Pergamon

Tetrahedron Letters 40 (1999) 8513–8514

TETRAHEDRON LETTERS

A direct synthesis of aflatoxin M_2

George A. Kraus * and Xuemei Wang

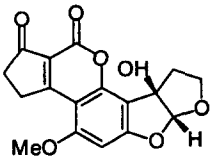
Department of Chemistry, Iowa State University, Ames, IA 50011, USA

Received 26 July 1999; revised 22 September 1999; accepted 23 September 1999

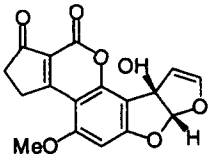
Abstract

A six-step synthesis of aflatoxin M_2 starting from 1,3,5-trimethoxybenzene is described. The key step is the addition of dichloromethyllithium.

The aflatoxins comprise a class of naturally-occurring mycotoxins which are significant health hazards. Many reports of the potent carcinogenicity of aflatoxins and the fact that aflatoxins have been detected in several foods have stimulated intense interest from toxicologists, chemists and government regulators.[1] Consequently, several methods have emerged for the detection and management of aflatoxins.[2] Aflatoxin M_2 (**1**) and M_1 (**2**) are found in milk. As part of a joint effort between toxicology and chemistry, the detection of this toxin was examined.



1



2

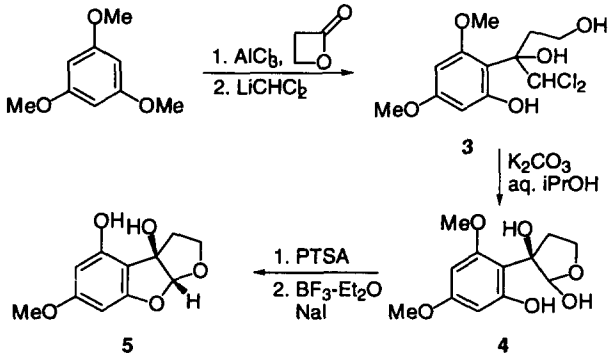
A concise synthesis of aflatoxin M_1 and M_2 was required. Although there have also been a considerable number of synthetic approaches to the aflatoxin skeleton, only a few of the approaches have culminated in total syntheses.[3] Recently, we described a synthesis of demethoxyaflatoxin B_2 using a silver-mediated cyclization reaction.[4] In the context of securing a flexible route to the aflatoxin M_2 system, we examined a route using dichloromethyllithium.[5]

Treatment of 1,3,5-trimethoxybenzene and propiolactone with aluminum chloride produced a dihydroxy ketone in 80–85% yield. Reaction of this ketone with 5 equivalents of dichloromethyllithium in THF afforded triol **3** in 93% yield. Hydrolysis using potassium carbonate in aqueous isopropanol furnished the hemiacetal **4** in 70% isolated yield. We recently demonstrated that this protocol for introducing a one-carbon fragment works well if there is a proximate hydroxyl group in the molecule.[6] Treatment of **4** with *p*-toluenesulfonic acid in warm methylene chloride over 4 hours produced a tricyclic

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01820-1

alcohol in 74% yield. Demethylation with boron trifluoride etherate and excess sodium iodide afforded the desired phenol **5** in 71% yield as the only isolated compound.[7] These conditions proved to be superior to using boron trichloride. The structure of phenol **5** was supported by 2D NOESY experiments.[8] The selectivity of this demethylation may be due to coordination with the tertiary hydroxyl group.



The conversion of the phenol **5** to aflatoxin M_2 has already been achieved in one step by Buchi.[9] Therefore, the synthesis of **5** constitutes a formal total synthesis of aflatoxin M_2.

This synthetic route is direct and flexible. The overall yield over five steps is 26%. This route will permit the ready synthesis of analogs suitable for the detection and analysis of aflatoxin M_2. The synthesis of other members of the aflatoxin family is in progress.

References

1. Mycotoxins — Economic and Health Risks (Council for Ag. Sci. and Tech., Ames, 1989).
2. De Boevere, C.; Van Peteghen, C. *Anal. Chim. Acta* **1993**, *275*, 341. Cathey, C. G.; Huang, Z. G.; Sarr, A. B.; Clement, B. A.; Phillips, T. D. *J. Dairy Sci*, **1994**, *75*, 1223.
3. Buchi, G.; Francisco, M. A.; Lusch, J. M.; Schuda, P. F. *J. Am. Chem. Soc.* **1981**, *103*, 3497. Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 39, and references cited therein. Castellina, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1006. Kraus, G. A.; Thomas, P. J.; Schwinden, M. D. *Tetrahedron Lett.* **1990**, *31*, 1819.
4. Kraus, G. A.; Johnston, B.; Applegate, J. *J. Org. Chem.* **1991**, *56*, 5688.
5. Kraus, G. A.; Wang, X. *Synlett* **1999**, 1395.
6. Wang, X. Thesis, Iowa State University, 1999.
7. Vankar, Y. D.; Rao, C. T. *J. Chem. Res., Synop.* **1985**, 232.
8. To a solution of ketone (0.226 g, 1 mmol) and CH_2Cl_2 (5 mmol) in THF (10 mL) at –78°C, LiTMP [3 mmol, prepared from tetramethylpiperidine (0.423 g, 3 mmol) and *n*-BuLi (1.2 mL of 2.5M solution in hexanes)] was added slowly. The reaction was stirred at –78°C for 3 h (TLC). NH_4Cl solution was added at –78°C. The reaction was extracted with ether, washed with brine, dried, concentrated and residue was purified by sgc (4:1, hexane:ethyl acetate) to give **3**: ^1H NMR ($CDCl_3$) 6.35 (s, 1H), 6.06 (d, *J*=2.4 Hz, 1H), 6.98 (d, *J*=2.4 Hz, 1H), 4.2–4.3 (m, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 2.2–2.8 (m, 2H); ^{13}C NMR ($CDCl_3$) 161.1, 156.9, 103.2, 95.3, 91.3, 86.0, 78.3, 60.7, 55.6, 37.7. To **3** (100 mg, 0.4 mmol) in ^{i}PrOH (5 mL) and water (5 mL), K_2CO_3 (100 mg) was added. The mixture was stirred at rt for 2 h. After removal of ^{i}PrOH, the water layer was saturated with NaCl and extracted with ethyl acetate. The organic phase was dried, concentrated and residue purified by sgc (1:1, hexanes:ethyl acetate) to give **4**: ^1H NMR ($CDCl_3$) 6.05 (d, *J*=2.4 Hz, 1H), 5.95 (d, *J*=2.4 Hz, 1H), 5.22 (s, 1H), 4.2 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 2.5–2.8 (m, 2H); ^{13}C NMR ($CDCl_3$) 162.2, 146.9, 111.0, 68.4, 50.1, 44.5, 43.5, 33.2, 25.0, 21.2, 20.6.
9. Schuda, P. *Top. Curr. Chem.* **1980**, *91*, 75.