Tetrahedron Vol. 45, No. 19, pp. 6113 to 6126, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

Preparation of 5-Bromotetronates [4-Alkoxy-5-bromo-2(5H)-furanones] and a New Concept for the Synthesis of Aflatoxins and Related Structure Types. Tributyltin Hydride versus Palladium-Promoted Intramolecular Hydroarylation.*

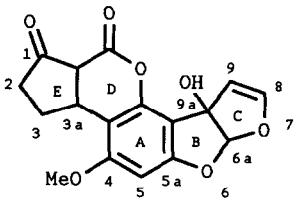
H.MARTIN R. HOFFMANN, BORIS SCHMIDT, and STEFAN WOLFF
Department of Organic Chemistry, University of Hannover,
Schneiderberg 1 B, D-3000 Hannover, F.R. Germany

(*Received in Germany* 18 *April* 1989)

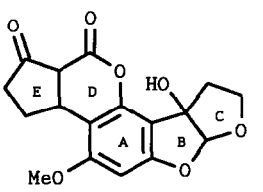
Abstract - The coupling of suitably functionalized o-iodophenols (e.g. **6**) with 4-alkoxy-5-bromo-2(5H)-furanones (5-bromotetronates) (**10a-e**) gave precyclic aflatoxin M_1 A-C building blocks (**7**, **14**, **17c**). Two cyclization modes for obtaining the ABC-moiety were investigated and compared. Whereas the Bu_3SnH-induced reaction worked well for simple model compounds, it failed for the more functionalized compounds. The palladium-mediated procedure allowed the synthesis of potential aflatoxin M_1 precursors such as **18c**. An improved procedure for obtaining O-alkylated tetronates (**9a-g**) is described. The tetronates were converted into 5-bromotetronates (**10a-e, h**) under controlled free radical conditions. For example, the narthogenin precursor **10a** was prepared to the exclusion of undesired isomer **11**, in 62% yield. Finally, other benzoannulated heterodiquinanes, e.g. a desoxyeserolin precursor **24**, were obtained by both cyclization procedures in good to excellent yield.

Introduction. Current Status of Aflatoxin M Synthesis.

Of the various aflatoxins known[1] the M-series (milk toxin) is important from several points of view. There is a general need for studies of biological activities and metabolism, as the role of aflatoxins as agents of foodborne diseases of humans and animals is clearly recognized. There is also a need for these compounds as analytical standard, for example in the dairy industry.[1c] The high price of aflatoxin M_1[1d] and aflatoxin M_2[1d] reflects the difficulties of obtaining and isolating these metabolites from natural sources. By virtue of its angular hydroxy group at C-9a, the bicyclic acetal grouping and oxygen functionality, the aflatoxin M-series represents a considerable synthetic challenge. In fact, there are only two syntheses of aflatoxin M_1, published some time ago and due to Buechi. The first synthesis is linear (A + B → AB → ABC),[2] whereas the second is convergent (A and C are combined to ABC in one step).[3] Rings D/E have been constructed by a von Pechmann reaction.[2-4] Buechi has pointed out that the



1 aflatoxin M_1

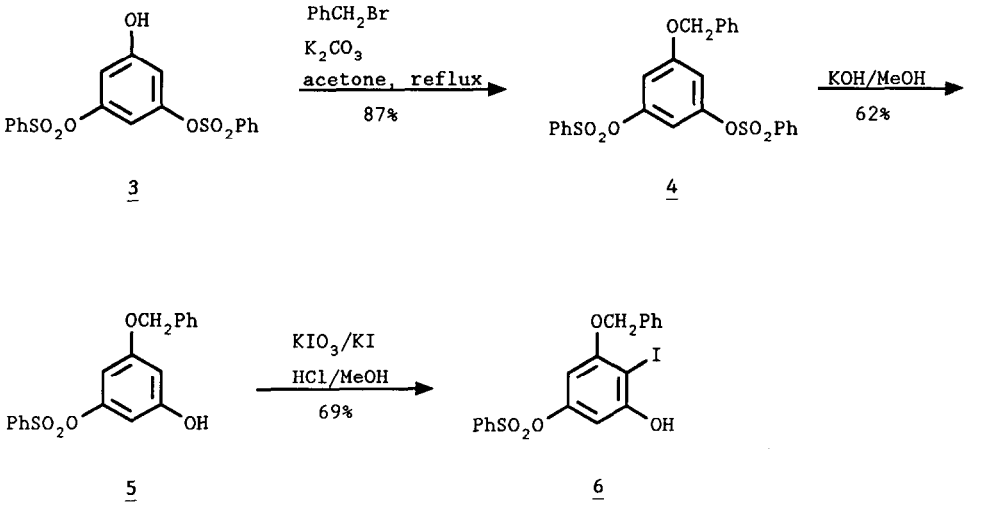


2 aflatoxin M_2

synthesis of aflatoxin M_1 "is not an organic synthesis type of preparation".[3]

Our own approach consists of coupling two suitably functionalized A-ring and C-ring building blocks to the acetal AC, which is then cyclized to ABC in the key step.

Regiocontrolled Differentiation of the Hydroxy Groups in Phloroglucinol and Regiocontrolled Electrophilic Iodination.

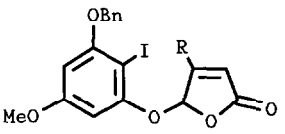


3 4 5 6

Scheme 1

The selective mono- and dialkylation of the hydroxy groups in phloroglucinol is difficult. We therefore started with bis(benzenesulfonyl) derivative[5,6] **3** which is readily obtainable by monodesulfonylation of the tris-(benzenesulfonyl) derivative. Monobenzylation (**3** → **4**) and another selective monodesulfonylation gave **5**, which was iodinated to give **6**. As is turned out, the sulfonyl group in **6** was also useful in the steps to follow. The

group appears to direct iodination of **5** into the para position preferentially (**5** → **6**). More generally, it reduces the electron-density of the phloroglucinol ring. A deactivated phloroglucinol was important in the palladium-mediated cyclization: In the absence of the sulfonyl group, e.g. with 3-benzyloxy-5-methoxy derivative **7** the cyclization did not take place (see also Scheme 5 below).

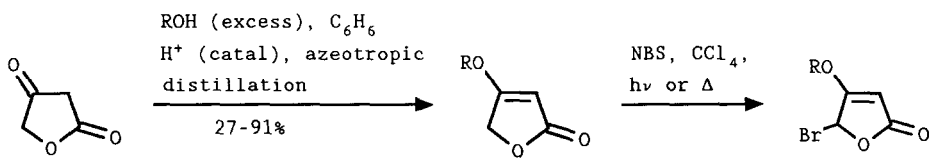


7 R=$OCH_2CH_2SiMe_3$

Preparation of C-Ring Precursors.

Previously, O-alkylated tetronic acids **9** were prepared by S_N2-alkylation of tetronates.[7] Very recently, Zimmer et al.[8] have condensed tetronic acid **8**

Table 1. Preparation of O-Alkylated Tetronic Acids **9** and Conversion into 5-Bromo-2(5H)furanones **10**



8 9 10

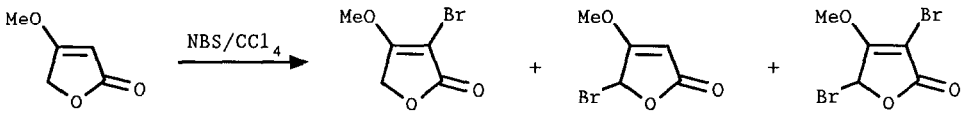
9	R-	**9** Yield [%]	**10**	**10** Yield [%]
9a	CH_3	81[a]	**10a**	62
9b	$CH_2=CHCH_2CH_2$	91	**10b**	25
9c	$CH\equiv CCH_2CH_2$	81	**10c**	31
9d	$Me_3SiCH_2CH_2$	64	**10d**	83
9e	$CH_3(CH_2)_4$	91	**10e**	72
9f	$(CH_3)_2CH$	28		
9g	$(CH_3CH_2CH_2CH_2)_2CH$	27		
			10h (R=Ac)	90

[a] H_2SO_4 conc., rt, 15 h (no benzene).

with alcohols in the presence of excess conc. H_2SO_4. We have found it ad-

vantageous to use *catalytic* amounts of acid and ca. 3 equivalents of alcohol, and to remove the water formed by azeotropic distillation with benzene. Secondary alcohols appeared to react less satisfactorily by our procedure.

Bromination of the butenolides with N-bromosuccinimide/azo-bis-isobutyronitrile in CCl_4 occurred regioselectively at C-5, giving bromobutenolides **10**. Polar impurities including moisture and acid had to be excluded, because they tended to promote ionic reactions. Care had also to be taken during workup. We succeeded in isolating the TMSE ($Me_3SiCH_2CH_2$) protected butenolide **10d** as a crystalline solid. Previously, Reffstrup et al.[9] reported the bromination of 4-methoxy-2(5H)furanone (**9a**) with NBS in CCl_4, obtaining the 3-bromo derivative **11** and the desired 5-bromo derivative (**10a**)

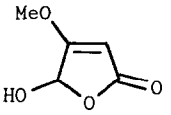


9a 11 (54%) 10a (9%) 12 (5%)

Scheme 2

in only 9% yield. We have found that exclusion of moisture and using anhydrous NBS (after recrystallization from water and prolonged drying) under controlled free radical conditions gave the 5-bromo derivative **10a** in 62% yield.

4-Alkoxy-5-bromo-2(5H)furanones (**10**) can be hydrolyzed to 3-alkoxy-4-hydroxy butenolides. For example, 5-hydroxy-4-methoxy-2(5H)furanone (**13**)



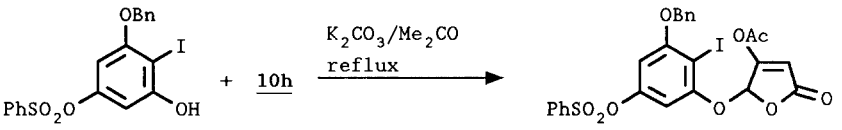
13

(narthogenin, from **10a**) is the aglycone of narthecide, which shows antibiotic activity.[9] O-Acylated derivative **10h** could also be obtained from 4-acetoxy-2(5H)furanone. However, not all O-protecting groups tolerated the NBS bromination. For example, the protecting group in **9** came off for R = OCH_2Ph, CH_2SMe, THP, and MEM ($-CH_2OCH_2CH_2OMe$).

Intermolecular Formation of Acetals (A+C → AC).

Coupling of the functionalized phloroglucinols, e.g. **6** with bromobuteno-

lides **10** was carried out advantageously under solid/liquid conditions (K_2CO_3/acetone). Even bromobutenolides which are prone to transesterification, such as 4-acetoxy-5-bromo-2(5H)furanone (**10h**), could be joined with **6** to the corresponding acetals, i.e. **14**.



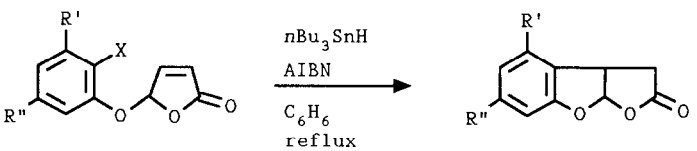
6 14

Scheme 3

Intramolecular Coupling (AC → ABC).

In work carried out concurrently with ours, Snieckus et al.[10] have recently reported the Bu_3SnH-induced cyclization of a number of AC acetals (**15a-c**). Whereas the simple model **15a** was reported to cyclize to **16a** in 42% yield, the more *highly* oxygenated bromophloroglucinol derivative **15c** was reported to cyclize to **16c** in 74% yield![10] In our experiments, the opposite trend was generally followed: the more oxygen is present, the more difficult the Bu_3SnH-induced cyclization becomes[11] (cf. **15d** vs. **15e**, and also work described below). The oxophilicity of tin seems to interfere.

Table 2. Bu_3SnH-Induced Cyclizations of **15a-e**.



15 16

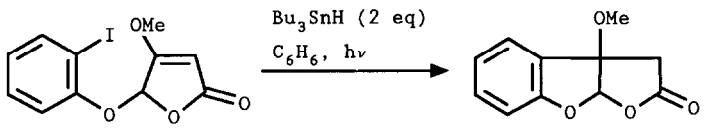
15	R′	R"	X	16 Yield [%]
a	OMe	H	I	42[a]
b	$MeOCH_2O$	H	I	79[a,c]
c	$MeOCH_2O$	MeO	Br	74[a,c]
d	H	H	I	86[b]
e	OCH_2Ph	OSO_2Ph	I	~ 28[b]

[a]Ref. 10; [b]ref.11; [c]cf. our discussion in the text.

Furthermore, in our work[12] bromophenol ethers (cf. **15c**, ref. 10) were always more difficult to cyclize than the corresponding iodoaromatics. We therefore suggest that in the absence of further experimental detail, the report by Snieckus et al.[10] be regarded with reserve (cf. below).

Entry into Aflatoxin M Building Blocks. Model Studies.

In contrast to phloroglucinol derivative **15e**, the simple iodoaromatic ethers **17a** could be cyclized with Bu_3SnH to **18a** in over 50% yield. How-

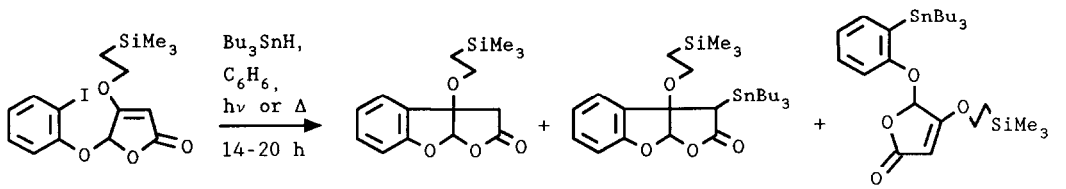


17a 18a 58%

Scheme 4

ever, all experiments to demethylate ether **18a** to the tertiary alcohol (cf. ref. 13) were not successful. For this reason we turned to the TMSE ($Me_3SiCH_2CH_2$) protecting group. A series of experiments with **17b** gave the desired **18b** and also tin-containing byproducts **19** and **20**, depending on the reaction conditions.

Table 3. Concentration and Radical Induction Effects on the Cyclization of **17b**.



17b 18b 19 20

Initial Concentration [mmol/l]	Bu_3SnH [mmol/l]	**18b** Yield [%]	**19**	**20**
6.7	7.3[a]	-	-	40
10	11[b]	53	4	9
10	20[c]	50	-	-

[a]AIBN 20%, Δ; [b]AIBN 2%, hν; [c]hν.

Because of the difficulties with tin we turned to a transition metal-mediated ring closure. We were pleased to find that the palladium-induced *intramolecular* hydroarylation[11] could be improved further and also applied to sterically more *hindered* C-ring precursors containing oxygen at the cyclization site. After model experiments with **17a, b** the protected phlorogluci-nol derivative **17c** was cyclized to the potential aflatoxin M_1 precursor **18c**. All three compounds **17a-c** gave similar yields (57-58%) in this step (Table 4). Replacement of the sulfonyl group in **17c** by a methyl group

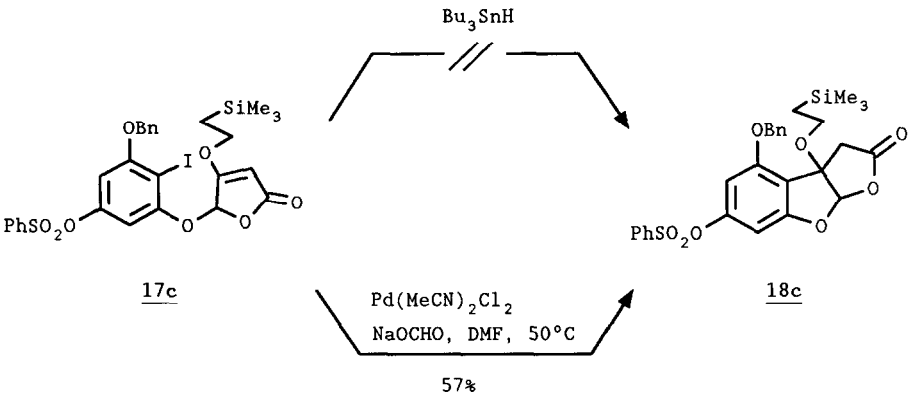
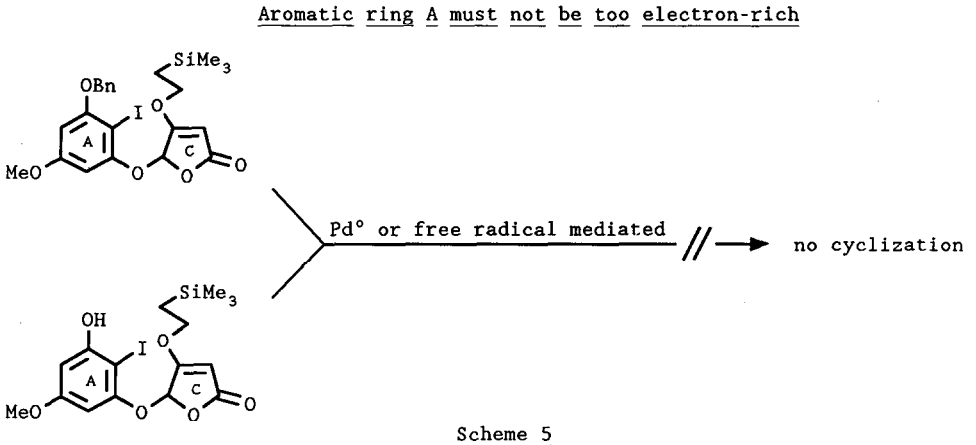


Table 4. Palladium-Promoted Cyclizations of **17a-c** to ABC-Building Blocks **18a-c**.

Compounds	**18** Yield [%]
17a → **18a**	57[a] (39[b])
17b → **18b**	58[a]
17c → **18c**	57[a,c]

[a] $Pd(MeCN)_2Cl_2$ (10 mol%), NaOCHO (1.4-1.8 equiv), $nBu_4N^+Cl^-$ (ca. 1.4-1.8 equiv), abs. DMF, 50-80°C; [b] $Pd(MeCN)_2Cl_2$ (4 mol%), $Et_3HN^+OCHO^-$ (2.2 equiv), DMF, 50°C; see ref.11; [c] Yield with respect to recovered **17c** (ca. 25% conversion; 55% yield at 56% conversion).

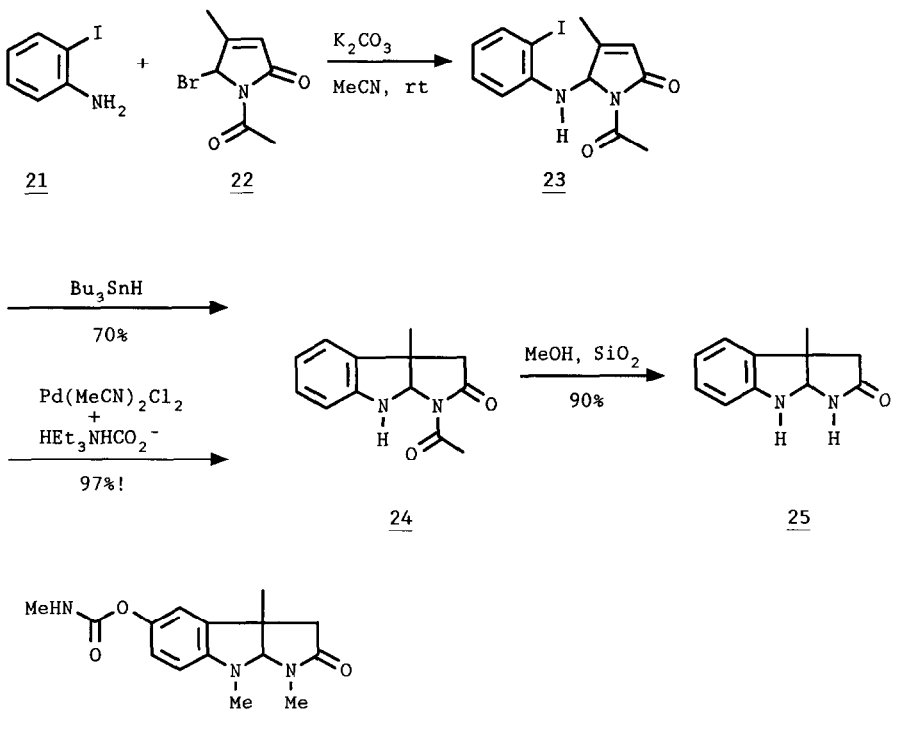
(cf. **7**) resulted in complete failure on attempted cyclization. Furthermore, attempts to cyclize **17c** with Bu_3SnH were not successful. Comparison with **17b** (Table 3) confirms our assumption that the high oxygen content of **17c** is once more responsible for the failure of the desired 5-exo-trig reaction (cf. above and Table 2). The cyclization fails also, if ring A is too electron-rich (Scheme 5).



Scheme 5

Other Benzoannulated Heterodiquinanes.

Structurally related heterodiquinanes have been built up in similar manner (Scheme 6). Coupling of *o*-iodoaniline (**21**) with acetylated 5-bromo-4-methylpyrrolidin-2-one (**22**) gave aminal **23**, which was cyclized with Bu_3SnH.



Scheme 6

The intramolecular hydroarylation with catalytic amounts of palladium in the presence of formate anion gave the desired tricycle **24** in reproducible 97% yield. Tetrahydropyrrolo[2,3b]indol-2-one (**25**) with its quaternary carbon C-3a is a model for physostigmine[14] (**26**), an indole alkaloid isolated from calabar beans.

Experimental

Preparation of O-Alkylated Tetronates. Procedure for **9b, 9c** and **9e**. 4-[3-Buten-1-oxy]-2(5H)furanone (**9b**). A solution of 4-hydroxy-2(5H)furanone (500 mg, 5 mmol), 3-butyn-1-ol (1.1 g, 15 mmol), p-toluenesulfonic acid (50 mg) in anhydrous benzene (50 ml) is introduced into a 50 ml round-bottomed flask equipped with reflux condenser and Dean-Stark separator and refluxed for 7 h. After cooling down to r.t., the solvent was evaporated in vacuo. The resulting yellow oil is purified by chromatography (EtOAc/PE 3:1). The light yellow oil crystallized over several weeks at -15°C, giving colorless prisms. Yield 700 mg (91%), mp 101-103°C. IR (cap. film) 1775s, 1746s, 1626s, 1321s, 1152s, 1053s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.54 (ddt, ^3J=8, ^4J=1, 2 H, H-2'), 4.13 (t, J=8, 2 H, OCH_2CH_2), 4.64 (d, 2 H, ^4J=1, H-5), 5.13 (dt, $^3J_{trans}$=10, ^4J=1, 1 H, H-4'), 5.15 (t, ^4J=1, 1 H, H-3), 5.16 (dt, $^3J_{cis}$=18, ^4J=1, 1 H, H-4'), 5.73 (ddt, $^3J_{trans}$=10, $^3J_{cis}$=18, ^3J=8, 1 H, H-3'). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.75 (t, C-2'), 67.82 (t, C-1'), 71.79 (t, C-5), 88.85 (d, C-3), 117.85 (t, C-4'), 133.25 (d, C-3'), 173.40 (s, C-4), 179.68 (s, C-2). MS for $C_8H_{10}O_3$ (154.1652) *m/z* 154 (M^+, 6), 121 (7), 120 (7), 99 (M^+-C_4H_7, 11), 83 (6), 69 (15), 55 (100).

4-[3-Butyn-1-oxy]-2(5H)furanone (**9c**) is obtained as light yellow, fine prisms (81%), mp 50-52°C. IR (cap. film) 3290m, 3130w, 1770s, 1745s, 1625s, 1370s, 1240s, 1155s, 1050s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.07 (t, ^4J= 2.5, 1 H, H-4'), 2.70 (dt, ^4J=2.5, ^3J=6.5, 2 H, H-2'), 4.14 (t, J=6.5, 2 H, OCH_2), 4.86 (d, ^4J=1, 2 H, H-5), 5.13 (t, ^4J=1, 1 H, H-3). MS for $C_8H_8O_3$ (152.1494) *m/z* 152 (M^+, 5), 124 (5), 123 (25), 107 (6), 96 (17), 69 (45), 53 (100).

4-[2-(Trimethylsilyl)eth-1-oxy]-2(5H)furanone (**9d**) is obtained as shining leaflets, 1285 mg (64%), mp 91-93°C. IR (KBr) 3100w, 2960m, 1775s, 1740s, 1630s, 1450s, 1335s, 1250s, 1180s, 1155s, 1070m, 1040s, 880s, 840s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9 H, CH_3), 1.16 (m, 2 H, $SiCH_2$), 4.16 (m, 2 H, OCH_2CH_2), 4.64 (d, ^4J=1.5, 2 H, H-5), 5.17 (t, ^4J=1.5, 1 H, H-3). MS for $C_9H_{16}O_3Si$ (200.953) *m/z* 174 (3), 173 (5), 172 (25), 159 (3), 158 (5), 157 (40), 129 (15), 101 (60), 99 (29), 74 (8), 73 (TMS, 100).

4-[Pent-1-oxy]-2(5H)furanone (**9e**) is obtained as a green-yellow oil (91%). IR (cap. film) 1770s, 1745s, 1630s, 1365s, 1320s, 1235s, 1150s, 1050s, 970s, 880s, 800s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (m, 3 H, CH_3), 1.40 (m, 4 H, CH_2), 1.80 (m, 2 H, OCH_2CH_2), 4.06 (t, ^3J=7, 2 H, OCH_2), 4.66 (d, ^4J=1, 2 H, H-5), 5.09 (t, ^4J=1, 1 H, H-3). MS for $C_9H_{14}O_3$ (170.2078) *m/z* 171 (1), 170 (4), 169 (41), 154 (2), 141 (2), 137 (3), 112 (38), 101 (22), 64 (17), 44 (100).

4-[1-Methyleth-1-oxy]-2(5H)furanone (**9f**)[8], 22 mg (28% with respect to 55% conversion), mp 42-43°C. Spectroscopic data identical with literature. MS for $C_7H_{10}O_3$ (142.1548) *m/z* 143 (5), 142 (61), 101 (83), 69 (53), 43 (100).

4-[1-Butylpent-1-oxy]-2(5H)furanone (**9g**) was isolated in solution with nonan-5-ol, ca. 27% yield. ^1H NMR (200 MHz, $CDCl_3$) (crude product) δ 0.92 (t, J=7, 6 H, CH_3), 1.20-1.50 (m, 12 H, CH_2), 4.13 (q, J=6.5, 1 H, OCH), 4.62 (d, ^4J=1, 2 H, H-5), 5.05 (t, ^4J=1, 1 H, H-3).

Preparation of Bromobutenolides. Photochemically Induced Bromination. 4-Methoxy-2(5H)furanone (**9a**) (115 mg, 1 mmol) in anhydrous CCl_4 (10 ml) under N_2 is injected into a photoreactor containing finely powdered, colorless NBS (190 mg, 1.05 mmol). The reaction mixture is cooled externally with ice and irradiated for 6.5 h with a mercury high pressure lamp (Philips HPK 125 W). The resulting succinimide is filtered off, and the residue is washed with cold CCl_4. The combined filtrates were freed from solvent under vacuum and chromatographed (EtOAc/PE 4:1). Apart from some educt **9a** (10 mg) the desired product **10a** is isolated (110 mg, 62% with respect to recovered starting material). Spectroscopic data identical with literature.[9]

Thermally Induced Bromination. 5-Bromo-4-[3-buten-1-oxy]-2,5-dihydrofuran-2-one (**10b**).
^{1}H NMR (200 MHz, $CDCl_3$) δ 2.6 (tdt, ^3J=7, ^4J=1, 2 H, H-2′), 4.18 (t, J=7, 1 H, OCH_AH_B), 4.185 (t, J=7, 1 H, OCH_AH_B), 5.18 (td, $^3J_{cis}$=10, ^4J=1, 1 H, H-4′), 5.20 (td, $^3J_{trans}$=18, ^4J=2, 1 H), 5.22 (s, 1 H, H-3), 5.84 (ddt, $^3J_{cis}$=10, $^3J_{trans}$=18, $^3J_{3',2'}$= 7, 1 H, H-3′), 6.62 (s, 1 H, H-5).

5-Bromo-4-[3-butyn-1-oxy]-2(5H)furanone (**10c**). 3-Bromo-4-[3-butyn-1-oxy]-2(5H)furanone (12%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.09 (t, ^4J=2.5, 1 H, H-4′), 2.71 (dt, ^3J=7, ^4J=2.5, 2 H, H-2′), 4.24 (t, ^3J=7, 2 H, OCH_2), 4.75 (s, 2 H, H-5). 5-Bromo-4-[3-butyn-1-oxy]-2(5H)furanone (31%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.09 (t, ^4J=2.5, 1 H, H-4′), 2.72 (dt, ^3J=7, ^4J=2.5, 2 H, H-2′), 4.30 (t, ^3J=7, 2 H, OCH_2), 5.20 (s, 1 H, H-3), 6.62 (s, 1 H, H-5).

5-Bromo-4-[2-(trimethylsilyl)ethoxy]-2(5H)furanone (**10d**). 4-[2-(Trimethylsilyleth-1-oxy]-2(5H)furanone (775 mg, 3.80 mmol), colorless, finely divided NBS (780 mg, 4.2 mmol) and AIBN (10 mg, mmol) are suspended with anhydrous CCl_4 (40 ml) in a 50 ml round-bottomed flask. The flask and reflux condenser are flushed with N_2 for 10 min, and the suspension is refluxed for 2 h under N_2. Initially, the color of the supernatant solution changes from yellow to deep-orange, and again after 2 h the color turns light within 5 min. The color changes and the floating succinimide indicates the end of the reaction. The reaction mixture is cooled for 2 h at 0°C, the succinimide is filtered off and washed with cold CCl_4. The combined filtrates are concentrated in vacuo, and the resulting sensitive orange-brown oil is flash-chromatographed (CH_2Cl_2), giving a clear oil which crystallizes overnight at -15°C, colorless needles. Yield 890 mg (83%), mp 58 - 59°C. IR (cap. film) 1790s, 1780s, 1630s, 1465m, 1340s, 1290s, 1250s, 1190m, 1140m, 1045s, 970m, 935m, 860s, 840s, 800m, cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9 H, CH_3), 1.2 (m, 2 H, H-2′), 4.2 (m, 2 H, H-1′), 5.16 (s, 1 H, H-3), 5.6 (s, 1 H, H-5). MS for $C_9H_{15}BrO_3Si$ (279.205) *m/z* 251 (3), 249 (3), 236 (9), 234 (9), 208 (5), 206 (5), 170 (17), 138 (16), 136 (16), 125 (8), 101 (TMSE, 37), 73 (TMS, 100), 69 (27).

5-Bromo-4-[pent-1-oxy]-2(5H)furanone (**10e**) is prepared as **10d**, light yellow oil, 72%. IR (cap.film) 2960s, 1790s, 1636s, 1466m, 1349s, 1289s, 1191m, 1142m, 1045s, 947m, 861s, cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, ^3J=8, 3 H, CH_3), 1.38-1.48 (m, 4 H, CH_2), 1.94 (m, 2 H, OCH_2CH_2), 4.11 (t, ^3J=7, 1 H, OCH_AH_B), 4.12 (t, ^3J=7, 1 H, OCH_AH_B), 5.14 (s, 1 H, H-3), 6.62 (s, 1 H, H-5). MS for $C_9H_{13}O_3Br$ (249.1039) *m/z* 250 (0.5), 249 (1), 248 (0.5), 200 (12), 168 (95), 100 (6), 99 (100), 71 (22), 69 (49).

4-Acetoxy-5-bromo-2(5H)furanone (**10h**) is obtained as a yellow oil (>90%). IR 1800s, 1750w, 1720w, 1630m, 1165s, 1130s, 1040s, cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.37 (s, 3 H, OCH_3), 6.26 (d, J=0.5, H-3), 6.78 (d, J=0.5, H-5). MS for $C_6H_5BrO_4$ (221.00) *m/z* 141 (M^+-Br, 23), 99 (14), 69 (49), 44 (100).

Coupling of Iodoaromatics with Bromobutenolides. Procedure for 5-(5-Benzenesulfonyloxy-3-benzyloxy-2-iodophenoxy)-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone (**17c**). 1-Benzenesulfonyloxy-3-benzyloxy-5-hydroxy-4-iodobenzene[11] (**6**) (308 mg, 0.63 mmol) is dissolved in anhydrous acetone (20 ml) in a 25 ml flask. 5-Bromo-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone (180

mg, 0.64 mmol) and K_2CO_3 (180 mg, 1.3 mmol) are added. The mixture is refluxed under N_2 for 14 h, and the solvent is evaporated under reduced pressure. Column chromatography (MTB/PE 1:1) affords **17c** as a light yellow, crystalline solid, 400 mg (93%), 52-54°C. IR ($CHCl_3$) 1790s, 1760m, 1640s, 1595m, 1450m, 1420m, 1380s, 1295m, 1195s, 1115s, 1000s, 860s, 840m, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (m, 9 H, $SiCH_3$), 1.18-1.24 (m, 2 H, $SiCH_2$), 4.12 (m, 2 H, OCH_2CH_2), 5.06 (s, 2 H, $PhCH_2$), 5.15 (s, 1 H, H-3), 5.82 (s, 1 H, H-5), 6.38 (d, ^4J=2, 1 H, H-4'), 6.48 (d, ^4J=2, 1 H, H-6'), 7.3-7.5 (m, 5 H, $C_6H_5CH_2$), 7.15-7.9 (m, 5 H, $C_6H_5SO_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.45 (q, $SiCH_3$), 17.3 (t, $SiCH_2$), 71.36 (t, OCH_2CH_2), 72.07 (t, OCH_2Ph), 90.17 (s, C-I), 90.27 (d, C-3), 97.1 (d, C-5), 102.88 (d, C-4'), 103.677 (d, C-6'), 127.27-129.4 (10 d, 10 C), 134.633 (s, OCH_2CC_2), 135.583 (s, CSO_3), 151.17 (s, C-1'), 156.78 (s, C-3'), 158.255 (s, C-5'), 169.49 (s, C-4), 174.56 (s, C-2). MS (180°C) for $C_{28}H_{29}IO_8SSi$ (680.5818) *m/z* 682 (0.5), 681 (1), 680 (2), 679 (5), 678 (14), 629 (5), 602 (6), 554 (19), 553 (32), 481 (12), 477 (18), 427 (23), 355 (8), 170 (11), 91 (100).

5-[5-Benzenesulfonyloxy-3-benzyloxy-2-iodophenoxy]-4-acetoxy-2(5H)furanone (**14**) is obtained as a viscous liquid (70%). IR ($CHCl_3$) 1711s, 1598bs, 1450s, 1432s, 1377s, 1193s, 1140s, 1093s, 1001, 848s, cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 2.16 (s, 3 H, AcO), 4.88 (s, 1 H, H-3), 4.99 (s, 2 H, $PhCH_2$), 5.68 (s, 1 H, H-5), 6.1-6.3 (m, 2 H, H-4'+6'), 7.34-7.45 (m, 5 H, $C_6H_5CH_2$), 7.5-7.9 (m, 5 H, $PhSO_3$). MS (310°C) for $C_{25}H_{19}IO_9S$ (622.3902) *m/z* 622 (1), 481 (3), 406 (6), 392 (5), 356 (2), 355 (2), 342 (2), 341 (2), 140 (37), 91 (81), 43 (100).

5-[2-Iodophenoxy]-4-methoxy-2(5H)furanone (**17a**) is obtained as a light yellow solid (93%), mp 88-90°C. IR 1790s, 1760m, 1645s, 1470m, 1450m, 1390m, 1305m, 1255m, 1080m, 1020m, 990m, 890m, cm^{-1}. ^1H NMR δ 4.00 (s, 3 H, OCH_3), 5.25 (s, 1 H, H-3), 6.07 (s, 1 H, H-5), 6.82-7.82 (4m, 4 H_{arom}). ^{13}C NMR δ 50.98 (q, OCH_3), 87.46 (s, C-2'), 90.70, 92.46 (d, C-3,5), 117.14 (d, C-6'), 125.88 (d, C-4'), 129.80 (d, C-5'), 139.80 (d, C-3'), 155.53 (s, C-1'), 169.22 (s, C-4), 175.97 (s, C-2). MS (60°C) for $C_{11}H_9IO_4$ (332.09) *m/z* 332 (M^+, 25), 219 (3), 190 (2), 149 (2), 113 (100), 92 (3), 85 (16).

5-[*o*-Iodophenoxy]-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone (**17b**) is obtained as colorless tetragonal crystals, 95%, mp 62-63°C. IR ($CHCl_3$) 1790 s, 1760m, 1640s, 1480s, 1440m, 1400m, 1365s, 1300s, 1190m, 1150m, 1125m, 1080s, 1040m, 1025m, 1010s, 925m, 880m, 860m, 840s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (m, 9 H, $SiCH_3$), 1.23 (m, 2 H, $SiCH_2$), 4.21 (dd, ^3J=8, ^2J=18, 1 H, $OCH_AH_BCH_2$), 4.24 (dd, ^3J=8, ^2J=18, 1 H, $OCH_AH_BCH_2$), 5.17 (d, ^4J=0.5, 1 H, H-3), 6.03 (d, ^4J=0.5, 1 H, H-5), 6.8-7.8 (m, 4 H_{arom}). MS (30°C) for $C_{15}H_{19}IO_4Si$ (418.29) *m/z* 418 (19), 417 (3), 343 (2), 292 (3), 291 (1), 219 (C_6H_4IO, 100), 202 (1), 191 (2), 190 (1), 69 (45), 68 (29).

Tributyltin Hydride-Mediated Cyclization. Photochemically-Induced Cyclization, AIBN Added.[15] 3a-[2-(Trimethylsily)eth-1-oxy]-3a,8a-dihydrofuro[2,3b]benzofuran-2(3H)-one (**18b**). 5-[*o*-Iodophenoxy]-4-[2- (trimethylsilyl)-eth-1-oxy]-2(5H)furanone (420 mg, 1 mmol), AIBN (3 mg, 0.02 mmol) and Bu_3SnH (330 mg, 1.13 mmol) are dissolved in anhydrous benzene (100 ml) and introduced into the photoreactor (see above). The solution is flushed with N_2, stirred vigorously and irradiated at 15°C for 20 h. The benzene is evaporated in vacuo, the resulting yellow residue is taken up in Et_2O (20 ml) and stirred vigorously with aqueous saturated NaF-solution (10 ml) for 20 h. The organic layer is separated, and the aqueous phase is re-extracted with Et_2O (3x20 mL). The combined organic layers are concentrated under reduced pressure and filtered through finely divided silica gel (flash gel, solvent Et_2O) and evaporated to leave a yellow oil which is purified by chromatography (50 g of flashgel, PE, then CH_2Cl_2). The tributyltin containing compounds are collected in the PE-fractions as follows: 10 mg tributyl tinhydride, 25 mg 3-(tributylstannyl)-3a-[2-(trimethylsilyl)eth-1--oxy]-3a,8a-dihydrofuro[2,3b]benzofuran-2(3H)-one, 50 mg 5-[*o*-(tributylstannyl)phenoxy]-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone. The desired

product **18b** is collected in the CH_2Cl_2-fractions, 155 mg, 53%.

3-(Tributylstannyl)-3a-[2-(trimethylsilyl)eth-1-oxy]-3a,8a-dihydrofuro[2,3b]benzofuran-2(3H)-one (**19**), 25 mg, 4%. IR (cap. film) 1800s, 1600m, 1465 s, 1250s, 1057s, 1007bs, 859s, 839s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ -0.06 (m, 9 H, $SiCH_3$), 0.85 (t, ^3J=8.5, 2 H, $SiCH_2$), 0.85-0.97 (m, 9 H, CH_2CH_3), 1.2-1.5 (m, 12 H, CH_2), 1.5-1.65 (m, 6 H, $SnCH_2$), 2.26 (m, 1 H, H-3), 3.18 (dt, ^2J=8.5, ^3J=8, 1 H, OCH_AH_B), 3.22 (dt, ^2J=8.5, ^3J=8, 1 H, OCH_AH_B), 6.2 (s, 1 H, H-8a), 6.95-7.4 (m, 4 H_{arom}). MS (40°C) for $C_{27}H_{46}O_4SiSn$ (581.4335) *m/z* 422 (1), 420 (1), 365 (18), 361 (100), 359 (74), 357 (44), 304 (24), 289 (TBT, 24), 269 (44), 225 (45), 194 (23), 182 (43).

5-[o-(Tributylstannyl)phenoxy]-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone (**20**), 50 mg (9%). IR (cap. film) 2873m, 2255w, 1796s, 1727s, 1477m, 1465s, 1289s, 1251m, 1074m, 999s, 839s. ^1H NMR (200 MHz, $CDCl_3$) δ -0.06 (m, 9 H, $SiCH_3$), 0.8-1.0 (m, 11 H, CH_3, $SiCH_2$), 1.2-1.5 (m, 12 H, CH_2), 1.55-1.85 (m, 6 H, $SnCH_2$), 4.2 (m, 2 H, OCH_2), 5.31 (s, 1 H, H-3), 6.18 (s, 1 H, H-5), 6.95-7.75 (m, 4 H_{arom}). MS for $C_{27}H_{46}O_4SiSn$ (581.4335) *m/z* 361 (19), 269 (19), 267 (7), 170 (100), 168 (46), 140 (13).

Palladium-Mediated Cyclization. Dihydrofuro-3a-methoxy [2,3b]benzofuran-2(3H)-one (**18a**). 5-[o-Iodophenoxy]-4-methoxy-2(5H)furanone (**17a**) (340 mg, 1.0 mmol) in 5 ml of anhydrous DMF, sodium formate (100 mg, 1.4 mmol), anhydrous tetra-*n*-butylammonium chloride (TBACl) (400 mg, 1.44 mmol) and bis(acetonitrile)palladium dichloride (20 mg, 0.077 mmol) are introduced into a 10 ml round-bottomed flask under N_2. The solution is stirred under N_2 and r.t. for 10 min. The light brown clear solution is heated within 3 min to 90°C. Within 15 min the solution turns darkbrown and finely-divided palladium is precipitated. After 30 min at 90°C the solution is cooled to r.t., and 20 mL of water is added. The cloudy brown suspension is extracted with CH_2Cl_2 (4x10 ml), the organic layer is washed with water (2x10 ml) and dried ($MgSO_4$). The solvent is evaporated under reduced pressure, leaving a brown oil which is chromatographed (MTB/PE 1:1) to give feathery needles of **18a** (120mg, 57%), mp 79°C. IR ($CHCl_3$) 1800s, 1615w, 1600m, 1475s, 1330m, 1270m, 1170s, 1105m, 1015s, 975s, 910s,840w, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.12 (s, 3 H, OCH_3), 3.18 (dd, ^2J=18, 2 H, H-3), 6.28 (s, 1 H, H-3a), 6.95-7.42 (m, 4 H_{arom}). MS for $C_{11}H_{10}O_4$ (206.19995) *m/z* 206 (M^+, 16), 176 (100), 106 (2), 149 (3), 121 (7), 118 (8), 84 (5), 77 (6), 65 (5).
Tricycle **18b** is obtained by the same procedure, colorless oil (58%), spectroscopic data (cf. above).

6-Benzenesulfonyloxy-4-benzoxy-3a-[2-(trimethylsilyl)eth-1-oxy]-3a,8a-dihydrofuro[2,3b]benzofuran-2(3H)-one (**18c**). 5-(5-Benzenesulfonyloxy-3-benzyloxy-2-iodophenoxy)-4-[2-(trimethylsilyl)eth-1-oxy]-2(5H)furanone (**17c**) (680 mg, 1.0 mmol), sodium formate (120 mg, 1.76 mmol), TBACl (500 mg, 1.75 mmol) are dissolved in anhydrous DMF (4 ml) under N_2. $Pd(MeCN)_2Cl_2$ (30 mg, 0.11 mmol) in DMF (1 ml) are syringed in and the resulting clear light brown solution is stirred at 50°C (contact thermometer). After 14 h all palladium has been precipitated, the solution is concentrated under reduced pressure (1 mbar), and the resulting black residue is chromatographed (MTB/PE 1:1). Product **18c** is obtained as a colorless oil, and educt **17c** (510 mg) is recovered. Yield: 80 mg (57% at 25% conversion). IR ($CHCl_3$) 1801s, 1613s, 1490w, 1450w, 1434 m, 1381s, 1290w, 1251s, 1112m, 1091s, 1003s, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.00-0.08 (m, 9 H, $SiCH_3$), 0.92 (t, ^3J=8, 2 H, $SiCH_2$), 3.16 (d, ^2J=18, 1 H, H_B-3), 3.37 (dt, ^3J=8, ^2J=8.5, 1 H, OCH_AHCH_2), 3.47 (dt, ^3J=8, ^2J=8.5, 1 H, $OCHH_BCH_2$), 3.5 (d, ^2J=18, 1 H, H_A-3), 5.1 (s, 2 H, $PhCH_2$), 6.24 (s, 1 H, H-8a), 6.3 (d, ^4J=2, 1 H, H-5), 6.48 (d, ^4J=2, 1 H, H-7), 7.4-7.5 (m, 5 H, $C_6H_5CH_2$), 7.55-7.96 (m, 5 H, $PhSO_3$). MS (140°C) for $C_{28}H_{30}O_8SSi$ (554.6917) *m/z* 555 (1), 554 (2), 553 (7), 437 (14), 347 (15), 279 (29), 166 (49), 149 (180), 91 (100).

1-Acetyl-5-bromo-4-methyl-1,5-dihydropyrrol-2-one (**22**) is obtained as described for **10d**, orange-colored oil (>90%). IR ($CHCl_3$) 1750s, 1710s, 1640m,

1385m, 1370m, 1340m, 1305s, 1280m, 1130m, 975m, 860m, cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 2.24 (dd, J=1.3, J=0.6, 3 H, CH_3), 2.54 (s, 3 H, $COCH_3$), 5.97 (q, J=1.3, 1 H, H-3), 6.45 (bs, 1 H, H-5). MS for $C_7H_8BrNO_2$ (218.11) m/z 138 (M^+-Br, 60), 96 (100), 68 (23), 44 (25).

1-Acetyl-5-(2-iodoanilino)-4-methyl-1,5-dihydropyrrol-2-one (**23**). 2-Iodoaniline (**21**) (660 mg, 3 mmol) and finely powdered K_2CO_3 (550mg, 4 mmol) in anhydrous acetonitrile (5 ml) are stirred for 30 min. Bromolactam **22** (1.1 g, 5 mmol) in acetonitrile (2 ml) is added with a perfusor and stirring within 6 h under N_2. After being stirred for 20 h, the mixture is filtered through silica gel (MTB). The solvent is evaporated and the remaining crude oil is flash-chromatographed (silica gel, MTB/PE 1:2). Besides educt **21** the aminal **23** is isolated. Yield: 780 mg (73%, 89% w.r.t. conversion of iodoaniline), mp 128-130°C. IR ($CHCl_3$) 3390bs, 1730s, 1695s, 1645w, 1585m, 1510m, 1460m, 1375m, 1335s, 1310s, 1270m, 1150m, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3 H, CH_3), 2.5 (s, 3 H, $COCH_3$), 4.88 (d, J=7, 1 H, NH), 5.89 (d, J=7, H-5), 6.0 (s, 1 H, H-3), 6.5-7.72 (m, 4 H_{arom}). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.09 (q, CH_3), 24.62 (q, $COCH_3$), 72.82 (d, C-5), 87.38 (s, C-2'), 113.36 (d, C-6'), 121.13 (d, C-4'), 122.74 (d, C-3), 129.25 (d, C-5'), 139.38 (d, C-3'), 144.19 (s, C-1'), 168.56 (s, $COCH_3$), 169.79 (s, C-2). MS (60°C) for $C_{13}H_{13}IN_2O_2$ (356.16) m/z 356 (M^+, 100), 313 (20), 229 (2), 218 (40), 160 (26), 149 (67), 134 (9), 96 (100), 71 (12), 57 (16), 44 (20). Anal. Calcd for $C_{13}H_{13}IN_2O_2$: C, 43.84; N, 7.87; H, 3.68. Found: C, 43.86; N, 7.79; H, 3.69.

1-Acetyl-3a-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3b]indol-2-one (**24**).
BU_3SnH-Method (cf. ref. 11). Yield 80 mg (70%), mp 86-87°C. IR 3450b, 1740 s, 1690s, 1610m, 1485s, 1470m, 1370s, 1295s, 1250s, 1110m, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3 H, CH_3), 2.48 (s, 3 H, OCH_3), 2.90 (dd, ^2J=-18, 2 H, H-3), 5.15 (bs, NH), 5.50 (d, J=1.5, 1 H, H-8a), 6.59 -7.13 (m, 4 H_{arom}). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.25 (q, CH_3), 25.31 (q, $COCH_3$), 44.42 (s, C-3a), 45.67 (t, C-3), 82.37 (d, C-8a), 109.34 (d, C-7), 119.55 (d, C-5), 122.87 (d, C-6), 128.87 (d, C-4), 133.20 (s, C-3b), 147.25 (s, C-7a), 172.59 (s, $COCH_3$), 173.47 (s, C-2). MS for $C_{13}H_{14}N_2O_2$ (230.39) m/z 230 (M^+, 30), 200 (11), 188 (6), 160 (8), 144 (11), 130 (6), 120 (4), 118 (5), 87 (13), 85 (74), 48 (18). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; N, 12.17; H, 6.31. Found: C, 67.60; N, 11.60; H, 6.22. Palladium-Method (cf. ref. 11). Yield 97%, spectroscopic data see above.

3a-Methyl-3,3a,8,8a-tetrahydropyrrolo[2,3b]indol-2-one (**25**). Tricycle **24** (230 mg, 1 mmol), silica gel (2 g) are stirred for 6 d in dry methanol at r.t. The silica gel is filtered off and rinsed thoroughly with acetone. After evaporation of the solvents product **25** is obtained as a colorless solid, 170 mg (90%), mp 166-168°C. IR 3450b, 1690s, 1610w, 1485m, 1470w, 1100m, 1075m, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3 H, CH_3), 2.68 (dd, ^2J=18, 2 H, H-3), 4.44 (bs, NH), 5.08 (s, 1 H, H-8a), 6.48 (bs, NH), 6.63-7.64 (3m, 4 H_{arom}). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.65 (q, CH_3), 43.96 (t, C-3), 49.79 (s, C-3a), 79.37 (d, C-8a), 110.43 (d, C-7), 120.07 (d, C-5), 123.13 (d, C-6), 128.63 (d, C-4), 135.12 (s, C-3b), 147.29 (s, C-7a), 176.79 (s, C-2). MS (150°C) for $C_{11}H_{12}N_2O$ (188.35) m/z 188 (M^+, 100), 160 (63), 146 (43), 145 (40), 144 (52), 130 (35), 105 (19), 77 (26), 55 (17).

References and Notes

Dedicated in Honor of Günther Ohloff on the Occasion of his 65th Birthday, July 21, 1989

[#] Abstracted in part from a lecture delivered at the International Symposium on Agricultural and Biological Aspects of Aflatoxin Related Health Hazards, New Dehli, India, March 22-25, 1989.

(1) (a) Bioactive Molecules, Vol. 1. Mycotoxins and Phycotoxins. Steyn, P.S.; Vleggaar, R., editors. Elsevier, Amsterdam, 1986. (b) Mykotoxine in Lebensmitteln, J. Reiss, ed. G. Fischer Verlag, Stuttgart 1981. (c) van Egmond, H.P.; Stavenuiter, J.F.C. *Tijdschrift voor Diergeneeskonde* **1985**, *110*, 1002. (d) ca $ 206/0.05 mg, Sigma Chemie, GmBH
(2) Büchi, G.; Weinreb, S.M. *J.Am.Chem.Soc.* **1969**, *91*, 5408. Büchi, G.; Weinreb, S.M. *J.Am.Chem.Soc.* **1971**, *93*, 746.
(3) Büchi, G.; Liesch, J.M.; Francisco, M.A.; Schuda, P.F. *J.Am.Chem. Soc.* **1981**, *103*, 3497.
(4) Schuda, P.F. *Top.Curr.Chem.* **1980**, *91*, 75.
(5) Sánchez-Obregón, R.; Hurtado, G.; Barrios, H.; Ortiz, B.; Yuste, F. *Org.Prep.Proced.Int.* **1986**, *18*, 145.
(6) Kampouris, E.M. *J.Chem.Soc.* **1965**, 2651.
(7) Boll, P.M.; Reffstrup, T.; Schnedler Wengel, A. *Tetrahedron* **1979**, *35*, 2181.
(8) Zimmer, H.; Amer, A.; Pham, C.V.; Grob Schmidt, D. *J.Org.Chem.* **1988**, *53*, 3368.
(9) Reffstrup, T.; Boll, P.M. *Phytochemistry* **1979**, *18*, 325.
(10) Cuevas, J.C.; Quesnelle, C.; Sloan, C.P.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. Snieckus, V. *Bull.Chim.Soc.Fr.* **1988**, 67-68.
(11) Wolff, S.; Hoffmann, H.M.R. *Synthesis* **1988**, 760.
(12) Wolff, S. Ph.D. Thesis, University of Hannover, 1988.
(13) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681.
(14) Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J.Org.Chem.* **1986**, *51*, 3007.
(15) Stork, G.; Baine, N.H. *J.Am.Chem.Soc.* **1982**, *104*, 2321.
(16) Clauß, K. *Tetrahedron Lett.* **1974**, *14*, 1271. Plieninger, H.; Decker, M. *Liebigs Ann. Chem.* **1956**, *598*, 205.