J = 7.2 Hz), 4.12 (q, 2 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.58, 14.15, 24.87, 28.33, 29.15, 29.39, 29.52, 34.29, 35.92, 60.02, 119.49, 122.59, 122.72, 134.47, 173.82.

4-(Methylthio)-5-methyl-1,3-dithiolium Hexafluorophosphate (13) via 2-(Dimethylamino)-4-(methylthio)-5-methyl-2*H*-1,3-dithiole (11), from 5a. Compound **5a** (6.6 g, 20 mmol) was dissolved in 200 mL of absolute ethanol and cooled to 0 °C. Sodium borohydride (1 g) was added portionwise over 5 min and the mixture was stirred at 0 °C for 1 h. Petroleum ether (200 mL), ether (200 mL), and water (200 mL) were added. The organic phase was washed once with 100 mL of ice water, dried over $MgSO_4$, and filtered and the solvent evaporated to provide **11** as a yellow oil in 79% yield (3.28 g). Without purification the oil was added dropwise to ice-cold concentrated sulfuric acid (50 mL) under vigorous stirring. After 0.5 h the mixture was poured onto 150 g of crushed ice containing 10 mL of 60% hexafluorophosphoric acid whereupon **13** precipitated as white crystals. The product was filtered, the filtrate was extracted once with 100 mL of CH_2Cl_2, and the solid product was dissolved in the CH_2Cl_2 phase. After drying over $MgSO_4$, the filtered solution was concentrated to ca. 50 mL and the product was precipitated by addition of one volume of ether to yield 2.53 g of **13** as white crystals (41%): mp 130 °C; ^{1}H NMR (DMSO-d_6) δ 2.74 (s, 3 H), 2.82 (s, 3 H), 11.34 (s, 1 H). Anal. Calcd for $C_5H_7S_3PF_6$: C, 19.48; H, 2.29. Found: C, 19.51; H, 2.28.

4-Methyl-5-(octadecylthio)-1,3-dithiolium Hexafluorophosphate (14). Compound **14** was prepared via **12** from **5b** by a procedure identical with the one given above for **13**.

4,5-Dimethyl-4′,5′-bis(methylthio)-TTF (8), from 13. Compound **13** (1.0 g, 32 mmol) was dissolved in 10 mL of dry acetonitrile, and 0.5 mL of triethylamine was added dropwise. At first a maroon color was observed that rapidly faded while crystals of the orange-red product precipitated. After 5 min the product was filtered, washed with ethanol and petroleum ether, and dried in vacuo. After recrystallization from heptane, the yield of **8** was 0.252 g (49%): mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 6 H), 2.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 15.03, 19.19, 108.63, 120.60, 133.58. Anal. Calcd for $C_{10}H_{12}S_6$: C, 37.00; H, 3.73. Found: C, 36.72; H, 3.67.

4,5-Dimethyl-4′,5′-bis(octadecylthio)-TTF (9), from 14. Compound **14** (1.1 g, 1.9 mmol) was treated as above yielding 0.61 g **9** (40%): mp 85 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6 H, J = 7.6 Hz), 1.26 (s, 64 H), 2.11 (s, 6 H), 2.69 (t, 4 H, J = 7.9 Hz). Anal. Calcd for $C_{44}H_{80}S_6$: C, 65.94; H, 10.06. Found: C, 66.38; H, 10.16.

Acknowledgment. This work has been supported by the EEC ESPRIT BRA Programme through grant number 3314 and by the Danish Materials Technological Development Program.

Registry No. **2a**, 135146-89-3; **2b**, 135146-90-6; **2c**, 135146-91-7; **2d**, 135146-92-8; **2e**, 135146-93-9; **2f**, 135146-94-0; **2g**, 135146-95-1; **3a**, 135146-96-2; **3b**, 135146-97-3; **3c**, 135146-98-4; **3d**, 135146-99-5; **3e**, 135147-00-1; **4a**, 129119-29-5; **4b**, 135147-01-2; **4c**, 135147-02-3; **4d**, 135147-03-4; **4e**, 85102-68-7; **5a**, 135147-04-5; **5b**, 135147-05-6; **5c**, 135147-06-7; **5d**, 135147-07-8; **5e**, 135147-08-9; **5f**, 135147-09-0; **5g**, 135147-10-3; **5h**, 135147-11-4; **5i**, 135147-12-5; **5j**, 135147-13-6; **5k**, 135147-14-7; **5l**, 135147-15-8; **5m**, 135147-16-9; **5n**, 135147-17-0; **5o**, 135189-73-0; **5p**, 135147-18-1; **5q**, 135189-74-1; **6**, 122301-24-0; **8**, 107817-01-6; **9**, 135147-19-2; **10a**, 53278-41-4; **10b**, 135147-20-5; **10c**, 135147-21-6; **10d**, 58007-81-1; **10e**, 53278-47-0; **11**, 135147-22-7; **13**, 135147-24-9; **14**, 135147-26-1; $CH_3(CH_2)_3CH(Br)COOH$, 616-05-7; $CH_3(CH_2)_{15}CH(Br)COOH$, 142-94-9; PhCH(Br)COOH, 4870-65-9; $CH_3CH(Br)COOH$, 598-72-1.

A Direct Synthesis of Racemic Demethoxyaflatoxin B_2

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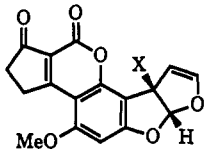
Received February 28, 1991

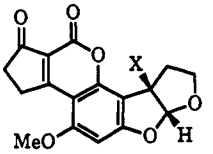
Aflatoxin analogue **19** was prepared by a direct sequence involving a novel silver-mediated cyclization to **12**, the Michael addition of **16** with **17**, and the oxidation of the Michael addition adduct. The overall yield of this six-step route is approximately 11%. The pathway is a flexible one that will permit the synthesis of analogues for toxicological analysis.

The aflatoxins 1–4 comprise a class of naturally occuring mycotoxins that 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 control of aflatoxins. There have also been a considerable number of synthetic approaches to the aflatoxin skeleton; however, only a few of the approaches have culminated in total syntheses.[2] A review by Schuda nicely summarizes the synthetic efforts of the Buchi research group.[3]

Recently, we described an approach to the aflatoxin M_2 skeleton using a type II photocyclization reaction to pre-



1: X = H
2: X = OH



3: X = H
4: X = OH

pare the 3-hydroxy-2,3-dihydrobenzofuran ring system.[4] In the context of securing a flexible route to the aflatoxin B_2 system, we examined the cyclization depicted below. Saegusa had reported that β-keto esters and β-diketones reacted with silver oxide in DMSO to form dimers.[5] We reasoned that the radical intermediate involved in the dimerization reaction might be employed to generate a furo[2,3-*b*]furan system if the reaction was conducted in the presence of an excess of 2,3-dihydrofuran. With ethyl

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(2) 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 therein. Castellina, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1006.
(3) Schuda, P. *Top. Curr. Chem.* **1980**, *91*, 75.
(4) Kraus, G. A., Thomas, P. J., Schwinden, M. D. *Tetrahedron Lett.* **1990**, *31*, 1819.
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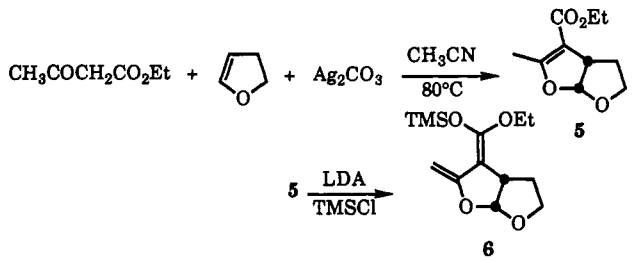
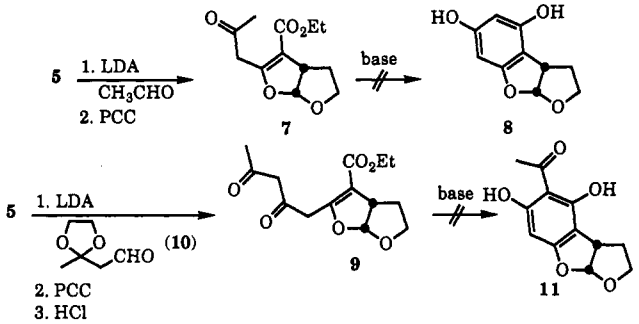


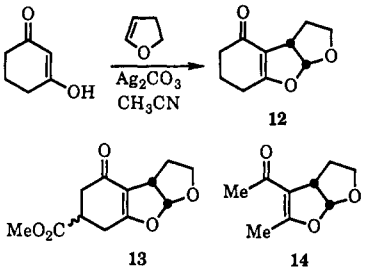
acetoacetate, silver carbonate, and 2,3-dihydrofuran, we obtained a 50% yield of **5**. Although Saegusa had used DMSO as the solvent, we found that acetonitrile was more convenient and afforded almost identical yields. Snider has made extensive use of manganic acetate chemistry in his innovative syntheses of polycyclic ring systems.[6] The reaction conditions usually involve solvents such as acetic acid. Our chemistry is complementary to the manganese chemistry in that mildly basic conditions are employed.

With **5** in hand, the strategy was to prepare diene **6** by standard silylation chemistry and to complete the preparation of the benzofuran skeleton by a Diels–Alder reaction. Unfortunately, the reaction of **5** with lithium diisopropylamide (LDA) and trimethylchlorosilane (TMSCl) did not provide **6**. The main product appeared to be that

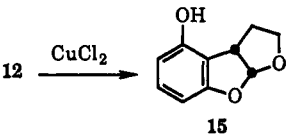


derived from C-silylation. This is an uncommon but not unprecedented result.[7] Examination of molecular models suggested that unfavorable steric interactions between the ethoxy group and the nearby methylene group in the tetrahydrofuran ring might encourage a silyl transfer from oxygen to carbon. The use of more reactive silylating agents (TMSOTf, *i*-Pr_2NEt) led to the decomposition of **5**, presumably due to the lability of the acetal subunit. Reaction of the enolate of **5** with acetaldehyde followed by buffered PCC oxidation afforded keto ester **7** in 44% yield. The reaction of **7** under a variety of conditions (NaOMe, MeOH, 25, 40, or 120 °C) led to either recovered starting material or to decomposition. The cyclization may have failed to produce **8** because the concentration of the requisite ketone enolate under the thermodynamic conditions might have been too low. Therefore, diketone **9** was prepared by the reaction of aldehyde **10**[8] with the enolate of **5** followed by PCC oxidation and deketalization with HCl. The cyclization of **9** was attempted using several bases (*t*-BuOLi, KOH, MeONa, LiH, *t*-BuOMg) at temperatures ranging from 25 to 80 °C. No trace of the desired resorcinol **11** was detected. At lower temperatures, diketone **9** was recovered. At higher temperatures, decomposition of **9** was observed.

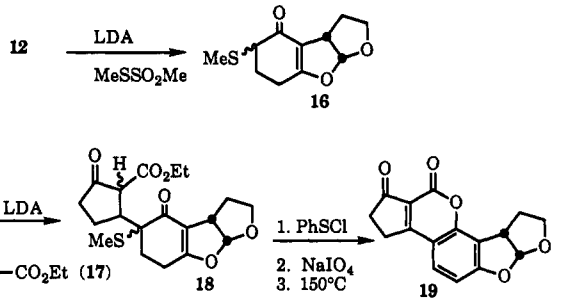
In view of these problems, it was decided to form the hexahydrofuro[2,3-*c*]benzofuran ring system directly by reaction of cyclohexane-1,3-dione with 2,3-dihydrofuran and silver carbonate. This reaction gave **12** in 60–76% yield. Similarly, ester **13** and ketone **14** were prepared in 63% and 53% yields, respectively.



Aromatization of **12** was next examined. Priority was given to those reactions that afforded a phenol-bearing functionality capable of eventual conversion into a methoxy group. Although phenol **15** was produced in 22% yield when **12** was treated with cupric chloride,[9] no efficient synthesis of a substituted phenol was achieved.



We next examined Michael addition reactions of the lithium enolate of **16**. Ketone **16** was prepared in 84% yield by reaction of the lithium enolate of **12** with $MeSSO_2Me$. We were pleased to discover that the diketo ester **18** could be prepared in 84% yield by reaction at −78 °C with keto ester **17**.[10] We were now able to construct the entire aflatoxin B_2 carbon skeleton in only three steps.



The NMR spectrum of **18** indicated that it was a mixture of a number of diastereomers. Reaction of **18** with PhSCl followed by oxidation of both sulfides with sodium periodate and heating at 150 °C for 7 h provided **19** in 18% isolated yield from **16**. The remainder of the material produced in this reaction was substantially less polar. Its NMR spectrum resembled that of the starting material; however, resubmission of this material to the reaction conditions did not afford **19**. Minor modifications of this route such as the use of PhSeCl instead of PhSCl or Michael addition of the corresponding keto sulfoxide to **17** resulted in much lower overall yields of **19**.

The synthesis of demethoxyaflatoxin B_2 (**19**) was achieved in only six steps in approximately 11% overall yield. The key step, the silver-mediated formation of a furo[2,3-*b*]furan, will undoubtedly be useful for the synthesis of other naural products. Studies on the toxicology

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of compounds 19 and 12 will be reported in due course.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Acetonitrile was purified by distillation from calcium hydride. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and chromatography. The purity of all title compounds was determined to be >90% by 300-MHz proton NMR and/or elemental analysis.

General Procedure for the Radical Cyclization. A suspension of dicarbonyl compound (1 equiv), vinyl ether (10 equiv), and freshly prepared silver carbonate (2 equiv) in dry MeCN (3 mL/mmol of dicarbonyl compound) was heated at reflux under nitrogen until TLC analysis indicated that no dicarbonyl compound remained. The mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was purified by sg chromatography using H:EA.

5: NMR ($CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3 H), 2.00–2.11 (m, 2 H), 2.23 (d, J = 1.8 Hz, 3 H), 3.62–3.79 (m, 2 H), 4.00–4.08 (m, 1 H), 4.10–4.28 (m, 2 H), 6.07 (d, J = 6.3 Hz, 1 H); IR (NaCl, neat) 2980, 1690, 1640 cm^{-1}; HRMS m/z for $C_{10}H_{14}O_4$, calcd 198.08921, measured 198.08866; ^{13}C NMR ($CDCl_3$) δ 13.72, 14.09, 31.31, 46.72, 59.13, 66.55, 103.13, 109.25, 164.92, 168.09; mp 41.5–45.5 °C; TLC (4:1 H:EA) R_f = 0.35.

12: light yellow oil; NMR ($CDCl_3$) δ 2.00–2.18 (m, 4 H), 2.30–2.40 (t, J = 6.6 Hz, 2 H), 2.40–2.55 (m, 2 H), 3.59–3.68 (m, 1 H), 3.68–3.80 (m, 1 H), 4.09 (td, J = 8.1, 0.6 Hz, 1 H), 6.24 (d, J = 5.7 Hz, 1 H); IR ($CDCl_3$) 2980, 1765 (w), 1720 (w), 1630 (br) cm^{-1}; HRMS m/z for $C_{10}H_{12}O_3$, calcd 180.07864, measured 180.078771 TLC (1:2 H:EA) R_f = 0.23. Anal. Calcd: C, 66.65; H, 6.71. Found: C, 65.18; H, 6.82.

13: NMR ($CDCl_3$) δ 6.24, 6.22 (d, J = 5.8 Hz, 1 H), 4.00–4.10 (m, 1 H), 3.68, 3.67 (s, 3 H), 3.50–3.65 (m, 1 H), 3.05–3.20 (m, 1 H), 2.60–2.85 (m, 3 H), 2.54–2.58 (m, 2 H), 1.98–2.10 (m, 2 H); IR (CH_2Cl_2) 2950, 2890, 1770, 1725, 1630 cm^{-1}; MS m/z 69, 123, 151, 161, 179, 207, 238; HRMS m/z for $C_{12}H_{14}O_5$, calcd 238.08412, measured 238.08462; ^{13}C NMR ($CDCl_3$) δ 191.67, 175.37, 175.27, 172.74, 172.88, 113.56, 113.55, 113.12, 67.79, 52.26, 43.57, 38.87, 38.59, 38.51, 30.02, 25.97; TLC (1:3 H:EA) R_f = 0.30; mp 56.5–57 °C.

14: NMR ($CDCl_3$) δ 1.96–2.18 (m, 2 H), 2.26 (d, J = 1.2 Hz, 3 H), 2.28 (s, 3 H), 3.62–3.74 (m, 1 H), 3.79 (t, J = 7.5 Hz, 1 H), 4.06 (td, J = 8.4, .6, 1 H), 6.09 (d, J = 6.3 Hz, 1 H); IR (NaCl, neat) 2980, 1740, 1715, 1668, 1620, 1600 cm^{-1}; HRMS m/z for $C_9H_{12}O_3$, calcd 168.07864, measured 168.07870; TLC (1:1 H:EA) R_f = 0.32.

Ethyl 2-(2,4-Dioxopentyl)furo[2,3-*b*]furan-3-carboxylate (9). To a solution of LDA (1.2 mmol, prepared from diisopropylamine and n-BuLi at 0 °C in 0.5 mL of THF at -78 °C was added ester 5 (0.198 g, 1.00 mmol) in 1.5 mL of THF over 2 min. The solution was stirred at -78 °C for 30 min. Aldehyde 10 (0.200 g, 1.5 mmol) in 1.5 mL of THF was added dropwise and the solution was allowed to warm to 0 °C. The solution was cooled to -78 °C, quenched with 0.13 mL of acetic acid, and diluted with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue (R_f(1:1 H:EA) = 0.25) was purified (sg, 1:1 H:EA).

To a suspension of PCC (0.289 g, 1.3 mmol) and Florisil (0.57 g) in CH_2Cl_2 (3 mL) was added the above alcohol (0.220 g, 0.67 mmol). After TLC showed that no alcohol remained, the suspension was poured into 40 mL of ether and filtered through Celite. The residue was dissolved in 1.1 mL of THF and 1.1 mL of 5% HCl and the solution was stirred for 22 h. After the usual workup, the residue was purified by sg chromatography using 2:1 H:EA to afford 0.07 g (45% yield) of 9. Compound 7 was prepared from ester 5 and acetaldehyde by the first two steps of this procedure.

7: NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3 H), 2.00–2.19 (m, 2 H), 2.23 (s, 3 H), 3.76–3.83 (m, 2 H), 3.80 (dd, J = 17.0, 42.2 Hz, 2 H), 4.02–4.12 (m, 1 H), 4.12–4.25 (m 2 H), 6.45 (d, J = 6 Hz, 1 H); IR (NaCl, neat) 2985, 2885, 1735, 1690, 1640 cm^{-1}; TLC (1:1 H:EA) R_f = 0.43.

9: NMR ($CDCl_3$) 1.28 (td, J = 7.1, 1.2 Hz, 3 H), 2.04 (s, 3 H), 2.05–2.17 (m, 2 H), 2.25 (s, 1 H), 3.65–3.85 (m, 4 H), 4.02–4.12 (m, 1 H), 4.12–4.25 (m, 2 H), 5.56 (s, 1 H), 6.15 (d, J = 6 Hz, 1 H); IR (NaCl, neat) 2980, 2880, 1695, 1640, 1610 cm^{-1}; HRMS m/z for $C_{14}H_{18}O_6$, calcd 282.11034, measured 282.11069; TLC (2:1 H:EA) R_f = 0.35.

2,3,3a,4,5,6,7,8a-Octahydro-5-(methylthio)[2,3-*b*]benzofuran-4-one (16). To a stirred solution of LDA [4.27 mmol, prepared from distilled diisopropylamine (4.66 mmol, 0.65 mL) and n-BuLi (4.27 mmol)] in 2 mL dry THF at -78 °C under nitrogen was added ketone 12 (0.70 g, 3.88 mmol) in 7.8 mL dry THF dropwise. After 30 min at -78 °C, $MeSSO_2Me$ (4.66 mmol, 0.48 mL) was added dropwise and the reaction mixture stirred to 0 °C. When the reaction appeared to be done by TLC, the mixture was recooled to -78 °C and quenched with 30 mL of a pH 7 buffer, the cooling bath was removed, and the solution was pH-adjusted to 6. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The crude sulfide (1.01 g) was purified by flash chromatography on sg (1:4 H:EA) to yield the keto sulfide 16 (0.74 g, 3.27 mmol) in 84% yield. Compound 16 was a light yellow oil.

16: NMR ($CDCl_3$) δ 2.04–2.08 (m, 2 H), 2.09–2.14 (m, 1 H), 2.17 and 2.20 (s, 3 H), 2.31–2.49 (m, 2 H), 2.60–2.82 (m, 1 H), 3.26 (t, J = 4.1 Hz, 3.60–3.78 (m, 2 H), 6.23 and 6.27 (d, J = 5.7 Hz, 1 H); IR (film) 2980, 1733, 1635, 1405 cm^{-1}; TLC (1:4 H:Ea) R_f = 0.53.

2,3,3a,4,5,6,7,8a-Octahydro-5-(methylthio)-5-(3-oxo-2-(1-oxo-2-oxabutyl)cyclopentyl)furo[2,3-*b*]benzofuran-4-one (18). To a solution of LDA (0.484 mmol, prepared from n-BuLi (0.484 mmol) and diisopropylamine (0.52 mmol) in 0.2 mL of THF at -78 °C) was added a solution of ketone 16 (0.100 g, 0.44 mmol) in 1 mL of THF over 2 min. The solution was stirred at -78 C for 30 min. Keto ester 17 (0.0746 g, 0.48 mmol) in 1 mL of THF was added dropwise and the solution was stirred at -78 °C for 30 min. Acetic acid was added to quench the reaction, water was added, and the aqueous layer was extracted with CH_2CL_2. The combined organic layers were dried and concentrated. The residue was purified by chromatography using 1:1 H:EA to afford 0.14 g (84% yield) of 18. Compound 18 was a light yellow oil.

18: NMR ($CDCl_3$) δ 1.25–1.32 (m, 3 H), 1.55–1.86 (m, 1 H), 1.90 and 1.98 (s, 3 H), 2.01–2.08 (m, 2 H), 2.10–2.14 (m, 1 H), 2.19 (d, J = 57 Hz, 1 H), 2.20–2.40 (m, 1 H), 2.41–2.48 (m, 2 H), 2.70–2.95 (m, 1 H), 3.15–3.29 (m, 1 h), 3.46–3.50 (m, 1 H), 3.55–3.80 (m, 3 H), 4.06–4.14 (m, 1 H), 4.14–4.25 (m, 2 H), 6.24 and 6.28 (bd, J = 6 Hz, 1 H); IR (film) 2980, 1750, 1720, 1635 cm^{-1}; TLC (1:4 H:EA) R_f = 0.55.

Demethoxyaflatoxin B_2 (19). To a stirred suspension of NaH (0.0098g, 0.41 mmol) (washed three times with hexanes and dried with N_2) in 2 mL of THF at 0 °C under N_2 was added the diketo ester 18 in 1 mL of THF. After 30 min at 0 °C, PhSCl was added (0.0684 g, 0.47 mmol), the solution was stirred for 5 min, the ice bath was removed, and the mixture was stirred at room temperature. TLC after 80 min and 140 min showed starting material, and after overnight showed little change. The reaction mixture was added dropwise to 10 mL each of ether, pentane, and saturated aqueous sodium bicarbonate, plus ice. The aqueous layer was extracted with 10 mL of 1:1 ether:pentane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The material was purified on a flash sg column to remove the PhSSPh (1:1 H:EA) to yield 0.13 g of crude material.

The bis-sulfide (0.13 g) was taken up in acetonitrile and cooled in an ice/salt bath, and 0.5 M aqueous $NaIO_4$ (1.06 mmol, 2.13 mL) was added dropwise. After being stirred at ice/salt temperture for 1 h, the mixture was stored in a refrigerator overnight. The flask was then removed from the refrigerator and the mixture was stirred at room temperature for 24 h, during which time a white precipitate formed. The mixture was filtered and extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to yield 0.10 g of the crude bis-sulfoxide.

The crude bis-sulfoxide was dissolved in 12 mL of dry toluene. The solution was degassed with argon for 10 min and then heated at 150 °C in a sealed tube for 7 h. The mixture was diluted with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography on sg (1:4 H:EA) yielded 0.0207 g (18% yield from 16) of the alfatoxin analogue 19. Compound 19 was a beige solid.

19: NMR ($CDCl_3$) δ 2.27-2.37 (m, 2 H), 2.70-2.77 (m, 2 H), 3.16-3.22 (m, 2 H), 3.62 (q, J_{AB} = 9, 17 Hz, 1 H), 4.12-4.26 (m, 2 H), 6.50 (d, J = 6 Hz, 1 H), 6.87 (d, J = 9 Hz, 1 H), 7.58 (d, J = 9 Hz, 1 H); IR (CH_2Cl_2) 3045, 1765, 1697, 1610 cm^{-1}; MS m/z 284; HRMS calcd 284.06847, measured 284.06826; ^{13}C NMR ($CDCl_3$) δ 24.50, 31.50, 34.90, 44.18, 67.80, 107.65, 112.38, 113.46, 114.82, 118.84, 127.35, 153.05, 155.11, 166.41, 176.54, 200.67; TLC (1:4 H:EA) R_f = 0.16.

Registry No. **5**, 135365-35-4; **6**, 135365-36-5; **7**, 135365-37-6; **9**, 135365-39-8; **10**, 18871-63-1; **12**, 135365-40-1; **13**, 135365-41-2; **14**, 135365-42-3; **15**, 135365-43-4; **16**, 135365-44-5; **17**, 57020-97-0; **18**, 135365-45-6; **19**, 135365-46-7; $MeSSO_2Me$, 2949-92-0; ethyl acetoacetate, 141-97-9; dihydrofuran, 1191-99-7; acetaldehyde, 75-07-0; 1,3-cyclohexanedione, 504-02-9; 2-hydroxy-6-oxo-1-cyclohexene-4-carboxylic acid, methyl ester, 135365-38-7; methyl acetylacetate, 105-45-3.

Supplementary Material Available: Proton NMR data for compounds **5**, **7**, **9**, **12-14**, and **16-18** (19 pages). Ordering information is given on any current masthead page.

Unusual Directive Effects in the Hydroboration of β,β-Disubstituted Enamines. Conversion of α-Substituted Aldehydes to the Corresponding Alkenes and β-Amino Alcohols†

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Received April 22, 1991

A comprehensive study of the conversion of β,β-disubstituted enamines into the corresponding alkenes and β-amino alcohols by hydroboration-elimination and hydroboration-oxidation, respectively, has been carried out. The amine moiety of β,β-disubstituted enamines was found to exert a decisive influence on the regioselectivity of the hydroboration reaction involving borane methyl sulfide (BMS). Thus, in the hydroboration of morpholino and piperidino enamines, the boron atom is initially placed predominantly in the α-position. Conversely, the pyrrolidino enamines direct the boron atom exclusively to the β-position. Three oxidizing agents, trimethylamine N-oxide, sodium perborate, and 30% hydrogen peroxide-solid sodium hydroxide, were tried in order to optimize the oxidation of the intermediate organoborane derivatives to the corresponding amino alcohols. Our results clearly indicated that 30% hydrogen peroxide-solid sodium hydroxide is best suited for this transformation. The yield of amino alcohol ranged from good to essentially quantitative. Enamines derived from β-aryl aldehydes, upon hydroboration with BMS followed by methanolysis and oxidation with neutral hydrogen peroxide, gave the corresponding 1,1-disubstituted alkenes. Contrary to the regioselectivity observed in the hydroboration reactions involving BMS, the hydroboration of β,β-disubstituted enamines using 9-borabicyclo[3.3.1]nonane (9-BBN) gave the trialkylborane intermediates in which the boron atom was placed exclusively at the β-position regardless of the amine moiety of the enamine. These trialkylborane derivatives were very stable and did not undergo the usual elimination reaction with either methanol or sodium hydroxide. However, on thermal decomposition, these afforded the corresponding 1,1-disubstituted alkenes in high yields.

Introduction

Many amino alcohols are important therapeutic agents for treating a wide variety of human diseases and disorders.[1] During the last five years, amino alcohols have also become extraordinarily important as chiral auxilliaries in organic synthesis.[2] In attempting to extend the existing methodology for the synthesis of β-amino alcohols[3] and alkenes[4] from enamines to β,β-disubstituted enamines, we discovered an unusual and unexpected directive effect of the amine moiety.

Nearly 25 years ago, the powerful directive effect exerted by a substituent on the hydroboration of substituted vinyl derivatives was thoroughly investigated by Pasto[5] and Brown[6] (Figure 1). The hydroboration of acetoxy- and chloro-substituted vinylic compounds yielded 30-85% of the α-adduct, respectively, while the ethoxy and secondary amino derivatives gave virtually quantitative β-substitution.[6] Additionally, these directive effects were further influenced by varying the parent hydrocarbon skeleton from a butenyl to an isobutenyl system, which resulted in a mixture of α- and β-adducts. Although there is one report that the piperidine enamine of 2-ethylbutyraldehyde gave an α-aminoborane on hydroboration,[4a] the directive effects of the secondary amine moiety in the hydroboration of isobutenyl-type systems has never been investigated systematically. Consequently, we undertook a systematic study of the hydroboration of β,β-disubstituted enamines. During the course of this work on the hydroboration of β,β-disubstituted enamines and the subsequent transfor-

† Dedicated to Professor Joseph Bunnett on the occasion of his retirement.

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