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Formal Total Synthesis of (±)-Aflatoxin B_2 Utilizing the Rhodium Carbenoid Dipolar Cycloaddition

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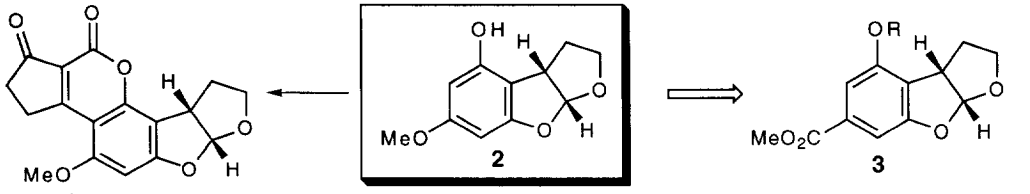
Key Words: rhodium acetate, diazocompound, total synthesis, Baeyer-Villiger, cycloaddition.

Abstract: *A formal total synthesis of (±)-aflatoxin B_2 has been completed using as the key step the rhodium-mediated dipolar cycloaddition of a cyclic rhodium carbenoid to dihydrofuran.*

Introduction

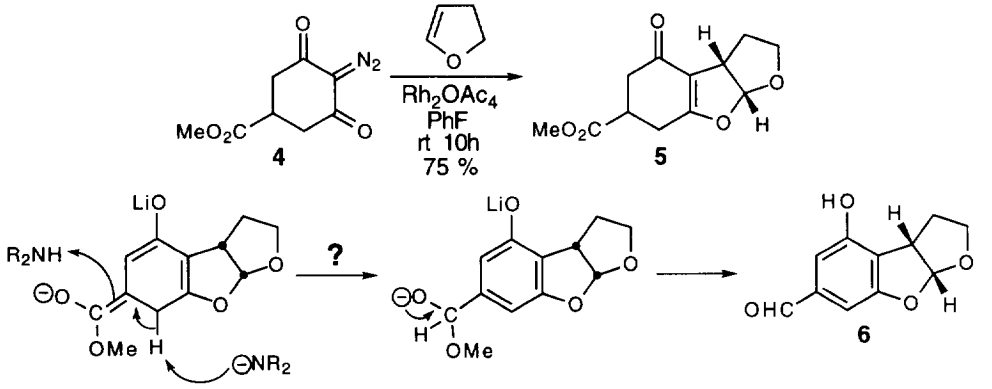
The complex polycyclic structures and potent biological activities of the aflatoxins[3] have made them important and challenging targets for total chemical synthesis. From Büchi's[4] and Robert's[5] initial work to more recent studies,[6] a key retrosynthetic strategy has been preparation of the tricyclic tetrahydrobenzofuro[2,3-*b*]furan ring system and a final, one step annulation of the cyclopentanocoumarin rings. Consequently, the preparation of compound **2** constitutes a formal synthesis of aflatoxin B_2 and was key to our retrosynthetic analysis. We have recently reported a number of advances in synthetic methodology and total synthesis based on the preparation of fused heterocyclic rings, such as the bis-tetrahydrofuran substructure contained within **2**, using the formal dipolar cycloaddition of cyclic diazodicarbonyl compounds with vinyl ethers mediated by dirhodium catalysts.[7] However, direct application of this methodology to the aflatoxins leads to difficulties because, in the required diazocompound precursor, the methoxy group would be located beta to a carbonyl group and therefore prone to elimination. Intermediate **3**, in which a methoxycarbonyl group serves as a surrogate for the methoxy group, was consequently chosen as a product reasonably available from the dipolar cycloaddition of dihydrofuran with compound **4**, which we have recently described.[8]



Results

The preparation of compound **4**[9] requires four steps from 3,4,5-trimethoxybenzoic acid and proceeds in 61% overall yield.[6] Its cycloaddition involving our previously-described protocol proceeds in excellent yield to form **5**,[10] establishing the tricyclic ring system in one step. This material had been earlier prepared in Kraus'

study of methodology for the synthesis of bis-THF ring systems; Kraus also reported the total synthesis of demethoxyaflatoxin B_2.[4] Efforts to transform the carbon bearing the methoxycarbonyl group in **5** to the ketone oxidation state focused initially on enolate chemistry. Treatment with 2 equivalents of LDA, in anticipation of selective oxygenation of the ester enolate and further oxidization of the α-hydroxyester, gives aldehyde **6**[11] regardless of whether an oxidant (O_2) or electrophile (R_3SiCl) is added. This transformation, which does not change the oxidation state of the compound overall, was unexpected, but it accomplishes two goals in one reaction: aromatizing the six-membered ring and setting the stage for a Baeyer-Villiger reaction to establish the aromatic oxygenation pattern. Under improved conditions, the transformation of **5** to **6** can be accomplished in 28% yield using 3 equivalents of LDA, with phenol **3** (R=H) also being obtained in 5% yield. While we have not determined the mechanism of this process, and know of no precedent, we suggest it involves tautomerization of the dienolate catalyzed by excess LDA and spectator diisopropylamine. This would initially give the salt of a hemiacetal, which would break down to the observed product.



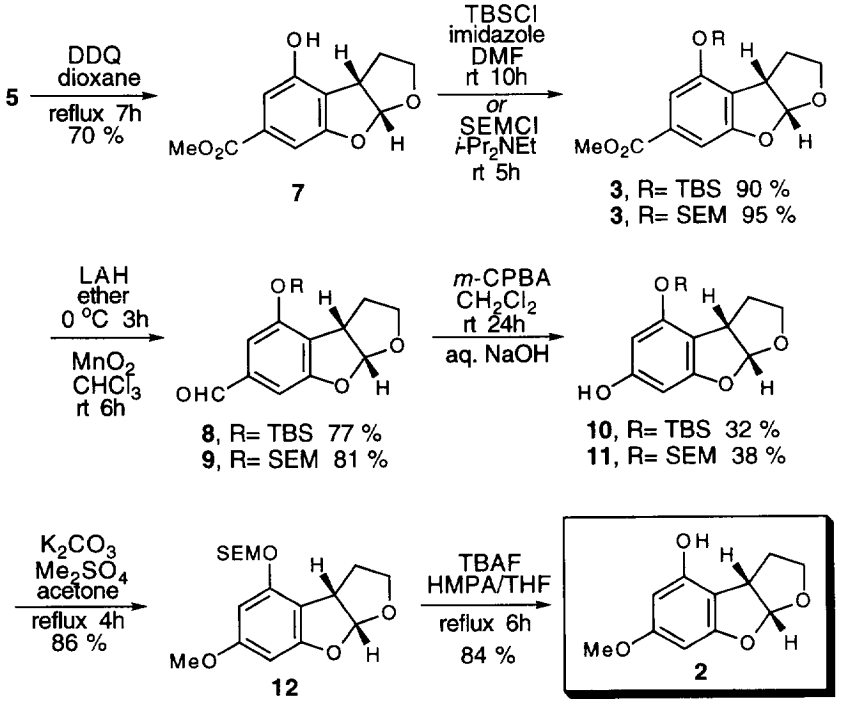
An alternative route is available to versions of aldehyde **6** protected with either silyl or acetal groups. Aromatization of **5** is readily accomplished with DDQ, and the resulting phenol **7**[12] can be protected with *tert*-butyldimethylsilyl chloride or (silylethoxy)methyl chloride in near-quantitative yield. A two-step reduction/oxidation protocol gives the aldehydes **8** and **9**.[13]

The Baeyer-Villiger oxidation of aromatic aldehydes is a well-studied transformation.[14] Aryl formates and benzoic acids are possible products, reflecting the migration of the hydrogen or the aryl group. The favored product is highly dependent on the substitution pattern in the aromatic ring and the oxidizing reagent. In the case of **8** and **9**, treatment with *m*-CPBA[15] leads to phenols **10**[16] or **11**[17] in modest yields after basic workup. The other products are the benzoic acids, which can be recycled to produce additional **8** or **9** by the same route applied to **3**. In the presence of KF,[18] *m*-CPBA oxidation leads to a slower reaction and reduced yield.

Completion of a formal synthesis of aflatoxin B_2 from compound **10** is straightforward, involving methylation to produce known compound **12**[19] which is deprotected by the Shirahama protocol to provide **2**.[20]

Conclusion

The overall yield of the most efficient version of this synthesis of **2** is 11%. It entails as few as nine chemical steps from commercially-available material. For comparison, earlier versions of the preparation of compound **2** have required at least ten steps but have proceeded in as high as 34% overall yield.



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2. Postdoctoral fellow of the Korea Science and Engineering Foundation.
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9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (d, J = 6.8 Hz, 1H), 3.15 (m, 1H), 3.74 (s, 3H); IR (neat) 2957, 2148, 1735, 1647, 1438, 1291, 1245, 1201, 1179, 1012, 913 cm^{-1}; **Anal**. Calcd. for $C_8H_8O_4N_2$: C, 48.98; H, 4.11. Found: C, 48.95; H, 4.15.
10. mp 63-64 °C; 1: 1 mixture of diastereomers by ^{1}H NMR; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98–2.08 (m, 2H), 2.54-2.64 (m, 2H), 2.66-2.81 (m, 2H), 3.01-3.14 (m, 1H), 3.56-3.65 (m, 2H), 3.69 and 3.70 (s, 3H,

-CO_2CH_3), 4.04-4.11 (m, 1H), 6.24 and 6.25 (d, J=5.8 and 5.9 Hz, 1H); IR (KBr) 2960, 1733, 1637, 1426, 1405, 1363, 1247, 1199, 1081, 1039, 949 cm^{-1}; **Anal**. Calcd. for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92. Found: C, 60.10; H, 5.97.

11. ^1H NMR (300 MHz, $CDCl_3$): δ 2.23-2.31 (m, 2H), 3.67 (m, 1H), 4.07-4.17 (m, 2H), 6.41 (d, J = 5.7 Hz, 1H), 6.62 (s, 1H), 6.90 (s, 1H), 6.97 (s, 1H), 9.82 (s, 1H, CHO).

12. mp 185-186 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20–2.27 (m, 2H), 3.60-3.68 (m, 1H), 3.89 (s, 3H), 4.05-4.14 (m, 2H), 5.81 (br s, 1H, -OH), 6.38 (d, J = 5.7 Hz, 1H), 7.05 (s, 1H), 7.15 (s, 1H); IR (KBr) 3305, 2997, 2960, 2888, 1685, 1603, 1440, 1375, 1314, 1285, 1255, 1096, 1083, 1059, 996, 954, 922, 867 cm^{-1}; **Anal**. Calcd. for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.89; H, 5.15.

13. ^1H NMR (300 MHz, $CDCl_3$): δ – 0.06 (s, 9H), 0.97 (dd, J = 8.3, 7.3 Hz, 2H), 2.20-2.25 (m, 2H), 3.62-3.65 (m, 1H), 3.77 (dd, J = 8.3, 7.3 Hz, 2H), 4.07 (m, 1H), 4.12 (m, 1H), 5.34 (s, 2H), 6.39 (d, J = 5.8 Hz, 1H), 7.19 (s, 1H), 7.25 (s, 1H), 9.87 (s, 1H, CHO); IR (neat) 2959, 2890, 1658, 1600, 1439, 1387, 1349, 1278, 1248, 1216, 1123, 1056, 954 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{24}O_5Si$: 336.1393. Found: 336.1392.

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16. ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 3H), 0.25 (s, 3H), 1.02 (s, 9H), 2.22-2.27 (m, 2H), 3.63-3.68 (m, 1H), 3.99 (m, 1H), 4.11 (m, 1H), 6.37 (d, J = 5.7 Hz, 1H), 6.14 (s, 1H), 6.22 (s, 1H), 8.23 (s, 1H, OH).

17. ^1H NMR (300 MHz, $CDCl_3$): δ – 0.07 (s, 9H), 0.97 (dd, J = 8.4 , 7.2 Hz, 2H), 2.10-2.18 (m, 2H), 3.61-3.69 (m, 1H), 3.74 (dd, J = 8.3, 7.2 Hz, 2H), 3.95 (m, 1H), 4.06 (m, 1H), 5.21 (s, 2H), 6.01 (s, 1H), 6.18,(s, 1H), 6.29 (d, J = 5.7 Hz, 1H); IR (neat) 3398, 2950, 1619, 1499, 1461, 1362, 1286 1247, 1135, 1055, 996, 956 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{24}O_5Si$: 324.1395. Found: 324.1406.

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19. ^1H NMR (300 MHz, $CDCl_3$): δ – 0.03 (s, 9H), 0.97 (dd, J = 8.4, 7.2 Hz, 2H), 2.13-2.22 (m, 2H), 3.60-3.69 (m, 1H), 3.74 (s, 3H), 3.72-3.79 (m, 2H), 3.97 (m, 1H), 4.06 (m, 1H), 5.22 (s, 2H), 6.08 (d, J = 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 6.30 (d, J = 5.7 Hz, 1H); IR (neat) 2940, 1612, 1501, 1440, 1410, 1308, 1284, 1248, 1143, 1054, 955 cm^{-1}.

20. mp 152-153 °C (lit. mp 153-154 °C); ^1H NMR (300 MHz, $CDCl_3$): δ 2.12-2.20 (m, 2H), 3.63-3.71 (m, 1H), 3.73 (s, 3H), 3.72-3.79 (m, 2H), 3.99 (m, 1H), 4.09 (m, 1H), 4.80 (br s, 1H, OH), 5.90 (d, J = 2.0 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 6.32 (d, J = 5.6 Hz, 1H).

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