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A Rapid Entry to Highly Functionalized *p*-Methoxybenzoates:

Synthesis of Aromatic Portion of Milberrycin β_3^{\dagger}

Atul S. Kotnis Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

<u>Summary</u>: A wide variety of easily accessible Hagemann's esters are converted to p-methoxybenzoates with iodine and methanol.

Nature has an abundance of natural products containing highly substituted aromatic compounds which possess a wide range of biological activity.¹ Successful synthetic approaches to these natural products must involve the efficient syntheses of highly substituted aryl intermediates. An important approach to highly substituted aryl compounds involves the ortho metallated alkylations of readily available aromatic substrates.² However, a basic limitation of this approach is a lack of convergency to such syntheses.

The milberrycins are a relatively new family of antibiotics with potent insecticidal activity.³ To date about twenty members of this family are known, the simplest being milberrycin β_3 which has been synthesized several times.⁴ Except in the Williams' approach,^{4b} the key precursor in all syntheses to milberrycin β_3 is a highly functionalized *p*-methoxybenzoate derivative.

Recently Smith and Kilenyi developed a novel two-step synthesis of p-hydroxybenzoates.⁵ Their approach utilizes a conjugated addition-elimination of Z-ethyl-3-bromopropenoate to the dianions of 1,3-diketones to give acceptable yields of 5,7-dioxoheptenoates (38-55%). The latter were then transformed to p-hydroxybenzoates (57-80%) on treatment with sodium ethoxide in ethanol via a cyclization-dehydration process.

Our approach to the regio-controlled synthesis of highly substituted *p*-methoxybenzoates involves an *inexpensive*, *high-yielding* synthesis from readily accessible Hagemann's esters.

The basis of our work is Tamura's⁶ approach to highly substituted anisoles by aromatization of cyclohexenones using iodine and methanol at reflux. In our studies of some of Tamura's examples two differences were observed: (a) lower reaction times (30 min instead of the earlier used 3 hours) and (b) overall 10-15% higher yields.

Aromatization of a wide variety of readily synthesized Hagemann's esters gave very high yields of *p*-methoxybenzoates which are listed in Table I. The product of the last entry is identical in all respects to the

Table I

Preparation of *p*-methoxybenzoates



same compound prepared by Smith's⁵ and Barrett's^{4e} groups for the lower aromatic portion of milberrycin β_3 .⁷ The requisite precursors for aromatization are all prepared via a Robinson annulation between the appropriate methyl vinyl ketones and ethyl aceto-acetates using Triton-B⁸ or ethanolic sodium ethoxide⁹ in a single step in greater than 70% vield.

The generality and brevity of this aromatization process, in addition to the high yields, makes it one of the most efficient syntheses of p-methoxybenzoates. The aromatized products can be transformed to p-methoxybenzoic acids,⁵ p-hydroxybenzoates,¹⁰ and 4-methoxy-2-phenol¹¹ which is a common subunit present in many marine natural products.¹² The application of this methodology to natural products syntheses is in progress and will be reported in the future.

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References and Notes

- 1. Scott, A. I.; Devon, T. K. "Handbook of Naturally Occurring Compounds", Academic Press, NY, 1972.
- 2. Beak, P.; Meyers, A. I. Acc. Chem. Res. 1986, 19, 356-363.
- 3. Mishima, H.; Tamura, C.; Kurabayashi, M. Tetrahedron Lett. 1975, 711.
- (a) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. J. Amer. Chem. Soc. 1986, <u>108</u>, 2662. (b) Williams, D. R.; Barner, B. A.; Philips, J. G.; Nishtani, K.; <u>ibid</u> 1982, <u>104</u>, 4708. (c) Baker, R.; O'Mahony, M. J.; Swain, C. J.; <u>J. Chem. Soc. Perkin Trans I</u> 1987, 1623. (d) Kocienski, P. J.; Yeates, C.; Street, S. D. A.; Campbell, S. F. <u>J. Chem. Soc. Perkin Trans I</u> 1987, 2171, 2183, 2189. (e) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. J. Org. Chem. 1986, <u>51</u>, 4840.
- Smith, A. B., III; Kilenyi, S. N. <u>Tetrahedron Lett</u>. 1985, <u>26</u>, 4419. Barrett <u>et al^{4e}</u> synthesized p-hydroxybenzoates by Diels-Alder reaction between an appropriate Danishefsky's diene and alkynyl ester followed by aqueous acidic workup in 52-74% yield. The p-hydroxybenzoates are then methylated using K₂CO₃/MeI. Our approach gives the methyl ether directly.
- 6. Tamaru, Y.; Yoshimoto, Y. Chem. and Ind. 1980, 888 and references cited therein.
- All Hagemann's esters and p-methoxybenzoates are characterized by 200 MHz ¹H NMR, IR and mass spectral analyses. Our aromatized product of entry 4 was identical to the same compound prepared by us, using Smith protocol and methylation of the p-hydroxybenzoate.

- 8. Ross, N. C.; Levine, R. J. Org. Chem. 1964, 29, 2346.
- 9. Barrett, J. W.; Cook, A. H.; Linstead, R. P. J. Chem. Soc. 1935, 1065.
- 10. Feutrill, G. I.; Mirrington, R. W. Tetrahedron Lett. 1970, 1327.
- The ester group was reduced to aldehyde, and a Baeyer Villiger oxidation on the aldehyde group results in the phenol. Godfrey, I. M.; Sargent, M. V.; Elix, J. A. J. Chem. Soc. Perkin Trans I 1974, 1353.
- 12. Faulkner, D. J.; Natural Product Reports 1988, 5, 613-663.

General procedure for aromatization. To a solution of 2 mmol of Hagemann's ester in 4 mL methanol was added 4 mmol of iodine beads. The solution was refluxed under nitrogen for 30 min, and the methanol was removed in vacuo. The residue was dissolved in benzene and the solution was washed with a saturated solution of sodium bicarbonate, sodium thiosulfate, 5% sodium hydroxide and water. The solution was dried over magnesium sulfate, and the benzene was removed in vacuo to give an oily residue. Flash chromatography of the residue on silica gel (ether/hexane 1.5:10) afforded the aromatized product.

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