to the 5α-epimer of **7** which could be epimerized to **7** by an oxidation-hydride reduction procedure.[5c] A more efficient alternative to this plan would be the initial α-functionalization of the starting furan **2a**. We now report the preparation of **2b** from **2a** and its conversion into the chloro epoxide **5b**. We also report a simple procedure using L-valinol for the preparation and separation of the two enantiomers of the chloro epoxide **5a**.



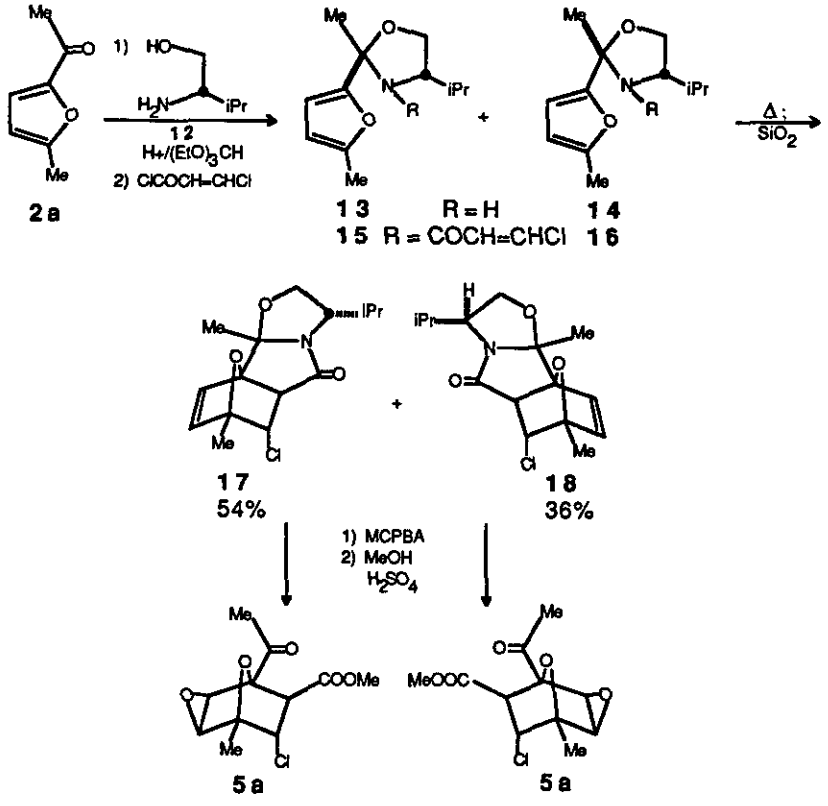
Treatment of **2a** with 1 equiv of LDA in the THF followed by trapping the enolate with TMSCl produced the silyl enol ether **8** which was oxidized with MCPBA to produce after hydrolysis in 90% yield the α-hydroxy ketone **9**.[6,7] Ketalization with ethylene glycol afforded **10** which was then benzylated under the normal conditions to give **11** in 54% yield for the two steps. A final acidic hydrolysis (95%) furnished the desired α-benzyloxy ketone **2b**,[8] thus making it available in 46% overall yield from **2a**.



Reaction of **2b** with 2-aminoethanol, triethyl orthoformate, and tosic acid produced in 97% yield the aminal which was immediately acylated with N-E-ß-chloroacryloyl chloride to furnish **3b** in 60% yield. Refluxing a solution of **3b** in toluene for 3 h produced a 90% yield of the cycloadduct **4b** as a single stereoisomer. Epoxidation of the olefin of **4b** with 1 equiv of MCPBA in dichloromethane at 0°C furnished in 94% yield the epoxide which was then subjected to acidic methanolysis (10% H_2SO_4 in MeOH, reflux, 20 h) to afford the epoxy ester **5b**. We are now investigating methods for the conversion of **5b** into **6b** and thence into **7**.

We also wished to develop a method for the easy preparation and separation of the optical isomers of **5** for the eventual construction of the bottom half of ivermectin in its correct, enantiomerically pure form. The use of L-valinol in place of 2-aminoethanol made this posible in a simple procedure. Treatment of **2a** with L-valinol **12** (TsOH, triethyl orthoformate) afforded in 84% yield a 1.5:1 mixture of the diastereomers **13** and **14**, respectively. The structures of these compounds (and therefore the subsequent amides and cycloadducts) were assigned on the basis that under these equilbrating conditions, the more stable diastereomer should be the major product. Since a furyl group is larger sterically than a methyl group, compound **13** (isopropyl cis to methyl and trans to furyl) would be expected to be the more stable

diastereomer.[9] These aminals could not be readily separated without decomposition and were therefore acylated as before (60%) to give the amides **15** and **16**, which could be separated chromatographically only with great difficulty. However, refluxing a toluene solution of **15** and **16** for 5h produced a 90% yield of the cycloadducts **17** and **18** which were readily



separated by flash chromatography to give 54% of **17** and 36% of **18**. These compounds were then separately converted into the two enantiomers of **5a** by epoxidation and hydrolysis as before. Thus valinol serves as a recyclable resolving agent for the chromatographic separation of diastereomers. Efforts to prove the structure of the enantiomers and convert the correct one, presumably the less abundant, into optically active **7** are currently underway.

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REFERENCES

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2. UCLA Gold Shield Faculty Awardee, 1986-8; Glenn T. Seaborg Awardee, 1987.
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5. For recent synthetic work on the avermectins-milbemycins, see: H. G. Davies and R. H. Green, *Natural Prod. Rep.*, 1986, **3**, 87, and references therein.

6. All new compounds exhibited NMR, IR, MS, and high resolution MS or elemental analysis data in full accord with their assigned structures.

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8. The simple alternative of alkylating the α-ketal **9** with benzyl bromide to produce **2b** was unsuccessful due to decomposition of **9** upon treatment with a wide variety of bases.

9. MM2 calculations predict a 0.5 kcal energy difference between **13** and **14** favoring the former.

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