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Palladium Catalyzed Kinetic and Dynamic Kinetic Asymmetric Transformations of γ-Acyloxybutenolides. Enantioselective Total Synthesis of (+)-Aflatoxin B_1 and B_{2a}

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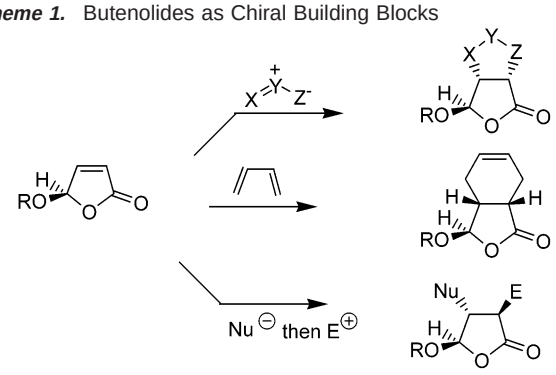
Abstract: The reaction of γ-*tert*-butoxycarbonyloxy-2-butenolide with phenol nucleophiles in the presence of a Pd(0) complex with chiral ligands may be performed under conditions that favor either a kinetic resolution or a kinetic asymmetric transformation (KAT) or dynamic kinetic asymmetric transformation (DYKAT). Performing the reaction at high concentration (0.5 M) in the presence of a carbonate base favors the former, i.e., KAT; whereas, running the reaction at 0.1M in the presence of tetra-*n*-butylammonium chloride favors the DYKAT process. Syntheses of aflatoxin B_1 and B_{2a} employs the DYKAT to introduce the stereochemistry. Starting with Pechmann condensation of the monomethyl ether of phloroglucinol, the requisite phenol nucleophile is constructed in two steps. The DYKAT proceeds with > 95% ee. A reductive Heck cyclization followed by a lanthanide catalyzed intramolecular acylation completes the synthesis of the pentacyclic nucleus in 3 steps. Reduction of the lactone provides aflatoxin B_{2a} and its dehydration product B_1. This synthetic strategy creates an asymmetric synthesis of the former in only 7 steps and the latter in 9 steps. Thus, the ultimate synthetic sequence involves **3** + **5** → **39** → **40** → **42** → **43** → **46** → **47** → **48** (aflatoxin B_{2a}) → **49** (aflatoxin B_1).

Butenolides as shown in Scheme 1 represent a potentially useful class of chiral building blocks wherein three contiguous stereocenters can be generated as shown in Scheme 1. In addition, the lactol also presents two chemodifferentiated carbonyl groups (oxidation states of an aldehyde and a carboxylic acid) for further elaboration. Feringa and co-workers developed a number of approaches to access such butenolides, the most attractive being an enzyme catalyzed esterification of the racemic lactol.[1,2] We were attracted to the question of inducing asymmetry in such racemic substrates using palladium catalyzed asymmetric allylic alkylations (AAA) for several reasons. First, this method offers an advantage over enzymatic methods because both enantiomers of the chiral catalysts are equally accessible. Second, in this approach, the enantioinduction event is frequently one of the steps of the normal synthetic sequence and, thus, not an additional one.

We chose to explore this concept in the context of developing a new synthetic strategy to the aflatoxins.[3] The aflatoxins[4] (Figure 1) are members of a large family of polyketide natural products known as the mycotoxins. These toxins are produced by the molds *Aspergillus flavus, A. parasiticus,* and *A. vericolor*

Scheme 1. Butenolides as Chiral Building Blocks



that infect a variety of agricultural products such as peanuts, rice, wheat, soybeans, wines, and also edible animal products such as meat, cheese, and butter. The widespread distribution of products suitable for generation of aflatoxins, coupled with their high toxicity and carcinogenicity, has produced a considerable amount of synthetic[5−7] and biological interest.

The synthesis of the aflatoxins presents several challenges. First, it requires the preparation of a highly substituted phloro-

(1) For enzyme catalyzed KAT of butenolides, see: (a) Feringa, B. L.; de Lange, B.; de Jong, J. C. *J. Org. Chem.* **1989**, *54*, 2471. (b) Wijnand, S. F.; Kob, J.; de Lange, B.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4775. (c) van der Deen, H.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *Tetrahedron Lett.* **1994**, *35*, 8441.

(2) For enzyme catalyzed DYKAT of butenolides, see: van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801.

(3) For a preliminary communication of this work, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.

(4) For a review see: (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. In *The Natural Coumarins*; Wiley: New York, 1982; pp 227−269. (b) Busby, W. F.; Wogan, G. N. In *Chemical Carcinogens*, Searle, C., Ed.; American Chemical Society: Washington, 1984; Vol. 182, pp 945−1136. (c) Schuda, P. F. *Top. Curr. Chem.* **1980**, *91*, 75. d. Minto, R. E.; Townsend, C. A. *Chem. Rev.* **1997**, *97*, 2537.

(5) For total syntheses, see: (a) Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F.; Schneider, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 6745. (b) Roberts, J. C.; Sheppard, A. H.; Knight, J. A.; Roffey, P. *J. Chem. Soc. C* **1968**, 22. (c) Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746.

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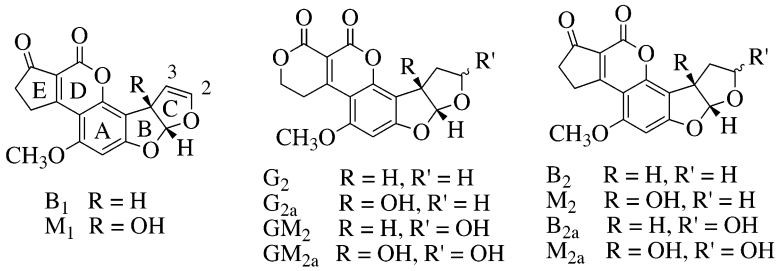
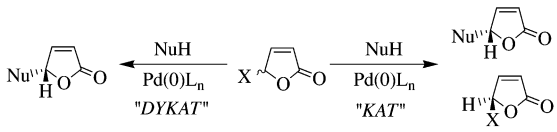


Figure 1. Aflatoxins.

glucinol core (ring A) in which all the aromatic carbons are differentially substituted. Not only must a pentasubstituted aromatic ring be constructed, but also it must be accomplished in a regioselective manner. Second, an enantioselective synthesis of furobenzofurans (rings B and C) is required. Ideally, the synthesis of the B and C rings would allow entry into vinyl ether (aflatoxin B_1), saturated furan (aflatoxin B_2) and hemiacetal (aflatoxin B_{2a}) functionalities present in the aflatoxins. Finally, a synthesis of a bicyclic coumarin system (rings D and E) is needed. Once again, the synthesis should be flexible enough to allow for the preparation of the cyclopentanone (aflatoxin B_1) and lactone (aflatoxin G_2) E-rings. Notably, despite the fact that the first syntheses of these molecules were completed over 30 years ago,[5] no total synthesis in which the chirality is created by a catalytic enantioselective reaction[7] has been described.

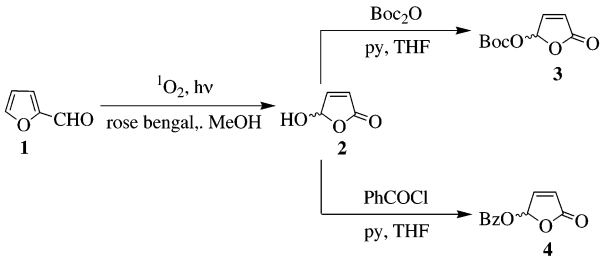
Palladium catalyzed asymmetric allylic alkylation (AAA) offers a potential method for the enantioselective preparation of butenolides. This method offers an advantage over the traditional kinetic resolution because it not only resolves the enantiomers but also replaces the γ-substituent in the starting butenolide with a nucleophile.[8] The coordination of palladium, ligated with chiral ligands, to the butenolide forms diastereomeric η^2-olefin complexes and therefore provides a possible mechanism for kinetic asymmetric transformation, KAT (eq 1).[9] Alternatively, if the coordination is reversible then the ionization of the diastereotopic leaving groups becomes a potential enantiodetermining step for the KAT.[10] A more desirable transformation requires the conversion of both enantiomers of a racemic starting butenolide to a single enantiomer of product (DYKAT).[11] However, this requires a racemization of either the starting butenolide or the π-allylpalladium intermediate. Herein is described the development of both the palladium catalyzed KAT and DYKAT of butenolides and the application of this process to the enantioselective total synthesis of the aflatoxins.



(1)

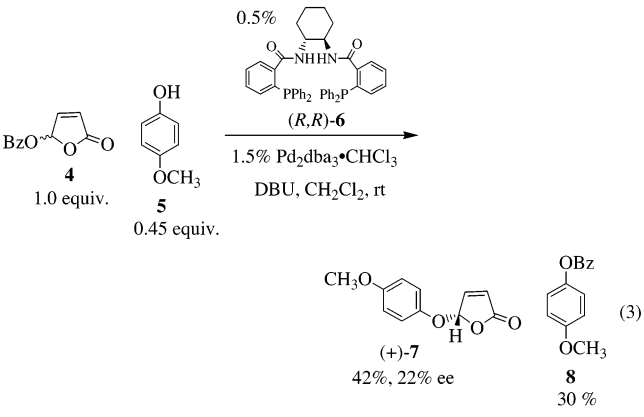
Results

The required racemic butenolides were prepared in a two step sequence from furfural (**1**) (eq 2). Reaction of **1** with singlet oxygen produced γ-hydroxybutenolide **2**.[12] Crude **2** was not purified but reacted directly with di-*tert*-butyl dicarbonate to produce allyl carbonate **3**. Alternatively, the crude hemi-acetal could be readily converted into allyl benzoate **4** by reaction with benzoyl chloride.



(2)

Palladium Catalyzed KAT with Phenol Nucleophiles. With the butenolides in hand, we first examined the palladium catalyzed KAT of benzoate **4** utilizing 0.45 equivalents of 4-methoxyphenol (**5**) as a nucleophile (eq 3). Palladium catalyzed reaction of **4** with phenol **5**, in the presence of ligand **6**, provided aryl ether **7** in moderate yield (42%) and with moderate enantioselectivity (22% ee). Furthermore, the reaction was complicated by the formation of aryl benzoate **8**.



(3)

(6) For formal syntheses, see: (a) Sloan, C. P.; Cuevas, J. C.; Quesnelle, C.; Sneickus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. (b) Hoffmann, H. M. R.; Schmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6113. (c) Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 39. (d) Koreeda, M.; Dixon, L. A.; Hsi, J. D. *Synlett.* **1993**, 555. (e) Pirrung, M. C.; Lee, Y. R. *Tetrahedron Lett.* **1996**, *37*, 2391. (f) Kraus, G. A.; Wang. X. *Tetrahedron Lett.* **1999**, *40*, 8513. (g) Noland, W. E.; Kedrowski, B. L. *Org. Lett.* **2000**, *2*, 2109.

(7) For enantioselective formal syntheses, see: (a) Marino, J. P. *Pure Appl. Chem.* **1993**, *68*, 667. (b) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775. c. Bando, T.; Shishido, K. *Synlett* **1997**, 665.

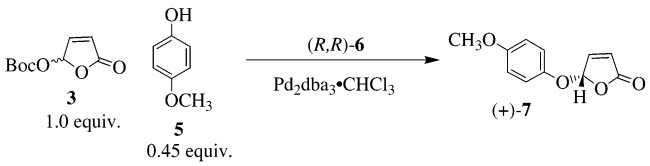
(8) This transformation has been accomplished in two steps utilizing resolution and then palladium catalyzed reaction. (a) van der Deen, H.; van Oeveren, A.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 1755 (b) Cuiper, A. D.: Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 655.

(9) For an example of coordination of enantiotopic olefin faces as the enantiodetermining step, see: Trost, B. M.; Asakawa, N. *Synlett* 1999, 1491.

(10) For examples of ionization of enantiotopic leaving groups as the enantiodetermining step, see: (a) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5974, and references therein.

(11) For examples of palladium catalyzed DYKAT, see: (a) Trost, B. M.; Patterson, D. E.; Hembre, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 10 834. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968

Table 1. Pd Catalyzed KAT of γ-Hydroxybutenolides with *p*-Methoxyphenol as a Nucleophile



	mol % Pd_2dba_3	mol % **6**	conditions	**7** yield[a], ee[b]	rec'd **3** ee[b]
1	5	15	0.1 M CH_2Cl_2, rt, 10 h	90%, 47%	nd
2	0.5	1.5	0.1 M CH_2Cl_2, rt, 10 h	82%, 58%	47%
3	0.5	1.5	0.1 M CH_2Cl_2, −30 °C, 16 h	62%, 64%	nd
4	0.25	0.75	0.1 M CH_2Cl_2, −30 °C, 16 h	47%, 66%	nd
5	0.5	1.5	0.1 M CH_2Cl_2, −78 °C, 10 h	32%, 63%	nd
6	0.5	1.5	0.1 M THF, −30 °C, 10 h	72%, 87−90%	nd
7	0.5	1.5	0.5 M CH_2Cl_2, 15% Cs_2CO_3, rt, 16 h	90%. 87−90%	14−44%
8	0.5	1.5	0.5 M CH_2Cl_2, 45% Na_2CO_3, rt, 12 h	91%, 89%	64%

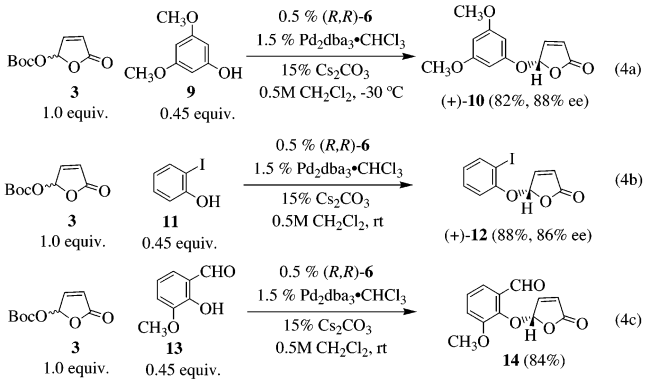
[a] % yield based on 5. [b] % ee determined by chiral HPLC.

To avoid the complications due to the transesterification reaction of benzoate **4**, we turned to *tert*-butyl carbonate **3** as the substrate for the palladium catalyzed reaction (Table 1). Gratifyingly, reaction of 0.45 equivs of **5** with butenolide **3**, utilizing 5% Pd_2dba_3 and 15% of **6** as catalyst, furnished aryl ether **7** in 90% yield, but only 47% enantiomeric excess (entry 1). A 10-fold decrease in catalyst loading, to 0.5% Pd_2dba_3 and 1.5% of **6**, increased the enantioselectivity of the reaction to 58% ee without a significant effect on the yield (entry 2). Lowering the reaction temperature, to −30 °C (entries 3 and 4) or −78 °C (entry 5), did not significantly increase the enantioselectivity of the reaction but resulted in a decrease in yield.

Several factors could be responsible for the moderate enantioselectivities obtained thus far in the palladium catalyzed KAT of **3**. First, ligand **6** could be providing poor selectivity in the enantiodetermining event, either the coordination or ionization. Alternatively, ligand **6** could generate the π-allylpalladium complex with excellent diastereoselectivity; however, the rate of facial exchange of the palladium is greater than the rate of nucleophilic addition of phenol. The possible mechanisms for facial exchange will be discussed in detail in the context of the kinetic dynamic asymmetric transformations (DYKAT)[15] of **3**. The active nucleophile is presumably the phenoxide generated from deprotonation of **5** by the carbonate produced from ionization of **7**. Since only a small amount of base, and therefore nucleophile, is present in the reaction mixture, it is possible that the rate of nucleophilic addition would be relatively slow.

To examine if the latter scenario was operating, base was added to increase the concentration of deprotonated phenol. This should increase the rate of nucleophilic attack relative to equilibration of the kinetically generated π-allyl intermediate. To further increase the rate of nucleophilic addition, the reaction concentration of butenolide **3** was increased from 0.1 M to 0.5 M. Indeed, with the higher reaction concentration and the addition of 15% cesium carbonate the enantiomeric excess of **7** increased to 87−90% (entry 7). The enantiomeric excess of recovered **3** ranged from 16 to 44%. Replacing cesium carbonate with sodium carbonate produced a similar result (entry 8). The lower enantiomeric excess obtained for the recovered butenolide **3** suggested that the reaction could be carried out to greater conversion of **3**. A discussion of the possible reasons for the low enantiomeric excess of recovered **3** and our attempts to take advantage of this to transform the KAT into a DYKAT will be discussed in the context of the DYKAT reaction.

Utilizing these reaction conditions, several phenols participated in the palladium catalyzed KAT of butenolide **3** (eq 4a−c). For example, as depicted in eq 4a, palladium catalyzed reaction of **3** with 0.45 equivs of 3,5-dimethoxyphenol (**9**) produced aryl ether **10** in 82% yield (based on **9**) and 88% enantiomeric excess (by chiral HPLC). 2-Iodophenol (**11**) participated equally well in the palladium catalyzed KAT (eq 4b), furnishing aryl ether **12** in 88% yield and 86% enantiomeric excess (by chiral HPLC). *ortho*-Disubstituted phenol **13** also reacted well (eq 4c) with **3** to afford aryl ether **14**. Unfortunately, the enantiomeric excess of **14** could not be determined by either chiral HPLC or by a chiral shift experiment.



To establish the absolute stereochemistry of the palladium catalyzed KAT of **3,** we undertook a synthesis of the Büchi lactone (**20**). Our synthesis begins with the regioselective bromination of **15** utilizing 2,4,4,6-tetrabromocyclohexadienone as the brominating agent, thereby affording **16** in 48% yield (Scheme 2). Bromination of **15** using traditional brominating agents (Br_2 or NBS) produced a mixture of mono-, di- and tribrominated products.[13] Catechol **16** was protected by treatment with sodium hydride followed by addition of *tert*-butylchlorodimethylsilane to afford monosilyl ether **17** in 50% yield. Palladium catalyzed AAA of 0.45 equivs phenol **17** with butenolide **3**, utilizing the standard conditions, proceeded

(12) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2059.
(13) Kiehlmm, E.; Lavener, R. W. *Can. J. Chem.* **1989**, *67*, 335.
(14) Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 1229.
(15) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910.

Scheme 2. Asymmetric Synthesis of Büchi Lactone

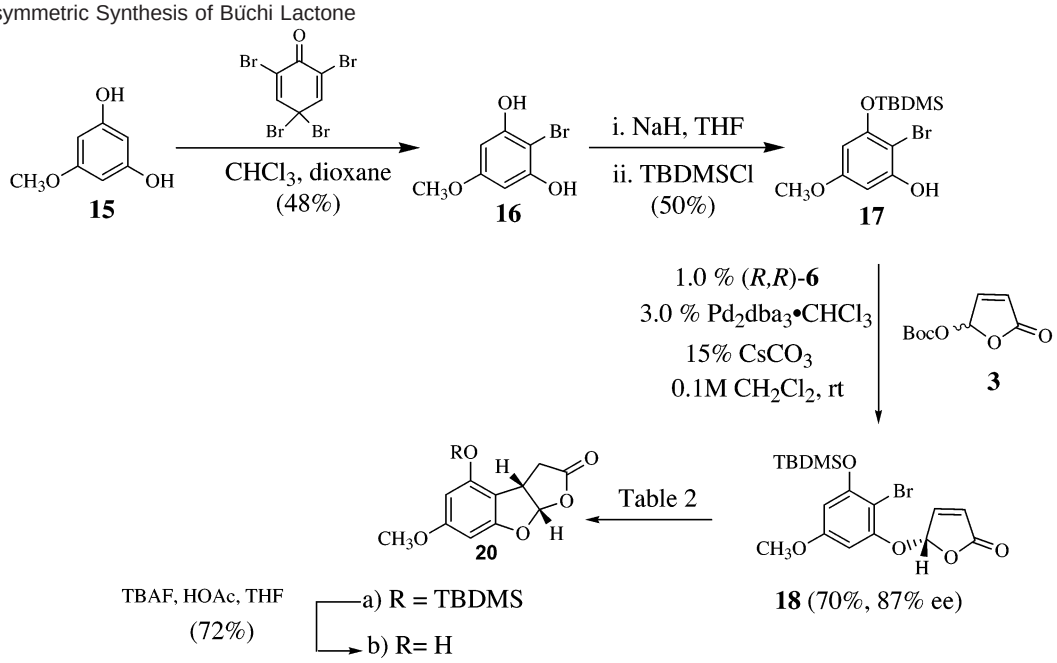
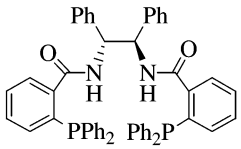


Table 2. Cyclization to Form the Benzofuran of the Büchi Lactone

	conditions	result
1	Bu_3SnH, AIBN, C_6H_6, 80 °C	mainly **17**
2	10% $Pd(OAc)_2$, 10% dppp, HCOOH, TEA, DMF, rt	mainly **17**
3	10% $(CH_3CN)_2PdCl_2$, HCOOH, TEA, DMF, 50 °C	mainly **17**
4	10% $Pd(OAc)_2$, HCOOH, TEA, CH_3CN, rt	no reaction
5	1 equiv. Et_3B, O_2, Bu_3SnH, C_6H_6, rt	no reaction
6	10% Et_3B, O_2 Ph_3SnH, C_6H_6, rt	33% **20a**
7	10% Et_3B, O_2 Ph_3SnH, BF_3•OEt_2, C_6H_6, rt	complex mixture
8	10% Et_3B, O_2, $(TMS)_3SiH$, C_6H_6, rt	15% **20a**
9	$Ni(acac)_2$, Et_3Al, Ph_3P, Et_2O, 40 °C	complex mixture
10	*n*-BuMgBr, $MnCl_2$, THF, rt	complex mixture
11	i, *n*-BuLi, THF −100 °C ii. CuCN, LiCl	complex mixture

smoothly to afford aryl ether **18** in 70% yield and 87% ee (by chiral HPLC). Changing the base from cesium carbonate to sodium carbonate dropped the enantioselectivity to 76% enantiomeric excess. Varying the ligand from **6** to the diphenyldiamine-based ligand **19** also had a detrimental effect on the enantioselectivity (64% yield, 69% ee).



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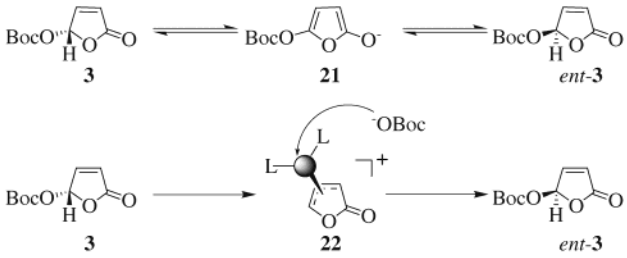
With aryl ether **18** in hand we examined the cyclization to form furobenzofuran **20a** (Table 2). All attempts to effect an AIBN initiated radical cyclization[6a] failed to produce **20a** (entry 1). Our efforts to apply an intramolecular reductive Heck reaction (entries 2−4), including under the Hoffmann conditions,[6b] produced mainly ionization of phenol **17**. Therefore, we turned to triethyl borane and oxygen as a low-temperature radical initiator. Using tributyltin hydride as the hydride source failed to produce any of the desired product (entry 5), however, triphenyltin hydride afforded the cyclized product **20a** in 33% yield (entry 6). Addition of a Lewis acid, boron trifluoride, had a detrimental effect on the reaction (entry 7). Replacing the tin hydride with tris(trimethylsilyl)hydride[14] produced **20a** in 15% yield (entry 8). Nickel(0) mediated cyclization produced a complex mixture of products, (entry 9) as did the manganese(II) mediated[15] radical reaction (entry 10). Generation of the higher order arylcuprate did give a trace amount of **20a** but was complicated by the formation of several byproducts (entry 11).

Scheme 3. Possible Mechanisms for Racemization of Starting Butenolide



Furobenzofuran **20a** was deprotected with tetrabutylammonum fluoride to afford the Büchi lactone **20b** in 72% yield. The absolute configuration of our lactone **20b** was determined by comparison to the rotation reported by Marino.[7] This comparison established the stereochemistry of aryl ether **20b** as (*S*). The stereochemistry of the remaining aryl ethers (see Table 1 and eq 4) were assigned by analogy to the stereochemistry of aryl ether **20b**.

Palladium Catalyzed DYKAT of 4-Acyloxy-2-Butenolide. The low enantiomeric excess often obtained for the recovered starting butenolides in the palladium catalyzed KAT (Table 1) suggests that the starting material is undergoing a racemization during the course of the reaction. We hypothesized that this racemization was occurring by one of two potential mechanisms (Scheme 3). Deprotonation of the allylic proton in starting butenolide **3** generates achiral enolate **21**. Reprotonation from the opposite face would generate *ent*-**3**. Alternatively, palladium catalyzed ionization of **3** produces π-allylpalladium complex **22**. Return of the leaving group, by nucleophilic attack on palladium followed by reductive elimination,[16] produces *ent*-**3**.

If these racemization mechanisms are operative during the course of the reaction, then it should be possible to carry out

Scheme 4. Possible Mechanisms for Pd Catalyzed DYKAT of γ-Hydroxybutenolides

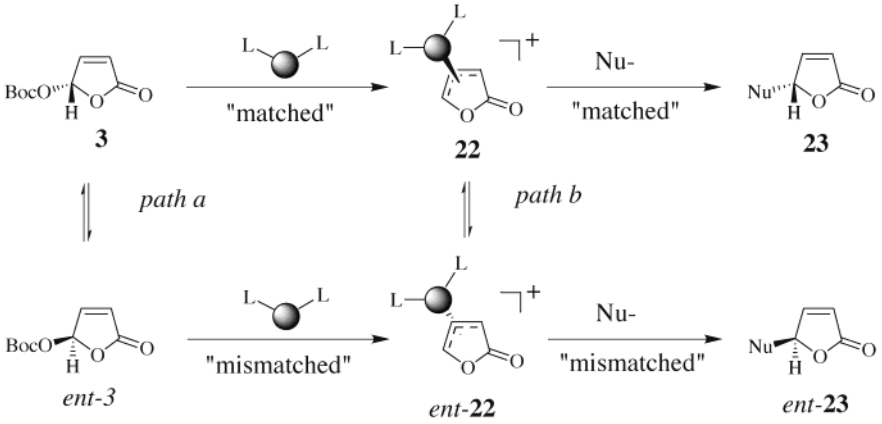
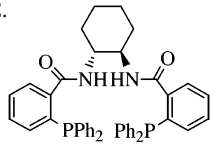


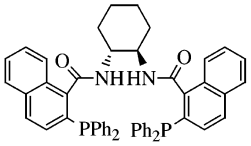
Table 3. Pd Catlayzed DYKAT of γ-Hydroxybutenolides with *p*-Methoxyphenol as a Nucleophile

	equiv **5**	mol % Pd_2bda_3	ligand (mol %)	conditions	yield[a], ee[b]
1	1.0	0.5	**6** 1.5	0.2 M CH_2Cl_2, 15% Cs_2CO_3 rt, 16 h	80%, 24%
2	0.8	0.5	**6** 1.5	0.2 M CH_2Cl_2, 15% Cs_2CO_3 rt, 10 h	85%, 48%
3	0.85	2.5	**6** 7.5	0.1 M CH_2Cl_2, 15% Cs_2CO_3, 30% Bu_4NCl, 0 °C, 12 h	80%, 75%
4	1.0	1.0	**6** 3.0	0.1 M CH_2Cl_2, 30% Bu_4NCl, rt, 6 h	67%, 82%
5	1.0	1.0	**6** 3.0	0.1 M CH_2Cl_2, 30% Bu_4NCl, 0 °C, 12 h	74%, 84%
6	1.0	2.5	**6** 7.5	0.1 M CH_2Cl_2, 30% TBAT, 0 °C, 12 h	99%, 30%
7	1.0	1.0	**25** 3.0	0.1 M Ch_2Cl_2, 30% Bu_4NCl, 0 °C, 12 h	43%, 71%
8	1.0	2.5	**6** **7.5**	0.1 M Ch_2Cl, 30% Bu_4NCl, 0 °C, 12 h	90%, 65%

[a] % yield based on **5.83**. [b] % ee determined by chiral HPLC.



(*R*,*R*)-**6**



(*R*,*R*)-**25**

the palladium catalyzed AAA to greater than 50% conversion and still obtain good enantioselectivity (a dynamic kinetic asymmetric transformation, DYKAT). For this scenario to be successful, the rate of racemization of *ent*-**3** (path a, Scheme 4) must be greater than the "mismatched" ionization to form π-allylpalladium complex *ent*-**22**. Unfortunately, when one equivalent of *p*-methoxyphenol (**5**) was reacted with butenolide **3**, under the conditions developed for the KAT, aryl ether **7** was isolated with only 24% enantiomeric excess (Table 3, entry 1). Lowering the equivs of phenol **5** to 0.8, only slightly improved the enantiomeric excess of **7** to 48% (entry 2).

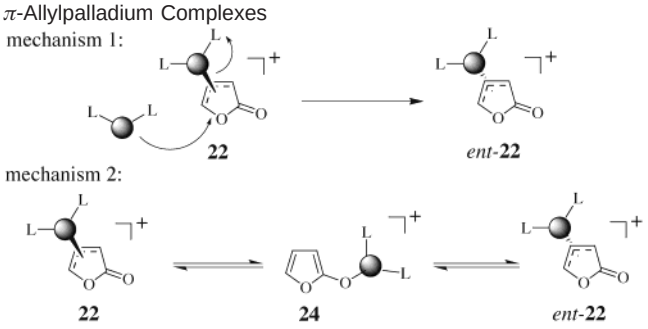
The fact that the enantiomeric excess of **7** substantially decreased with increased conversion suggests that the racemization (path a) of the starting butenolide (**3**) is slower than the rate of "mismatched" nucleophilic addition. Thus far, we have addressed this issue by rapidly trapping the kinetically formed π-allylpalladium complex (**22**) generated by a "matched" ionization (see Table 1). Our attempts to racemize the "mismatched" starting material (*ent*-**3**), to obtain aryl ether **7** in >50% conversion and with good enantiomeric excess failed (Table 3, entries 1 and 2). However, another alternative exists. If the π-allylpalladium complex (*ent*-**22**) generated from a "mismatched" ionization could be transformed into the "matched" π-allylpalladium complex (**22**) (path b) faster than it is trapped by nucleophile, then 100% conversion and good enantioselectivity of aryl ether **7** would be possible.

To discern whether the interconversion (path b) of π-allylpalladium complexes **22** and *ent*-**22** was possible, we returned to the question of why the enantioselectivity of the KAT transformation was lower in the absence of base (compare entries 2 and 7, Table 1). We have suggested that the addition of base improves the enantioselectivity of the KAT by trapping the kinetically formed "matched" π-allylpalladium complex **22**. It was unclear how the stereochemical integrity of **22** (i.e., its conversion to *ent*-**22**) deteriorated in the absence of rapid nucleophilic addition.

To account for this deterioration in enantiomeric excess, we examined two possible mechanisms for the interconversion of

(16) For enzyme catalyzed DYKAT of butenolides, see: van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801. For a discussion of this racemization mechanism for allylic acetates, see: Grennber, H.; Langer, V.; Bäckvall, J. E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190 and references therein.

Scheme 5. Possible Mechanism for Interconvesion of π-Allylpalladium Complexes

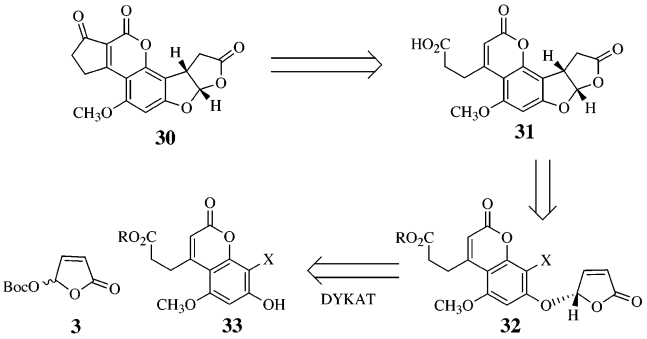


π-allylpalladium complexes **22** and *ent*-**22** (Scheme 5). One possible mechanism involves *anti*-addition of a second equiv of palladium(0) to π-allylpalladium **22** complex to produce *ent*-**22** (mechanism 1, Scheme 3).[17] The observation that lowering the catalyst loading from 5% to 0.5% increased the enantioselectivity of the KAT (compare entries 1 and 2, Table 1) is in accord with this π-allyl racemization mechanism. A second mechanistic (Scheme 5, mechanism 2) possibility relies on the formation of σ-palladium complex **24**. The aromaticity of the furan may provide the driving force to convert from the η^3-(**22**) to the η^1-complex (**24**). Rotation about the oxygen−palladium bond, followed by rehydridization to the π-allylpalladium complex, generates *ent*-**22**. This mechanistic hypothesis is supported by the observation that 1-acetyl-3-π-allylpalladium complexes undergo faster π-σ-π isomerization at the terminal carbon bearing the acetyl group.[18]

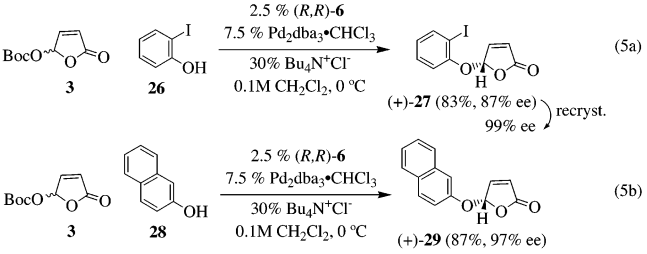
We postulated that to increase the enantioselectivity of the palladium catalyzed DYKAT, it was necessary to increase the rate of interconversion of **22** and *ent*-**22** by either of the mechanisms shown in Scheme 5. Halide ion, especially chloride, has been shown to promote the conversion η^3-allylpalladium complexes to η^1-complexes,[19] and therefore, should promote the interconversion of **22** and *ent*-**22 via** η^1-complex **24**. Indeed, addition of 30% tetrabutylammonium chloride to the reaction mixture increased the enantioselectivity of the DYKAT from 48% (Table 3, entry 2) to 75% (entry 3) ee. Slowing the rate of nucleophilic attack, by removing the cesium carbonate, further increased the enantiomeric excess of **7** to 82% (entry 4). Lowering the reaction temperature to 0 °C gave the best results, affording aryl ether **7** in 74% yield and 84% enantiomeric excess (entry 5). Changing the halide from chloride to fluoride (entry 6) or the ligand from phenylphosphine **6** to naphthylphosphine **25** (entry 7) had a deterimental effect on the enantioselectivity.

It remained unclear by which of the mechanisms in Scheme 5 π-allylpalladium complex **22** was undergoing facial interconversion. Although the addition of chloride suggests that the mechanism 2 is operating, it could also promote the Pd−Pd displacement mechanism. Addition of chloride to palladium(0) could form an anionic palladium chloride complex which would have increased nucleophilicity. To discern between the two mechanisms, the catalyst loading was increased from 0.5% (Table 4, entry 5) to 2.5% (entry 8). The increase in the concentration of palladium resulted in a decrease in the enantiomeric excess of **7** from 84% to 65%. Because an increase in palladium concentration would be expected to increase the rate of mechanism 1, this result is most consistent with mechanism 2 as the source of the facial interconversion of **22**.

Scheme 6. Retrosynthetic Analysis for the Synthesis of Aflatoxin B_1



Having established conditions to carry out the palladium catalyzed DYKAT of butenolide **3** with 4-methoxyphenol as a nucleophile, we examined two other phenols as nucleophiles (eq 5a,b). 2-Iodophenol participated equally well in the palladium catalyzed DYKAT (eq 5a), producing aryl ether **27** in 83% yield and 87% enantiomeric excess. A single recrystallization from methylene chloride: petroleum ether increased the enantiomeric excess of **27** to 99%. Butenolide **29** was prepared in 87% and 97% enantiomeric excess from the palladium catalyzed DYKAT of **3** and 2-naphthol (**28**) as shown in eq 5b. The steric bulk of 2-naphthol presumably decreases the rate of nucleophilic attack relative to equilibration and thus may be responsible for the enhanced enantioselectivity. On the other hand, an even more hindered phenol, 2,6-di-*tert*-butylphenol, did not react with butenolide **3** under the typical palladium catalyzed DYKAT.

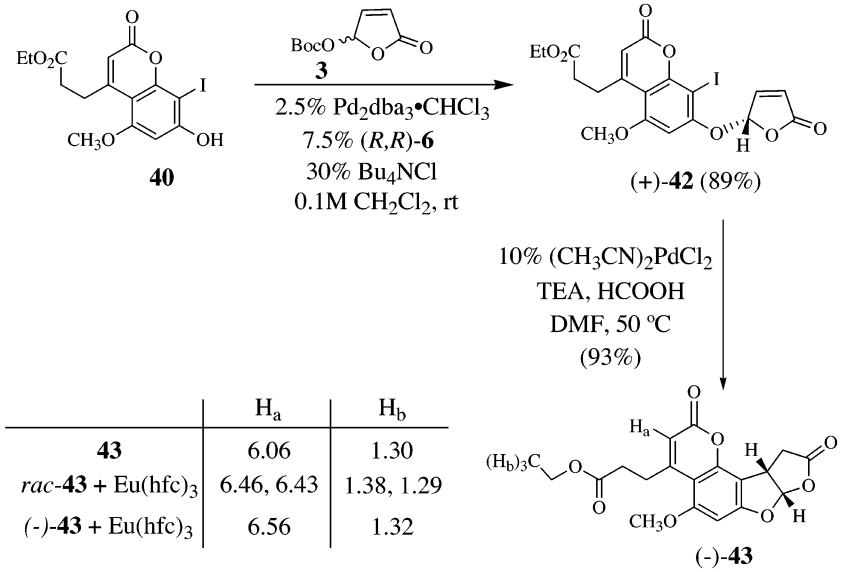


Enantioselective Total Synthesis of (−)-Aflatoxin B_1. Our retrosynthetic analysis of aflatoxin returned us to lactone **30**, which we felt could be constructed from acid **31** by a Friedel−Crafts acylation (Scheme 6). Tetracyclic acid **31** could be constructed by an intramolecular reductive Heck reaction of aryl halide **32**. Finally, the asymmetric synthesis of aryl ether **32** could be performed utilizing the palladium catalyzed DYKAT of butenolide **3** utilizing coumarin **33** as the nucleophile.

We first attempted to prepare the coumarin nucleophile (**33** in Scheme 6) by the palladium catalyzed coumarin formation.[20] Unfortunately, palladium catalyzed reaction of catechol **15** with both the ester (**34a**) and carboxylic acid (**34b**) substituted alkynoate failed to produce any of the desired coumarin (**33**). The failure of this reaction forced us to utilize alkynoate **34c**, from which the desired ester could be prepared from the ethyl

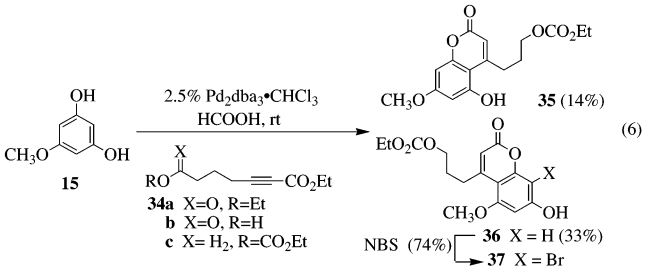
(17) For evidence of a Pd−Pd displacement mechanism see: Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.
(18) (a) Faller, J. W.; Tully, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 2676. (b) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. (c) Faller, J. W.; Thomsen, M. E. *J. Am. Chem. Soc.* **1969**, *91*, 6871.
(19) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.
(20) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305.

Scheme 7. Synthesis of the ABCD Ring System of the Aflatoxins



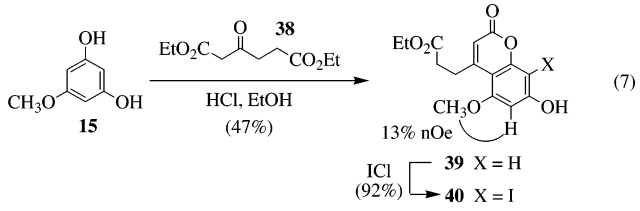
	H_a	H_b
43	6.06	1.30
rac-**43** + Eu(hfc)$_3$	6.46, 6.43	1.38, 1.29
(-)-**43** + Eu(hfc)$_3$	6.56	1.32

carbonate group by simple oxidation. Palladium catalyzed reaction of 2.5 equivs of alkynoate **34c** with catechol **15** afforded a 2.4:1 mixture (47% combined yield) of desired coumarin **36** and regioisomer **35** (eq 6). Reaction of **36** with bromine gave a mixture of **37** and the product derived from bromination of the coumarin ring. Chemoselective bromination of **36** was accomplished by treatment with *N*-bromosuccinimide (NBS) in chloroform to furnish **37** in 74% yield.



(6)

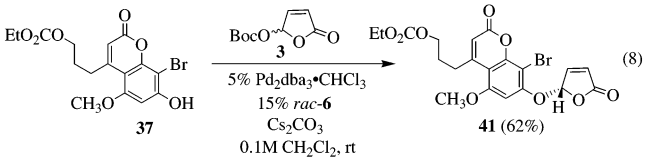
Alternatively, the desired ester substituted coumarin **40** could be prepared by a traditional Pechmann condensation (eq 7). Reaction of catechol **15** with β-ketoester **38**,[21] in the presence of hydrochloric acid, afforded a 1.4:1 mixture of regioisomeric coumarins from which **39** was isolated in 47% yield by fractional crystallization. Reaction of coumarin **39** with iodine monochloride produced aryl iodide **40** in 92% yield. The regioselectivity of the iodination was confirmed by a nOe experiment which showed a 13% enhancement of the aromatic proton when the methyl ether signal was irradiated.



(7)

(21) Wilen, S. H.; Shen, D.; Licata, J. M.; Balwin, E.; Russell, C. S. *Heterocycles* **1984**, *22*, 1747.

With the required *ortho*-halogenated phenols in hand, the palladium catalyzed reaction with butenolide **3** was examined. Palladium catalyzed reaction of 8-bromocoumarin **37** with butenolide **3** proceeded smoothly to afford aryl ether **41** in 62% yield (eq 8). Unfortunately, all attempts to affect the closure of ring B, from aryl bromide **41** were unsuccessful. Much like the attempted Heck cyclizations of aryl bromide **18** (see Table 2), all attempts at the reductive Heck cyclization of **41** resulted mainly in isolation of phenol **37**. Similarly, triethylboron initiated radical reaction of **37** also failed. Because the ABCD ring system (**31**) could not be produced from aryl bromide **37**, the enantioselectivity of the palladium catalyzed reaction used for its preparation was not investigated.

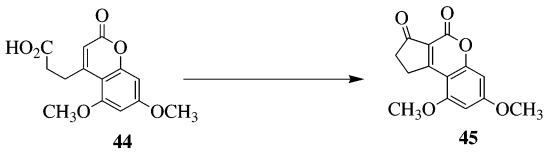


(8)

Because in our attempted Heck reaction the main competing process is ionization of the phenol, we felt that an increase in the rate of oxidative addition would allow for the Heck reaction to compete with the ionization. Therefore, we focused on aryl iodide **40** as the nucleophile in the palladium catalyzed DYKAT of butenolide **3** (Scheme 7). We were pleased to find that the sterically demanding coumarin **40** readily reacted with 1.2 equivs of butenolide **3**, under the typical conditions for the DYKAT, to produce aryl ether **42** in 89% yield. Unfortunately, at this stage, we were unable to determine the enantiomeric excess of **42** using either HPLC or ^{1}H NMR chiral shift experiments

Gratifyingly, intramolecular reductive Heck reaction of iodide **42** in the absence of phosphine ligands produced tetracyclic coumarin **43** in 93% yield (Scheme 7). The efficacy of this Heck reaction in the absence of phosphine ligands may be due to a combination of factors. As indicated by the failure of the Heck reaction of aryl bromide **41**, the use of an aryl iodide is essential. In accord with the results of Hoffmann and co-workers,[6b] the presence of the electron-withdrawing coumarin ring may also enhance the rate of the Heck reaction. At this stage, we were

Table 4. Preparation of ADE ring system by Friedel-Crafts Acylation



44 **45**

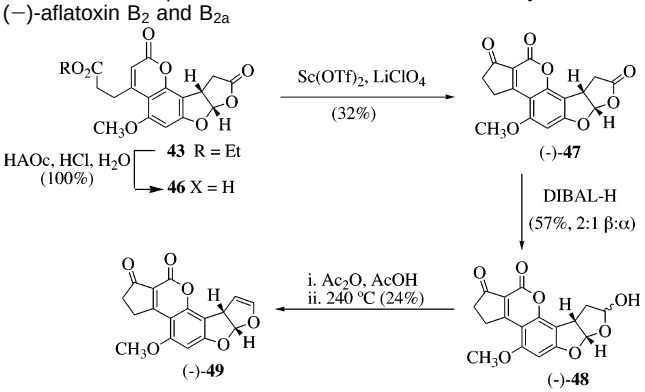
	conditions	**5.141** % yield
1	i ($COCl_2$ ii. 3eq. $AlCl_3$, CH_2Cl_2, rt	31
2	i $(COCl)_2$ ii. 1eq. $Sc(OTf)_2$, CH_2Cl_2, rt	46
3	i $(COCl)_2$ ii. 1eq. $Sc(OTf)_2$, 1 eq. HOTf, CH_2Cl_2, rt	64
4	i $(CF_3CO)_2O$ ii. 1eq. $Sc(OTf)_2$, CH_2Cl_2, 40 °C	NR
5	i $(CF_3CO)_2O$ ii. 1eq. $ZnCl_2$, HOAc, 60 °C	NR
6	HF, -78 °C to rt	36
7	1eq. $Sc(OTf)_2$, CH_3NO_2, 60 °C	NR
8	1eq. $Sc(OTf)_2$, 5eq. $LiClO_4$, CH_3NO_2, 60 °C	79

able to determine the enantiomeric excess of **43** by ^{1}H NMR chiral shift experiment. Both the enantiotopic coumarin proton (H_a, δ 6.06) and the ester proton (H_b, δ 1.30) were resolved utilizing $Eu(hfc)_3$ as the shift reagent. From the integration of the 500 MHz ^{1}H NMR signals for these protons, the enantiomeric excess of **43** was found to be >95%.

Conversion of the methyl ester analogue of **43** to aflatoxin B_1 had already been described by Büchi.[5a] Büchi used a two step sequence involving hydrolysis of the ester to the acid, followed by in situ generation of the acid chloride which was subjected to a Friedel−Crafts acylation utilizing stoichiometric aluminum trichloride. The low yield of the Friedel−Crafts acylation, presumably due to the use of stoichiometric quantities of a rather harsh Lewis acid, prompted us to investigate alternative methods to generate the ring E cylopentanone. To this end, acid **44** was prepared as a model system. A variety of conditions were examined for the Friedel−Crafts cyclization of acid **44** to cyclopentanone **45**[22] (Table 4). Utilizing Büchi's aluminum trichloride mediated reaction of the in situ generated acid chloride afforded tricyclic coumarin in 31% yield (entry 1). Switching to a milder Lewis acid, scandium(+2) triflate[23] increased the yield of **45** to 46% (entry 2). The yield of the scandium triflate mediated cyclization of the acid chloride could be improved to 64% by the addition of triflic acid (entry 3). In situ generation of the trifluoroactetate mixed anhydride of **44** followed by reaction with either scandium(+2) triflate (entry 4) or zinc(+2) chloride (entry 5) did not produce any of the cyclized product **45**. We also investigated the use of the carboxylic acid, without generation of the acid chloride, as the acylating agent. Reaction of acid **44** with neat hydrofluoric acid[24] produced coumarin **45** in 36% yield (entry 6). Scandium(+2) triflate in nitromethane failed to produce any of the desired product (entry 7). However, addition of 5 equivs of lithium perchlorate[23b] to the reaction mixture furnished cyclopentanone **45** in 79% yield (entry 8).

Having established three sets of conditions for preparation of the cyclopentanone ring, we investigated the application of these conditions to the formation of ring E of aflatoxin. Hydrolysis of ethyl ester **43** to acid **46** was accomplished in quantitative yield by reaction with hydrochloric acid/acetic acid in water (Scheme 8). Formation of the acid chloride from **46**, followed by reaction with scandium(+2) triflate and triflic acid resulted in mainly decomposition. Treatment of acid **46** with hydrofluoric acid produced only a trace of the desired product **47**. Fortunately, reaction of acid **46** with scandium(+2) triflate and lithium perchlorate in nitromethane afforded a 32% yield of pentacyclic coumarin **47**. The absolute configuration of **47** was confirmed by comparison of the optical rotation of our synthetic **47** ($[\alpha]_D = -511°$ (c = 0.6, 10:1 $CHCl_3$:methanol)) to that reported by Büchi for **47** (lit.[5a] $[\alpha]_D = -544°$ (c = 0.0145, 10:1 $CHCl_3$:methanol)) prepared from natural (−)-aflatoxin B_1. Furthermore, lactone **47** was converted into aflatoxin B_1 (**49**) by a sequence similar to that described by Büchi and co-workers. Reduction of **47** with di-*iso*-butylaluminum hydride afforded aflatoxin B_{2a} (**48**) as a 2:1 mixture of β and α anomers.[25] Conversion of **48** to aflatoxin B_1 (**49**) was carried out as described by Büchi. The ^{1}H NMR and optical rotation of our synthetic **49** matched that reported for natural aflatoxin B_1.[26]

Scheme 8. Completion of the Enantioselective Total Synthesis of (−)-aflatoxin B_2 and B_{2a}



Conclusion

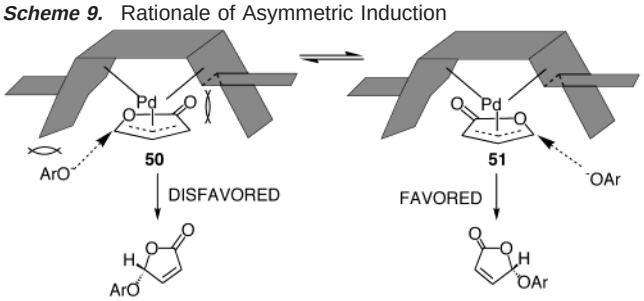
In conclusion, we have developed a new palladium catalyzed AAA for the asymmetric synthesis of 4-acyloxy-2-butenolides. Initially, a palladium catalyzed kinetic asymmetric transformation (KAT) of γ-acyloxybutenolides, using phenol nucleophiles, was developed (Table 1). For good enantioselectivity (82−90% ee) in the palladium KAT, conditions which favor nucleophilic addition to the kinetically generated π-allylpalladium complex are required.

A more efficient palladium catalyzed dynamic kinetic asymmetric transformation (DYKAT) of γ-acyloxybutenolides was also developed. Conditions in which nucleophilic attack on the equilibrating "matched" and "mismatched" π-allylpalladium complexes (a Curtin-Hammett situation) in the enantiodetermining step produce the best enantioselectivities in the DYKAT. A novel mechanism, involving an *O*-bound palladium enolate (Scheme 5), is proposed to be responsible for the equilibration of the π-allylpalladium intermediates.

The sense of the asymmetric induction can be understood from our model[27] as shown by the cartoons in Scheme 9. In the

(22) Asao, T.; Büchi, G.; Adbel-Kader, M. M.; Chang, S. B.; Wick, E. L.; Wogan, G. N. *J. Am. Chem. Soc.* **1965**, *87*, 882.
(23) (a) Kobayshi, S. *Pure Appl. Chem.* **1998**, *70*, 1019. (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 4183. (c) Kobayashi, S.; Iwamoto, S. *Tetrahedron Lett.* **1998**, *39*, 4697.
(24) For examples of HF mediated Friedel−Crafts cyclizations of carboxylic acids see: (a) Chung, Y.-S.; Kruk, H.; Barizo, O. M.; Katz, M.; Lee-Ruff, E. *J. Org. Chem.* **1987**, *52*, 1284. (b) Konieczny, M.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 2158. (c) Veeraraghavan, S.; Jostmeyer, S.; Myers, J.; Wiley Jr., J. C. *J. Org. Chem.* **1987**, *52*, 1355.
(25) Assignment of the β and α anomers was made by comparison of the ^{1}H NMR data reported for ring ABC hemiacetals, see: Bujons, J.; Sánchez-Baeza, F.; Messenguer, A. *Tetrahedron* **1994**, *25*, 7597.
(26) Asao, T.; Büchi, G.; Abdel-Kader, M. M.; Chang, S. B.; Wick, E. L.; Wogan, G. N. *J. Am. Chem. Soc.* **1963**, *85*, 1705.

Scheme 9. Rationale of Asymmetric Induction



transition state depicted by cartoon **50**, the incoming phenoxide nucleophile encounters a significant steric interaction with the front left 'wall" created by one of the aromatic rings on phosphorus. In contrast, there is significantly less steric interaction between the incoming nucleophile and the chiral ligand in transition state **51**. Additionally, steric interactions between the carbonyl group and the back right "wall" in **50** may further destabilize this transition state compared to the diastereomeric one (**51**). Thus, the more stable diastereomeric transition state (**51**) for nucleophilic addition accounts for the absolute configuration.

Utilizing the palladium catalyzed DYKAT, we have completed the first enantioselective total synthesis of (−)-aflatoxins B_{2a} (**48**) and B_1 (**49**) in a highly concise manner. Palladium catalyzed DYKAT of coumarin **40**, available in two steps from phloroglucinol monomethyl ether, and butenolide **3** gave aryl ether **43** in 89% yield. The B ring furan was formed via an intramolecular reductive Heck reaction, producing the ABCD ring system in 93% yield and >95% enantiomeric excess. After hydrolysis of ester **43**, scandium triflate mediated intramolecular Friedel−Crafts acylation installs the ring E cyclopentanone, and completes the synthesis of (−)-aflatoxin B lactone (**47**) in a total of 6 steps. The completed synthesis of (−)-aflatoxin B_{2a} requires only one more step and that of B_1 two steps from B_{2a}.

Experimental Section

2-*tert*-Butoxycarbonyloxy-5-oxo-2,5-dihydrofuran 3. Following the procedure of Gollnick and Griesbeck[12] into a solution of furfural (**1**) (110 mL, 1.2 mol) and rose bengal (400 mg, 0.39 mol) in methanol (900 mL) was bubbled oxygen gas and the pink/orange solution irradiated by a 450W Ace medium-pressure Hg lamp (quartz filter) for 8h. The solution was concentrated in vacuo to afford crude **2** (117 g, 94%) as an orange paste which was used in subsequent reactions without further purification.

A solution of crude **2** (2.50 g, 24.9 mmol) in dry THF (50 mL) and pyridine (5 mL) was treated with di-*tert*-butyl dicarbonate (6.54 g, 30.0 mmol). The resulting brown reaction mixture was stirred at room temperature for 12h, then diluted with diethyl ether (50 mL). The brown solution was washed with sodium bisulfate (2 × 25 mL), brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo to afford a brown solid. Flash chromatography eluting with 30% ethyl acetate: pentanes afforded a yellow tinged solid, which was recrystallized from methylene chloride: petroleum ether to afford **3** (3.03 g, 61%) as a white solid, mp 96−7 °C.

IR (film): 2984, 1797, 1759, 1275, 1257, 1110, 1086 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.31 (dd, J = 5.7 and 1.3 Hz, 1H), 6.85 (t, J = 1.3 Hz, 1H), 6.31 (dd, J = 5.7 and 1.3 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.5, 151.0, 149.2, 127.4, 95.9, 84.8, 27.5. Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C; 54.11; H, 6.13.

2-(2-Iodophenoxy)-5-oxo-2,5-dihydrofuran 12[28] By the KAT of 3: A test tube containing **3** (20 mg, 0.100 mmol), cesium carbonate (5 mg, 15 μmol), Pd_2dba_3•$CHCl_3$ (1 mg, 1.0 μmol), and ligand (*R,R*)-**6** (2 mg, 2.9 μmol) was evacuated and refilled three times with argon. The test tube was charged with degassed methylene chloride (0.3 mL), and the purple reaction mixture was stirred for 20 min at room temperature. The yellow reaction mixture was treated with a solution of 2-iodophenol (**11**) (10 mg, 0.045 mmol) in methylene chloride (0.2 mL) and the resulting orange reaction mixture stirred at room temperature for 16h. The resulting yellow reaction mixture was absorbed onto silica and chromatographed eluting with 10% ethyl acetate: hexanes to afford aryl ether **12** (12 mg, 88%, 86% ee) as a white solid.

By the DYKAT of 3: A test tube containing **3** (200 mg, 1.00 mmol), 2-iodophenol (**11**) (180 mg, 0.818 mmol), tetrabutylammonium chloride (70 mg, 0.241 mmol), Pd_2dba_3·$CHCl_3$ (20 mg, 0.020 mmol), and ligand (*R,R*)-**6** (40 mg, 0.058 mmol) was evacuated and refilled three times with argon. The test tube was charged with degassed methylene chloride (8 mL), and the purple reaction mixture was stirred at 0 °C. After 12 h, the reaction mixture was concentrated in vacuo and chromatographed eluting with 2:1 petroleum ether: diethyl ether to afford aryl ether **12** (205 mg, 83%, 87% ee) as a white solid. Recrystallization from methylene chloride: petroleum ether gave **12** with 99% ee, mp 81−3 °C, lit.[12c] mp 80 °C

Enantiomers separated by HPLC using Chiralpak AD column with 90:10 heptanes: 2-propanol at 1.0 mL/min. Retention times: major enantiomer (**S**) 9.11 min. and minor (**R**) 7.95 min.

$[\alpha]_D$ (87% ee) = +78.5° (c = 1.27, CH_2Cl_2). IR(film): 3104, 2981, 2930, 1792, 1761, 1574, 1472, 1363, 1276, 1229, 1159, 1089, 1014, 968, 884, 851, 810, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.82 (dd, J = 7.8 and 1.5 Hz, 1H), 7.52 (dd, J = 5.7 and 1.2 Hz, 1H), 7.37 (m, 1H), 7.33 (dd, J = 8.0 and 1.2 Hz, 1H), 6.91 (td, J = 7.6 and 1.5 Hz, 1H), 6.40 (s, 1H), 6.38 (dd, J = 5.7 and 1.1 Hz, 1H), 6.36 (t, J = 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 169.6, 155.4, 149.6, 139.6, 129.8, 125.9, 125.4, 117.5, 101.4, 87.8.

2-(2-Naphthalene-2-yloxy)-5-oxo-2,5-dihydrofuran 29. A test tube containing **3** (83 mg, 0.416 mmol), 2-naphthol (**28**) (50 mg, 0.347 mmol), tetrabutylammonium chloride (30 mg, 0.103 mmol), Pd_2dba_3·$CHCl_3$ (9 mg, 0.009 mmol), and ligand (*R,R*)-**6** (18 mg, 0.028 mmol) was evacuated and refilled three times with argon. The test tube was charged with degassed methylene chloride (3.5 mL), and the purple reaction mixture was stirred at 0 °C. After 8 h, the reaction mixture was concentrated in vacuo and chromatographed eluting with 40% diethyl ether: petroleum ether to afford aryl ether **29** (68 mg, 87%, 97% ee) as a white solid. Recrystallization from methylene chloride: petroleum ether gave **29** as white needles, mp 72−74 °C.

Enantiomers separated by HPLC using Chiralpak AD column with 90:10 heptanes: 2-propanol at 1.0 mL/min. Retention times: major enantiomer (**S**) 12.98 min. and minor (**R**) 9.98 min.

$[\alpha]_D$ (97% ee) = +336.0° (c = 1.05, CH_2Cl_2). IR (film): 3120, 3057, 1793, 1759, 1631. 1600, 1511, 1466, 1367, 1252, 1213, 1162, 1095, 1020, 968, 886, 826 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.84 (d, J = 5.7 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.52 (td, J = 7.0 and 1.2 Hz, 1H), 7.45 (m, 2H), 7.28 (dd, J = 9.0 and 2.5 Hz, 1H), 6.54 (t, J = 1.1 Hz, 1H), 6.38 (dd, J = 5.7 and 1.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 169.9, 154.1, 149.8, 134.0, 130.2, 129.8, 127.6, 127.3, 126.7, 125.2, 124.9, 118.5, 111.4, 100.7. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.15; H, 4.36.

4-Carboethoxyethyl-7-hydroxy-5-methoxycoumarin 39. A solution of resorcinol **15** (2.0 g, 14.3 mmol) in ethanol (50 mL) was saturated with hydrogen chloride gas. To the resulting yellow solution was added ketoester **38** (5.0 g, 23 mmol) and the reaction mixture stirred at room temperature. After 3 d, the yellow suspension was diluted with water (50 mL) and extracted with methylene chloride (3 × 50 mL).

(27) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(28) Wolff, S.; Hoffman, H. M. R. *Synthesis* **1988**, 760.

The organic extracts were dried ($MgSO_4$) and concentrated to afford a yellow solid. Recrystallization from methylene chloride: petroleum ether afforded coumarin **39** (1.98 g, 47%) as a tan solid, mp 182−183 °C.

IR (film): 3095, 1742, 1680, 1601, 1553m 1466, 1349, 1285, 1182, 1160, 1118 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 9.80 (br s, 1H), 6.35 (d, J = 2.2 Hz, 1H), 6.21 (d, J = 2.2 Hz, 1H), 5.81 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.10 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 7.6 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): 172.1, 161.3, 161.0, 158.3, 156.8, 156.0, 109.7, 102.3, 96.3, 95.7, 60.3, 55.6, 33.6, 31.4, 13.9. Anal. Calcd for $C_{15}H_{16}O_8$: C, 61.63; H, 5.52. Found: C, 61.32; H, 5.57.

4-Carboethoxyethyl)-7-hydroxy-8-iodo-5-methoxycoumarin 40. To a solution of coumarin **39** (1.70 g, 5.82 mmol) in methylene chloride (30 mL) was added portionwise iodine monochloride (1.03 g, 6.40 mmol) and the resulting purple solution stirred at room temperature. After 30 min, the reaction mixture, which had become yellow, was carefully diluted with petroleum ether (20 mL). The precipitated solid was collected by suction filtration, washed with 1:1 methylene chloride: petroleum ether to afford iodide **40** (2.24 g, 92%) as a white solid, mp 204−205 °C.

IR (film): 3185, 1732, 1697, 1583, 1541, 1448, 1341, 1189, 1120, 833, 804 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 10.20 (br s, 1H), 6.47 (s, 1H), 5.89 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.14 (t, J = 7.6 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): 172.1, 160.6, 160.1, 158.5, 155.7, 155.5, 110.6, 103.3, 95.0, 93.5, 60.4, 55.6, 33.7, 31.4, 14.0. HRMS Calcd for $C_{15}H_{15}IO_6$: 417.9913. Found: 417.417.9918.

4−3-Carboethoxyethyl-8-iodo-5-methoxy-7-(5-oxo-2,5-dihydrofuran-2-yloxy)coumarin 42. A round-bottom flask containing coumarin **40** (200 mg, 0.431 mmol), **3** (103 mg, 0.517 mmol), Pd_2dba_3·$CHCl_3$ (11 mg, 0.011 mmol), ligand (*R*,*R*)-**6** (22 mg, 0.032 mmol) and tetrabutylammonium chloride (50 mg, 0.129 mmol) was subjected to three cycles of evacuation followed by filling with argon. To the purged flask was added freshly distilled methylene chloride (4 mL) and the resulting purple solution, which slowly becomes orange/brown in color, was stirred at room temperature. After 12 h, the resulting brown reaction mixture was concentrated in vacuo and chromatographed eluting with diethyl ether to afford aryl ether **42** (212 mg, 89%) as a slightly yellow solid. Recrystallization from chloroform: petroleum ether afforded **42** as a white solid, mp 198−199 °C.

$[\alpha]_D$= +71.9° (c = 0.77, CH_2Cl_2). IR (film): 3107, 2981, 1795, 1729, 1587, 1462, 1339, 1213, 1160, 1117, 1040, 1006, 881 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.59 (dd, J = 5.7 and 1.5 Hz, 1H), 6.84 (s, 1H), 6.45 (d, J = 5.7 Hz, 1H), 6.44 (d, J = 1.5 Hz, 1H), 6.15 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.00 (s, 3H), 3.29 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 172.1, 169.2, 159.4, 159.0, 158.7, 155.4, 155.1, 149.3, 125.7, 113.6, 107.1, 101.1, 97.0, 68.9, 60.8, 56.4, 33.7, 31.5, 14.2. Anal. Calcd for $C_{19}H_{17}IO_8$: C, 45.62; H, 3.43. Found: C, 45.47; H, 3.68.

2,3,3a,8a-Tetrahydro-2-oxo-4-hydroxy-6-methoxy-β-(2′-carboethoxyethyl)-5-furo[2,3-b]benzofuranacrylic acid δ-lactone 43. To an orange suspension of aryl iodide **42** (100 mg, 0.20 mmol) and bis-(acetonitrile)palladium(II) chloride (5 mg, 0.019 mmol) in DMF (2 mL) under argon, was added triethylamine (24 μL, 18.3 mmol) and the dark orange solution placed in a 60 °C oil bath. To the reaction mixture was added a DMF (1 mL) solution of triethylamine (53 μL, 40.8 mmol) and formic acid (15 μL, 18.4 mmol), and the resulting orange solution, which slowly became yellow, was heated for 1 h. The reaction mixture was taken into diethyl ether (50 mL) extracted with 1N hydrochloric acid (25 mL), 10% sodium bicarbonate (25 mL), brine (25 mL), dried ($MgSO_4$) and filtered. Slow addition of petroleum ether resulted in the crystallization of **43** (70 mg, 93%) as a white solid, mp 191−192 °C.

$[\alpha]_D$= −433.1° (c = 0.41, $CHCl_3$). IR (film): 2950, 1798, 1729, 1629, 1608, 1486, 1436, 1372, 1200, 1156, 1112, 986, 957 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 6.65 (d, J = 6.2 Hz, 1H), 6.46 (s, 1H), 6.06 (s, 1H), 4.40 (ddd, J = 9.5, 6.2 and 2.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.24 (m, 2H), 3.15 (dd, J = 18.7 and 9.5 Hz, 1H), 3.02 (dd, J = 18.7 and 2.2 Hz, 1H), 2.62 (t, J = 7.7 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 173.3, 172.2, 161.1, 160.2, 159.7, 156.4, 152.5, 111.5, 108.6, 105.8, 105.1, 91.1, 60.8, 56.4, 40.5, 33.8, 32.8, 31.9, 14.3. Anal. Calcd for $C_{19}H_{18}O_8$: C, 61.16; H, 4.84. Found: C, 61.16; H, 5.00.

Aflatoxin B lactone 47. A solution of ester **43** (25 mg, 0.0067 mmol) in acetic acid (1 mL), water (1 mL) and concentrated hydrochloric acid (0.5 mL) was stirred at room temperature. After 2 days the solvent was removed in vacuo to afford the acid **46** (23 mg, 100%) as a white solid used in subsequent reactions without further purification (judged to be >95:5 **46**:**43** by 500 MHz, ^1H NMR).

^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 6.64 (dd, J = 6.0 and 0.9 Hz, 1H), 6.44 (s, 1H), 6.07 (s, 1H), 4.40 (ddd, J = 9.5, 6.2 and 2.2 Hz, 1H), 3.92 (s, 3H), 3.24 (m, 2H), 3.15 (dd, J = 18.7 and 9.5 Hz, 1H), 3.01 (dd, J = 18.7 and 2.2 Hz, 1H), 2.61 (m, 2H).

A solution of acid **46** (23 mg, 0.066 mmol), scandium trifluoromethanesulfonate (33 mg, 0.061 mmol) and lithium perchlorate (70 mg, 0.066 mmol) in dry nitromethane (0.7 mL) was heated at 60 °C for 4 h. The resulting brown solution was concentrated and chromatographed eluting with 1−2.5% methanol: methylene chloride to afford **47 (**7 mg, 32%) as a white solid, mp > 350 °C.

$[\alpha]_D$= −511° (c = 0.6, 10:1 $CHCl_3$: methanol), lit.[25] $[\alpha]_D$= −544° (c = 0.0145, 10:1 $CHCl_3$:methanol). IR (film): 2922, 2850, 1757, 1686, 1628, 1601, 1556, 1483, 1442, 1361, 1138, 1061, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 6.60 (d, J = 6.2 Hz, 1H), 6.40 (s, 1H), 4.31 (ddd, J = 9.3, 6.2. and 2.2 Hz, 1H), 3.88 (s, 3H), 3.34 (m, 2H), 3.06 (dd, J = 18.7 and 9.3 Hz, 1H), 2.85 (dd, J = 18.7 and 2.2 Hz, 1H), 2.55 (m, 2H). HRMS Calcd for $C_{17}H_{12}O_7$: 328.0583. Found 328.0582.

Aflatoxin B_{2a} 48. To solution of lactone **47** (7 mg, 0.021 mmol) in dry methylene chloride (0.5 mL), at −78 °C, was added 1.0M di-*iso*-butylaluminum hydride (50 mL, 0.05 mmol). After 1h, at −78 °C, the solution was treated sequentially with ethyl acetate (2 mL) and 2M Rochelle's salt (2 mL). After warming to room temperature the layers were separated, and the aqueous layer washed with ethyl acetate (3 × 5 mL), dried ($MgSO_4$) and concentrated in vacuo. Falsh chromatography eluting with 5% methanol: methylene chloride afforded **48 (**4 mg, 57%) as a white solid, mp 198−201 °C, lit.[29] mp 217 °C.

Characterized as a 2:1 mixture of β:α anomers. $[\alpha]_D$ = −428° (c = 0.4, 10:1 $CHCl_3$: methanol). IR (film): 3407. 2921, 2850, 1759, 1614, 1591, 1554, 1439, 1380, 1210, 1139, 1056, 828 cm^{-1}.

β anomer: ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 6.38 (d, J = 6.2 Hz, 1H), 6.19 (s, 1H), 5.60 (d, J = 5.0 Hz, 1H), 3.98 (dd, J = 8.2 and 6.2 Hz, 1H), 3.79 (s, 3H), 3.27 (t, J = 5.5 Hz, 2H), 2.47 (t, J = 5.5 Hz, 2H), 2.24 (d, J = 13.4 Hz, 1H), 2.18 (ddd, J = 13.4, 8.2 and 5.0 Hz, 1H).

α anomer: ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): 6.35 (d, J = 6.0 Hz, 1H), 6.21 (s, 1H), 5.34 (dd, J = 7.0 and Hz, 1H), 4.03 (ddd, J = 8.8, 6.0 and 2.0 Hz, 1H), 3.81 (s, 3H), 3.24 (t, J = 5.0 Hz, 2H), 2.48 (t, J = 5.0 Hz, 2H), 2.35 (ddd, J = 13.1, 4.4 and 2.0 Hz, 1H), 2.06 (ddd, J = 13.1, 8.8 and 7.0 Hz, 1H).

Aflatoxin B_1 49. A solution of aflatoxin B_{2a} (**48)** (4 mg, 0.012 mmol) in acetic acid (0.5 mL) was treated with acetic anhydride (0.1 mL) and the resulting clear solution was stirred at room temperature for 20 h. The solvents were removed in vacuo and the resulting pink solid dissolved in toluene (0.1 mL). The solution was heated at 240 °C in a small sealed tube for 15 min. The resulting brown solution was applied to a preparative TLC plate which was eluted with 5% methanol: methylene chloride to afford aflatoxin B_1 (**49**) (0.9 mg, 24%) as a white solid, mp 255−8 °C, lit.[25] mp 268−9 °C.

$[\alpha]_D$ = −549° (c = 0.09, $CHCl_3$), lit.[25] $[\alpha]_D$ = −562° (c = 0.115, $CHCl_3$). IR (film): 2948, 1758, 1688, 1630, 1595, 1555, 1484, 1441,

(29) Dutton, M. F.; Heathcote, J. G. *Chem. Ind.* **1968**, 418.

1375, 1304, 1230, 1202, 1130, 1070, 981, 929, 827, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 6.84 (d, $J = 7.0$ Hz, 1H), 6.49 (dd, $J = 2.7$ and 2.2 Hz, 1H), 6.45 (s, 1H), 5.51 (dd, $J = 2.7$ and 2.2 Hz, 1H), 4.80 (ddd, $J = 7.0$ and 2.7 and 2.2 Hz, 1H), 3.97 (s, 3H), 2.85 (m, 2H), 2.67 (t, $J = 5.4$ Hz, 2H).

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Supporting Information Available: Experimental procedures for the preparation of **4**, **7**, **10**, **14**, **17**, **18**, **20a**, **20b**, **35**−**37**, **41**, and **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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