



Advances in the Total Synthesis of Aflatoxins

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Abstract: Aflatoxins, which are produced by *Aspergillus flavus*, *Aspergillus nomius*, and *Aspergillus parasiticus*, are a group of pentacyclic natural products with difuran and coumarin skeletons. They mainly include aflatoxin B₁, B₂, G₁, G₂, M₁, and M₂. Biologically, aflatoxins are of concern to human health as they can be present as contaminants in food products. The unique skeletons of aflatoxins and their risk to human health have led to the publication of nine remarkable total syntheses (including three asymmetric syntheses) and ten formal total syntheses (including four asymmetric formal syntheses) of aflatoxins in the past 55 years. To better understand the mechanism of the biological activity of aflatoxins and their presence in samples from the food industry, this review summarizes progress in the total synthesis of aflatoxins.

Keywords: aflatoxins, natural products, contaminants, total syntheses, formal syntheses

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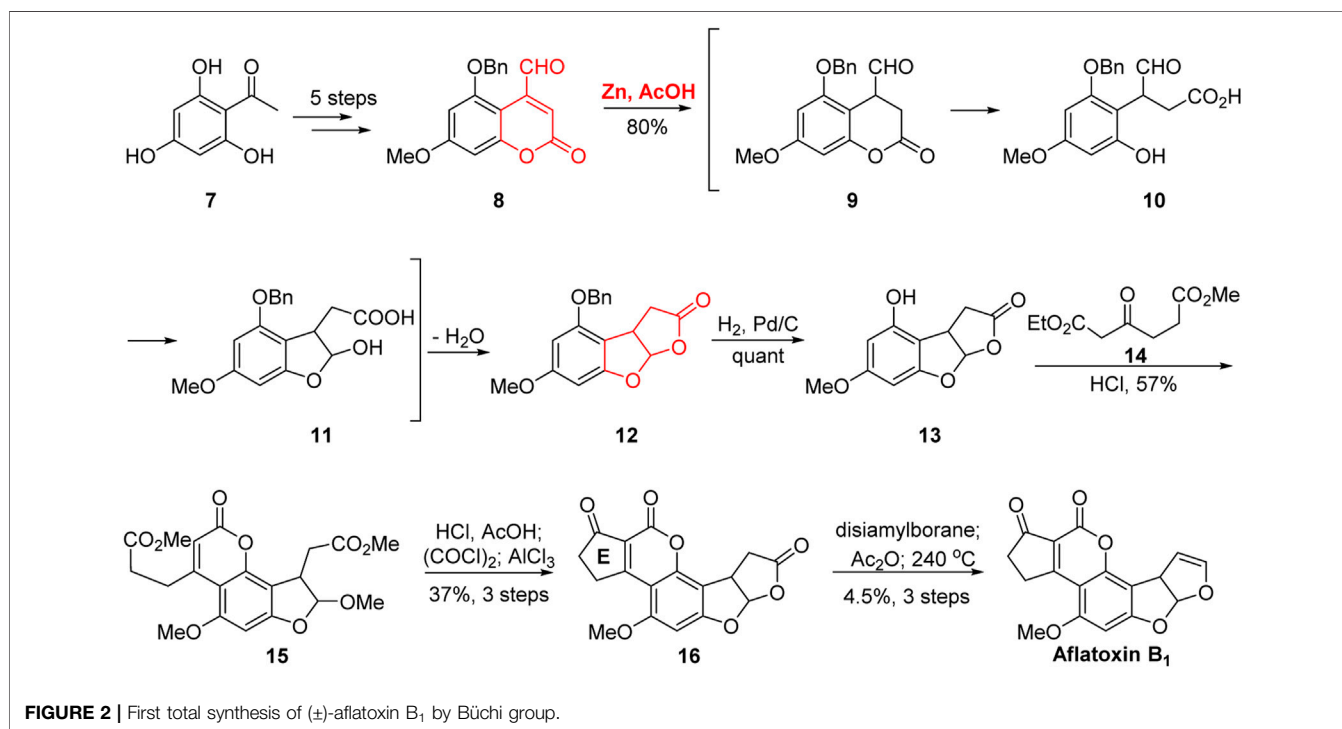
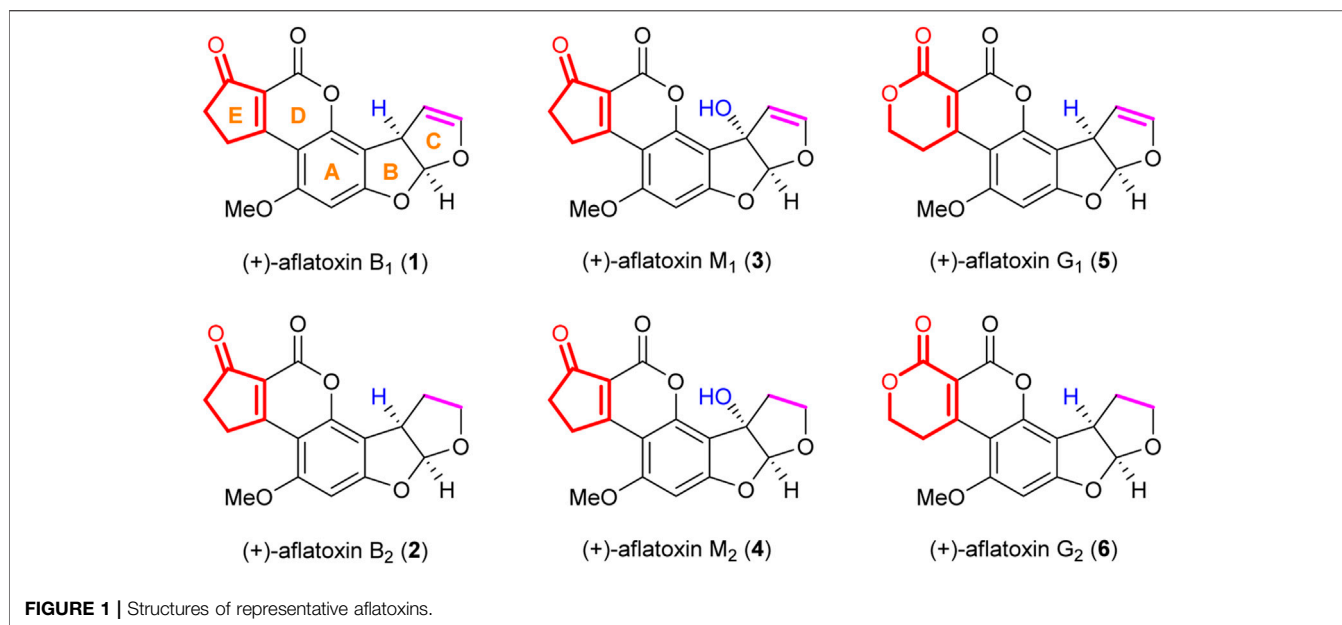
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1 INTRODUCTION

Aflatoxins (**Figure 1**) are a group of potent hepatocarcinogenic polyketide natural products produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* (Groopman et al., 2008; Bräse et al., 2009; Wu, 2014). Aflatoxin B₁ (**1**) and G₁ (**5**) were first isolated together with aflatoxin B₂ (**2**) and G₂ (**6**) in 1963 (Hartley et al., 1963), and their structures were revealed in 1963 (G₁ and B₁) (Asao et al., 1963) and 1965 (G₂ and B₂) (Asao et al., 1965) by the group of Büchi. The absolute stereochemistry of the above four aflatoxins (G₁, B₁, G₂, and B₂) was determined by chemical degradation by Büchi's group (Brechtbühler-Bader et al., 1967). Aflatoxin M₁ (**3**) and M₂ (**4**) are hydroxylated metabolites of aflatoxin B₁ and B₂ (Bianco et al., 2012; Lee et al., 2017). Biologically, aflatoxins present a significant risk to human health as they can be present as contaminants in food products (Roze et al., 2013; Bashiry et al., 2021; Ismail et al., 2021; Mollayusefian et al., 2021). Aflatoxins are classified as hepatocarcinogens; however, their effects on tissues other than the liver are mainly unclear (Wang et al., 2015; Schrenk et al., 2020). Thus, there is a need to obtain analytical samples from the food industry and understand the mechanism underlying the biological activity of aflatoxins.

Given the broad public health implications of aflatoxins, considerable progress has been made in the chemical synthesis of aflatoxins since the first synthesis of racemic aflatoxins by the groups of Büchi and Roberts in the 1960s (Büchi et al., 1966). The mechanisms of the biological activities of many complex natural products, including aflatoxins, remain unknown due to the impracticality of isolating the products from their natural sources; the only alternative to obtaining the natural products is practical total synthesis. Thus, to better understand the effects of aflatoxins, this article reviews important developments in the organic total synthesis of aflatoxins during the past 55 years.



2 TOTAL SYNTHESIS OF RACEMIC AFLATOXINS

2.1 First Total Synthesis of (±)-Aflatoxin B₁ by Büchi Group

The Büchi group has made outstanding contributions to the chemical total synthesis of aflatoxins. This group has completed several total syntheses of challenging molecules in the aflatoxin

family. These syntheses are characterized by Pechmann condensation and cascade reduction rearrangement.

As early as 1966, Büchi's group (Büchi et al., 1966; Büchi et al., 1967) completed the first total synthesis of aflatoxin B₁, as shown in Figure 2. The aldehyde **8** was obtained from acetyl benzene **7** through five steps: non-selective acylation, methylation, deacylation, selective benzylation, veticienylation, and allyl oxidation. In the presence of Zn/AcOH, the tricyclic skeleton

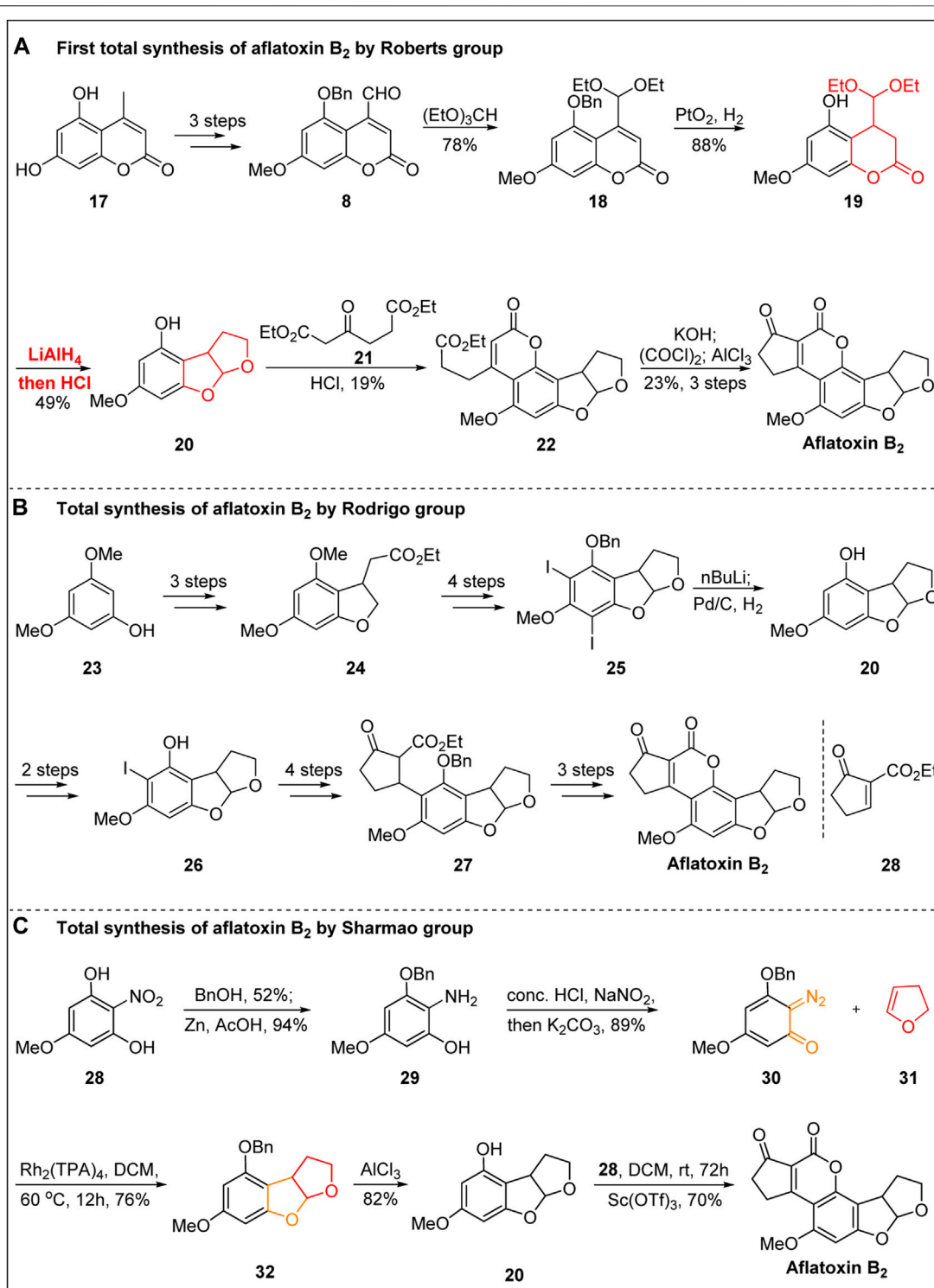


FIGURE 3 | Total synthesis of (±)-aflatoxin B₂.

12 was efficiently constructed. The cascade reaction proceeded in three steps: 1) the reduction of the double bond of coumarin **8** in the presence of Zn/AcOH; 2) the ring opening of the lactone

under the action of glacial acetic acid; and 3) the formation of a hemiacetal between the free phenol and aldehyde groups. The construction of the tricyclic framework was then completed via

esterification reaction followed by the removal of the benzyl protecting group to realize the tricyclic intermediate **13**.

Next, in the presence of hydrochloric acid in methanol, the D-ring was constructed via Pechmann condensation reaction with the β -keto ester **14**. Notably, the C-ring was opened in the presence of hydrochloric acid in methanol. Subsequently, under the action of hydrochloric acid and acetic acid, the two ester groups underwent acetal methyl hydrolysis, leading to the re-cyclization of the C-ring. After the activation of the carboxyl group, the E-ring **16** was constructed via Friedel–Crafts reaction catalyzed by AlCl_3 . Aflatoxin B_1 was synthesized by the selective reduction of the C-ring, acylation of the hemiacetal hydroxyl, and pyrolysis at 240°C . The first total synthesis of aflatoxin B_1 was completed in 13 steps with a 0.9% total yield.

2.2 Total Synthesis of (\pm)-Aflatoxin B_2

Aflatoxin B_1 also attracted the attention of Roberts' group because of its unique chemical structure, although Büchi's group was first to report the total synthesis of aflatoxin B_1 . Roberts' group (Roberts et al., 1968) then switched their focus to the total synthesis of aflatoxin B_2 . In 1967, the total synthesis of aflatoxin B_2 in 10 steps was reported for the first time, as shown in **Figure 3A**.

Using the same strategy reported by Büchi's group, starting from the coumarin **17**, the coumarin intermediate **8** containing an aldehyde group was obtained by selective methylation, benzylation, and allyl oxidation under the action of SeO_2 . After the aldehyde group was protected, the benzyl protecting group was removed, and the double bond was hydrogenated under the action of Adam's catalyst. Subsequently, under the action of LiAlH_4 , the ester group was reduced to an alcohol, and the aldehyde group was released in the presence of hydrochloric acid. The intramolecular acetal was spontaneously generated, and the synthesis of **20** was achieved. The first synthesis of aflatoxin B_2 was then achieved by Pechmann condensation and Friedel–Crafts acylation using the same strategy reported by Büchi's group.

In 1988, Rodrigo's group (Weeratunga et al., 1988) started to the total synthesis of (\pm)-aflatoxin B_2 starting from 3,5-dimethoxyphenol **23** and realized the construction of the B-ring through three steps: iodine substitution, alkylation, and intramolecular addition. The C-ring skeleton was then realized by reduction, selective demethylation, iodination, benzyl protection, and cyclization. After the deiodination and debenzyl reaction, the intermediate **20** was synthesized in 4% total yield.

In 1990, Rodrigo's group (Horne et al., 1990) reported the second total synthesis of aflatoxin B_2 after two years of trying and failing (**Figure 3B**). From the advanced intermediate **20**, the key precursor **26** was obtained through diiodization, selective deiodization, benzyl protection of phenolic OH, lithium halide exchange, and transfer metallization. The second synthesis of aflatoxin B_2 was then completed via the 1,4-addition of unsaturated cyclopentanone **28**, removal of the benzyl protective group, hydrolysis of the ester group under acidic conditions, spontaneous esterification, and DDQ oxidation. The total yield of aflatoxin B_2 in the above nine linear steps was 2.5%.

In 2021, an efficient approach for the total synthesis of aflatoxin B_2 was described by Sharmao's group (Paymode and Sharma, 2021) (**Figure 3C**). The key step involved in this synthesis is the Rh-catalyzed [3 + 2]-annulation of ortho-diazoquinone with enol ether. The key diazoquinone precursor **30** was obtained after mono-benylation, the reduction of the nitro group, and diazotization. The key Rh-catalyzed [3 + 2]-annulation of diazoquinone **30** with enol ether **31** was then carried out in the presence of $\text{Rh}_2(\text{OAc})_4$ in DCM, resulting in the annulation product **32**. The advanced intermediate **20** was then obtained after deprotecting the benzyl group using AlCl_3 . Finally, in the presence of the Lewis acid $\text{Sc}(\text{OTf})_3$ in DCM, as reported by Zu's group (Wang and Zu, 2019), the total synthesis of aflatoxin B_2 was completed via Pechmann-type annulation and aerobic oxidation.

2.3 First Total Synthesis of (\pm)-Aflatoxin M_1 by Büchi Group

In 1969, Büchi's group (Büchi and Weinreb, 1969) reported the first chemical total synthesis of aflatoxin M_1 , as shown in **Figure 4**. Based on the structural characteristic of aflatoxin M_1 , the dihydroxybenzofuranone **37** with a B-ring structure was used as the starting material, which created the conditions for the introduction of hydroxyl group and avoided the problem of constructing the B-ring. The hydroxyl-protected benzo furanone **38** was obtained after dimethylation, selective demethylation, and benzylation. The aldehyde **40** was then obtained via bromination (α -carbonyl group), substitution of benzyl alcohol, addition of allyl magnesium bromide to the ketone carbonyl group, and the oxidative fracturing of the double bond using osmium tetroxide. Two benzyl protection groups were removed by hydrogenation followed by the acylation of the phenol and hemiacetal hydroxyl groups and high-temperature pyrolysis (450°C), resulting in the construction of the C-ring double bond.

The free phenolic hydroxyl group in the A-ring was released via hydrolysis in the presence of weak base. The free phenolic compound **42** was then reacted with chlorinated unsaturated cyclopentanone **36** under the action of ZnCO_3 to efficiently construct a D,E-bicyclic compound. The specific reaction process was as follows. First, under the catalysis of Zn ion, the 1,4-addition reaction took place smoothly between the phenolic OH group in the ortho-position and the unsaturated carbonyl substrate **36**. Next, the chloride anion as the leaving group left to form the unsaturated carbonyl intermediate. Finally, under the action of ZnCO_3 , the phenolic OH group underwent transesterification to produce ethyl ester, thereby completing the first total synthesis of aflatoxin M_1 . This procedure represents a new solution for the synthesis of aflatoxins.

2.4 First Total Synthesis of (\pm)-Aflatoxin G_1 by Büchi Group

In 1971, Büchi's group (Büchi and Weinreb, 1971) optimized the synthesis of aflatoxin B_1 and completed the first total synthesis of

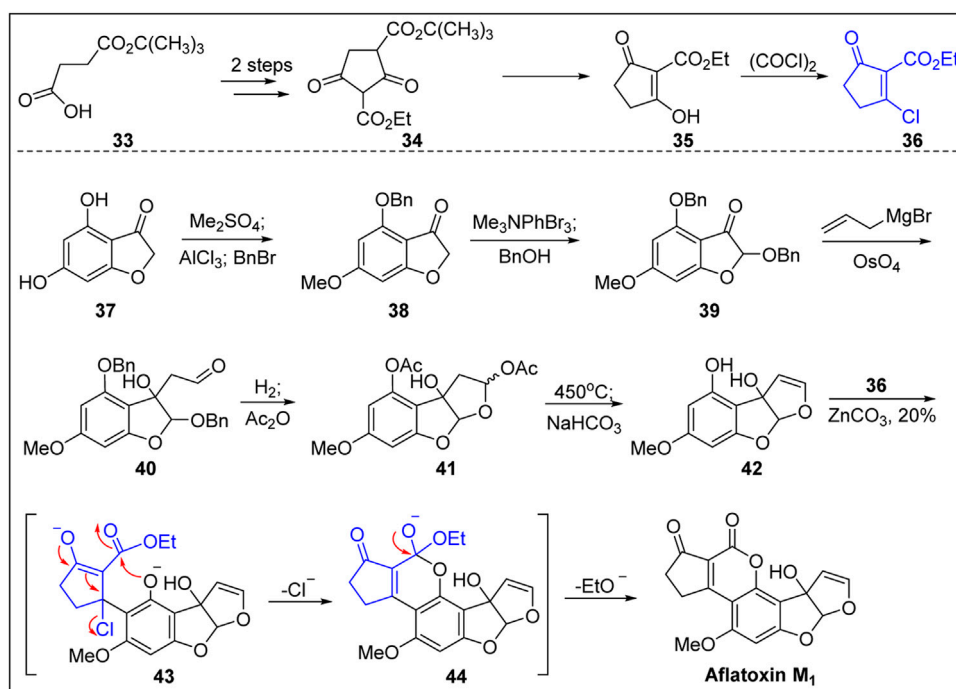


FIGURE 4 | First total synthesis of (±)-aflatoxin M_1 by Büchi group.

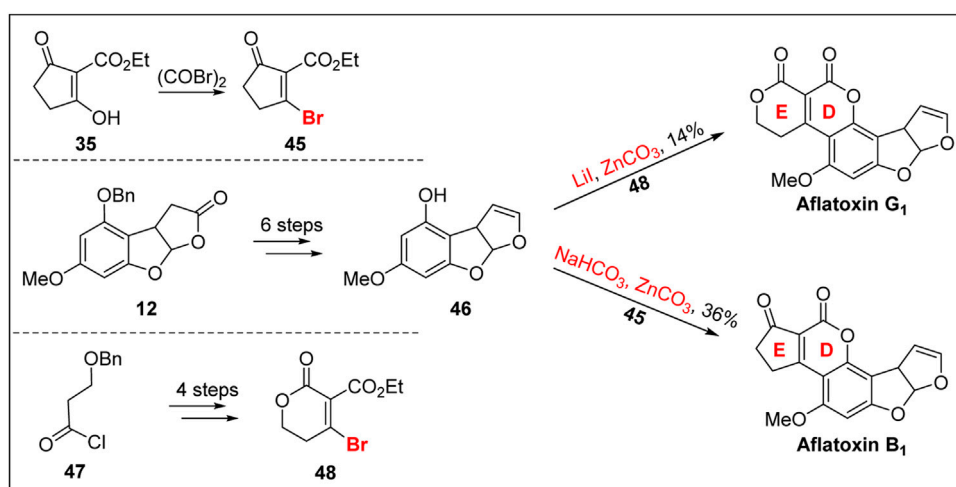


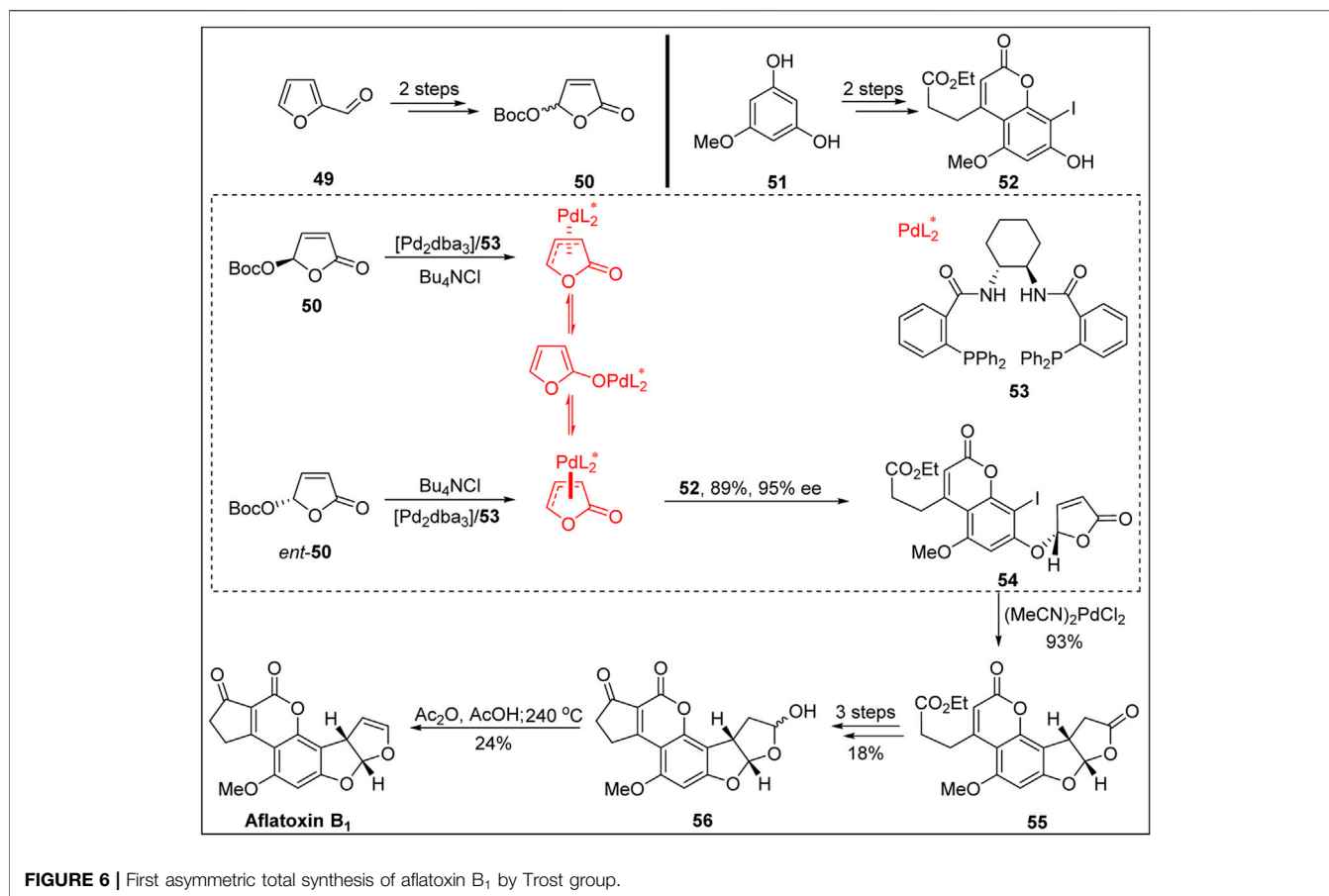
FIGURE 5 | First total synthesis of (±)-aflatoxin G_1 by Büchi group.

aflatoxin G_1 via a sequence of 1,4-addition, elimination, and transesterification reactions, as shown in **Figure 5**.

The synthesis of the advanced intermediate **46** was carried out from intermediate **12** through six steps: DIBAL-H reduction, acylation, hydrogenation of the benzyl group, acylation of the phenolic OH group, pyrolysis at high temperature (400°C), and deacylation. Finally, using the more active bromo-unsaturated cyclopentanone **45**, the D,E-bicyclic compound was formed in one step under reflux

with $ZnCO_3$ (130 equiv.). This method achieved the second-generation synthesis of aflatoxin B1 and provided an important reference for Corey's group to synthesize aflatoxin B₂.

In addition, Büchi's group reported the bromo-unsaturated cyclopentanone **45** to the bromo-unsaturated caprolactone **48**. Based on this strategy, Büchi's group achieved the chemical total synthesis of aflatoxin G_2 for the first time, although the operation is complicated, and the yield was only 14%. This marks an



important breakthrough in the synthesis of the G class of aflatoxins.

3 ASYMMETRIC TOTAL OF AFLATOXINS

3.1 First Asymmetric Total Synthesis of Aflatoxin B₁ by Trost Group

In 2003, Trost's group (Trost and Toste, 2003) achieved the first chemical synthesis of aflatoxin B₁ with high enantioselectivity via Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT), as shown in **Figure 6**.

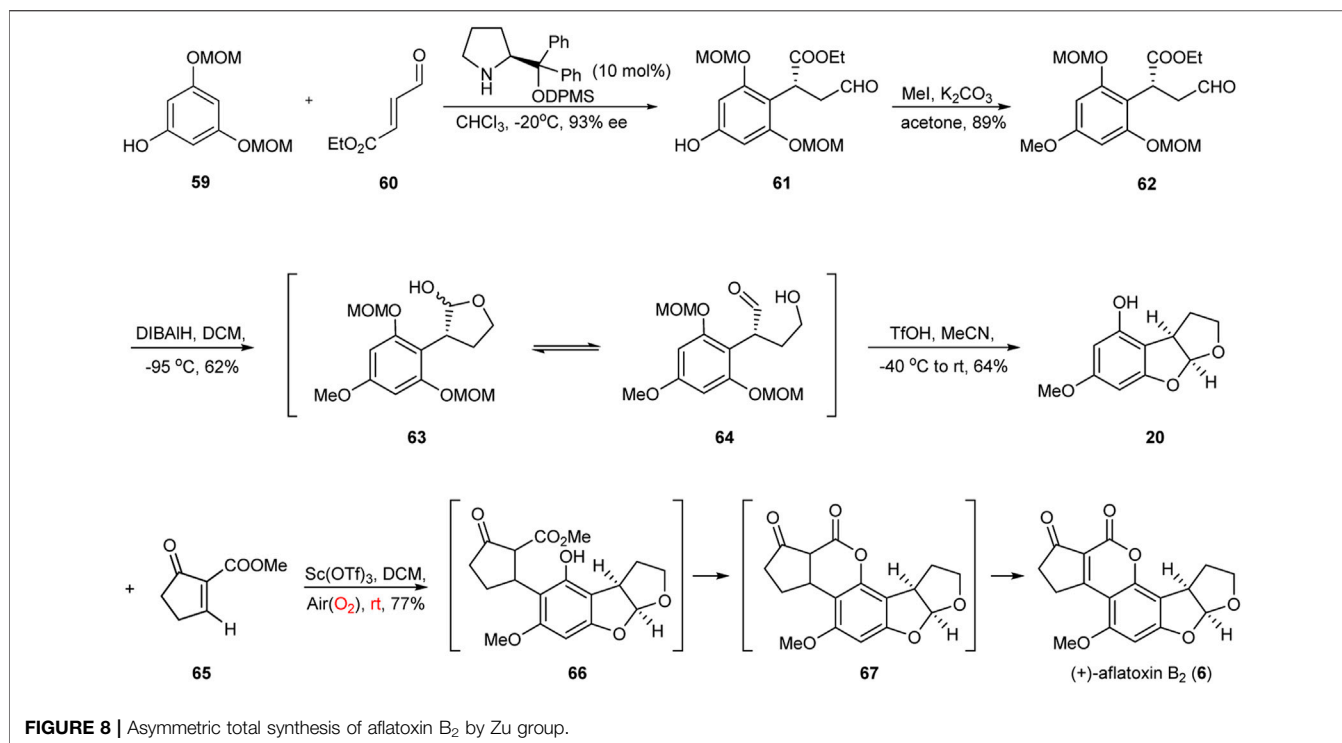
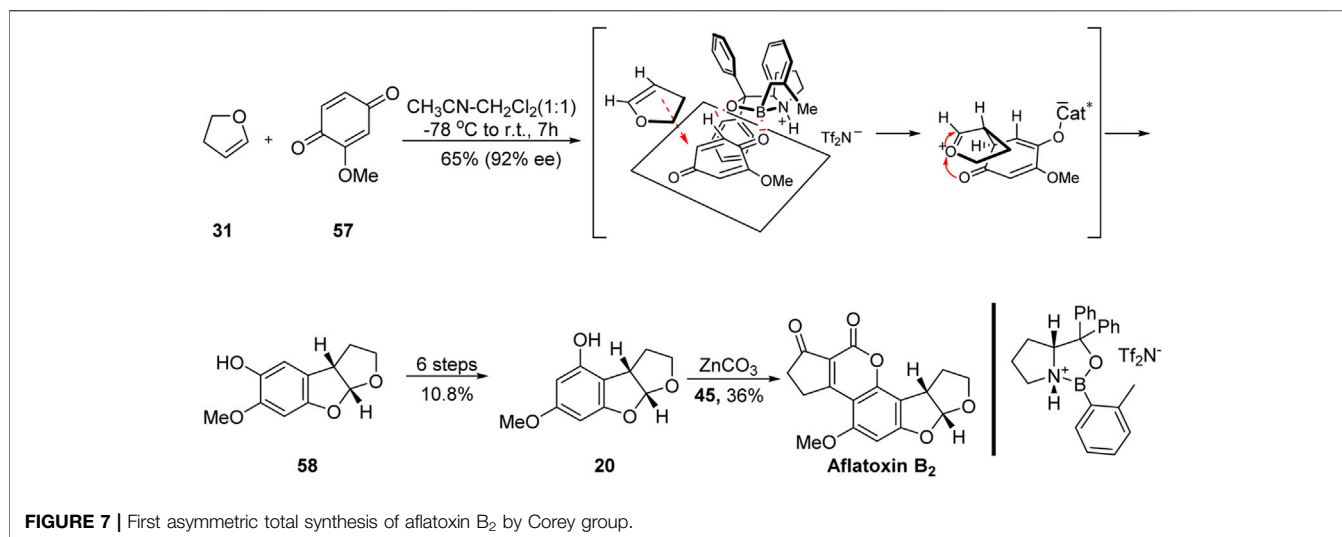
Based on the work of the Büchi and Roberts groups, the coumarin precursor was constructed via Pechmann reaction from 5-methoxy-*m*-catechol **51** and β -keto ester. The key precursor **52** was then obtained via regionally selective iodination in the presence of ICl. Next, Trost's group used their previously developed method (namely, the dynamic asymmetric transformation reaction of iodide and lactone under palladium catalysis) to construct the chiral center of the B-ring. The coupling product, which was obtained in high yield and with an excellent *ee* value, was subjected to intramolecular reduction via Heck reaction under standard conditions. The chiral center of the BC-ring was constructed

with a high *ee* value, and the coumarin product **55** with an ABCD four-ring skeleton was obtained. In a later work, the Büchi group achieved the construction of the E-ring through a related transformation and then completed the chiral synthesis of aflatoxin B_{2a} (**56**) via the selective reduction of the C-ring. Finally, aflatoxin B₁ was synthesized via the acylation of the hemiacetal hydroxyl group followed by pyrolysis at 240 °C. The total yield of aflatoxin B₁ in nine linear steps was 1.6%.

3.2 First Asymmetric Total Synthesis of Aflatoxin B₂ by Corey Group

In 2005, inspired by the excellent work of the Büchi and Noland groups (Büchi and Weinreb, 1971; Noland and Kedrowski, 2000), Corey's group (Zhou and Corey, 2005) reported the first asymmetric synthesis of aflatoxin B₂ based on the use of several advanced intermediates, as shown in **Figure 7**. The key intermediate **58** was obtained with high efficiency from dihydrofuran **31** and 1,4-benzoquinone **57** based on a highly enantioselective [3 + 2] cycloaddition catalyzed by an organoboron reagent. The highly efficient formation of the ABC ring system was achieved in only one step.

It should be noted that the key precursor **58** obtained using this method was not a good match for the A-ring of aflatoxin B₂.



The authors then followed the synthetic strategy of Noland's group (Noland and Kedrowski, 2000) (that is, Friedel–Crafts acylation, hydroxyl protection, 1,2-addition, DMP oxidation, oxygen insertion, saponification, and reduction) to obtain the advanced precursor **20**. Subsequently, they synthesized the Dering of aflatoxin B₂ using the reaction conditions employed by Büchi's group (Büchi and Weinreb, 1971). The first total synthesis of (+)-aflatoxin B₂ was achieved in 2.5% yield through eight linear steps.

3.3 Asymmetric Total Synthesis of Aflatoxin B₂ by Zu Group

In recent years, green and facile single-pot reactions have received considerable attention in the field of chemistry because they can give rise to complex structures in few synthetic steps and with simple starting materials (Newhouse et al., 2009; Trost, 1991; István T. Horváth and Anastas, 2007; Wender et al., 2008; Hayashi, 2016). In 2019, an efficient Sc(OTf)₃-promoted green and facile single-pot

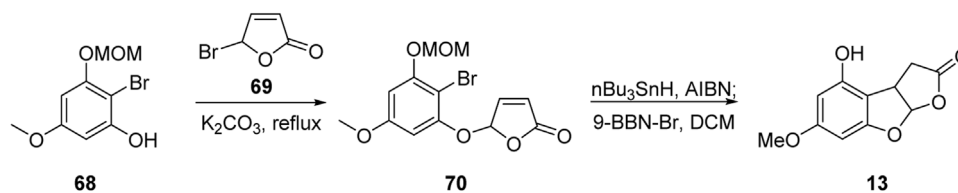


FIGURE 9 | Formal total synthesis of aflatoxin B₁ by Snieckus group.

reaction involving 1,4-addition, intramolecular lactonization, and spontaneous aerobic oxidation was developed by Zu's group (Wang and Zu, 2019) to synthesize the DE-ring system of aflatoxin B₂ (Figure 8).

The synthesis started from the known phloroglucinol derivative 59 and the α,β -unsaturated aldehyde 60. The enantioselective Friedel–Crafts alkylation of 59 with 60 provided the alkylation product 61, which was methylated with MeI in acetone to provide intermediate 62. It was gratifying to find that the partial reduction of the intermediate 62 with DIBALH in DCM at -95°C generated hemiacetal 63 and hydroxyl aldehyde 64 as an inseparable mixture in 62% yield. In the presence of TfOH in MeCN, the tricycle 20 was obtained via the cleavage of the MOM groups followed by intramolecular cyclization. Having successfully assembled tricycle 20, the group turned toward the final stage of the total synthesis of aflatoxin B₂: the Sc(OTf)₃-promoted one-pot sequential reaction. Finally, they successfully completed the required conversion in 77% yield using the Lewis acid Sc(OTf)₃, thereby achieving the asymmetric chemical total synthesis of (+)-aflatoxin B₂ with excellent atom-, redox-, and step-economy. This work also demonstrates that the application potential of the new developed strategy for the construction of benzyl chiral centers in the synthesis of complex molecules.

4 FORMAL TOTAL SYNTHESIS OF (\pm)-AFLATOXINS

4.1 Formal Total Synthesis of Aflatoxin B₁ by Snieckus Group

In 1988, Snieckus' group (Sloan et al., 1988) reported the formal total synthesis of aflatoxin B₁ based on radical cyclization, as shown in Figure 9. The radical precursor 70 was obtained via substitution reaction from o-bromophenol 68 and bromobutenolactone 69. The B-ring skeleton was then successfully constructed by intramolecular 1,4-addition mediated by free radicals. Finally, the MOM protecting group was removed to obtain the advanced intermediate 13. According to Büchi's strategy, the aflatoxin B₁ was successfully synthesized.

4.2 Formal Total Synthesis of Aflatoxin B₂ by Rapoport Group

In 1986, Rapoport's group (Castellino and Rapoport, 1986; Civitello and Rapoport, 1994) formally synthesized aflatoxin

B₂ via Oxaza–Cope rearrangement, as shown in Figure 10A. Hydroxylamine 71 and aldehyde 72 were condensed to obtain oxime compounds, which were refluxed in a sealing tube containing 3.9 M HCl in tetrahydrofuran for 24 h followed by Oxaza–Cope rearrangement, imine hydrolysis, tetrahydrofuran cleavage by chlorine, and spontaneous addition. Subsequently, one methyl sulfonyl group was removed by lithium hydroxide hydrolysis, and the C-ring was constructed under the catalysis of *p*-toluenesulfonic acid. The isomers 80 and 20 were then obtained in a 16:1 ratio. The formal total synthesis of aflatoxin B₂ was achieved in six steps with a total yield of 2.9%.

In 1993, Koreeda's group (Koreeda et al., 1993) formally synthesized aflatoxin B₂ through Kikuchi rearrangement, as shown in Figure 10B. Starting from benzoic acid 81, aldehyde 82 was obtained by esterification of carboxylic acid and selective methylation of phenol, followed by protection of phenol OH with SEM, reduction of ester group and subsequent oxidation. Then, they introduced side chain compound 83 containing double bond by Wittig reaction. The key precursor 83 was subjected to Kikuchi rearrangement in iodine, silver oxide, and dioxane/water system, resulting in chain-branching 1,2-migration product 86. After the removal of protective group and tandem cyclization reaction, the construction of advanced intermediate 20 was completed. It is worth to mention that Kikuchi rearrangement, as a newly developed method, plays an important role in the formal synthesis of aflatoxin B₂, which confirms that the advance of the method has important promoting value to the total synthesis.

In 2006, Quayle's group (Eastham et al., 2006; Eastham et al., 2008) reported an efficient method for the formal total synthesis of aflatoxin B₂ via Wulff–Dötz reaction, as shown in Figure 10C. Starting from the C-ring compound dihydrofuran 31, the B-ring skeleton was constructed by cobalt-mediated cyclization, and then 88 underwent a series of functional group transformations, such as ozone breaking and hydrazine to form a hydrazone, to obtain the key precursor of wulff–Dötz reaction. Then wulff–Dötz reaction of 89 with alkyne 90 in THF was performed to obtain the construction of A-ring. Finally, the formal synthesis of aflatoxin B₂ was successfully completed through simple transformation of 91.

4.3 Formal Total Synthesis of Aflatoxin M₂ by Kraus Group

In 1999, Kraus' group (Kraus and Wang, 1999) reported the first formal synthesis of aflatoxin M₂ via the 1,2-addition of dichloromethyl lithium to carbonyl, as shown in Figure 11.

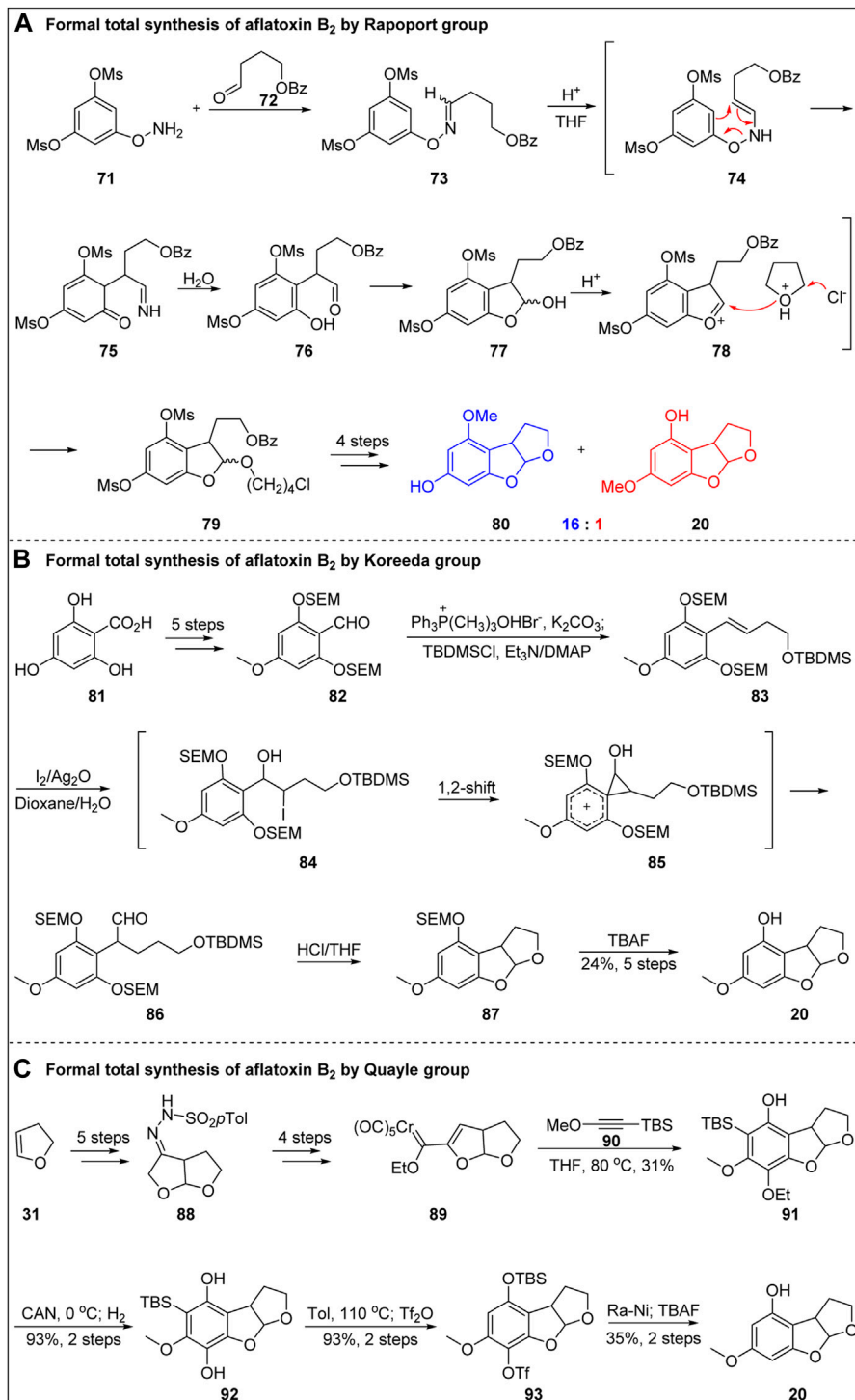


FIGURE 10 | Formal total synthesis of aflatoxin B₂.

The Friedel–Crafts acylation product **96** was obtained by the reaction of isotrimethoxybenzene **94** with propanolactone **95** under the catalysis of AlCl₃. Subsequently, **96** reacted with dichloromethyl lithium to obtain the key intermediate triol **97** via 1,2-addition. The hemiacetal intermediate **98** was hydrolyzed

and cyclized under the action of potassium carbonate in isopropyl solution.

The B-ring was then constructed under the catalysis of TsOH. Finally, **99** was subjected to selective demethylation under the action of BF₃•Et₂O, and the advanced intermediate

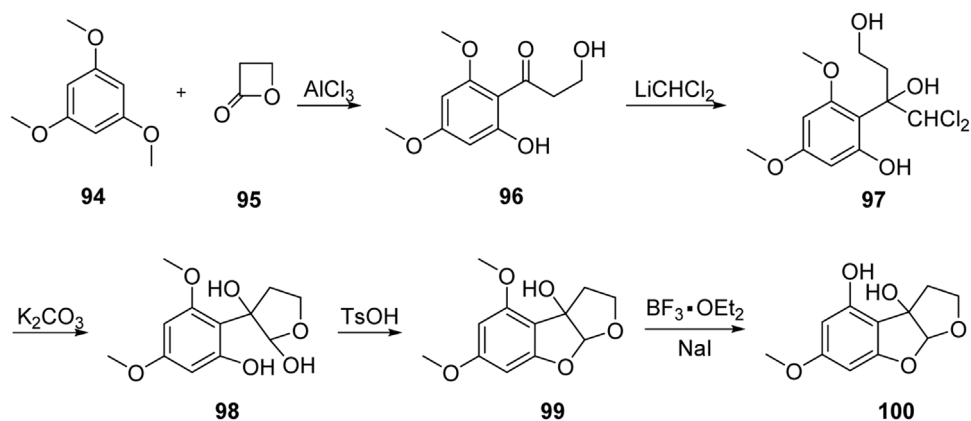


FIGURE 11 | Formal total synthesis of aflatoxin M_2 by Kraus group.

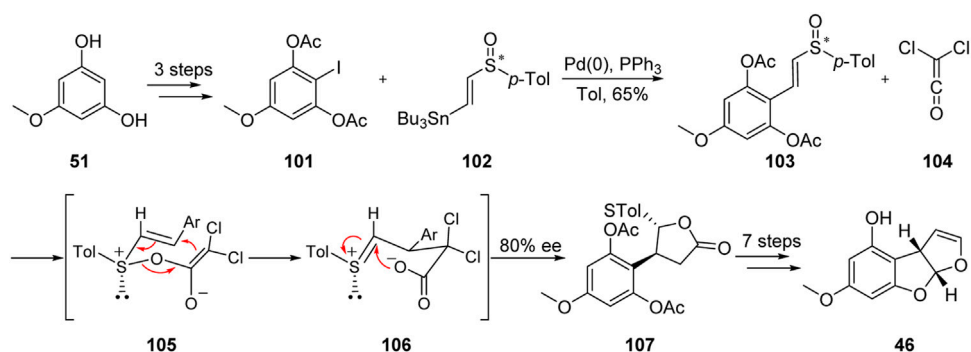


FIGURE 12 | Stereoselective formal total synthesis of aflatoxin B_1 by Marino group.

100 was synthesized in five steps with a total yield of 26%. Later, the chemical synthesis of aflatoxin M_2 was achieved based on Büchi's method for the total synthesis of aflatoxin M_1 .

5 ASYMMETRIC FORMAL TOTAL SYNTHESIS OF AFLATOXINS

5.1 Stereoselective Formal Total Synthesis of Aflatoxin B_1 by Marino Group

In 1993, the Marino group (Marino, 1993; Marino et al., 2011) described an efficient and stereoselective approach for the formal total synthesis of aflatoxin B_1 with 80% *ee*. This approach is characterized by the [3,3]- σ rearrangement of chiral vinyl sulfoxide **103** and dichloroethylene ketone **104**, as shown in Figure 12.

The key sulfoxide precursor **101** was obtained from diphenol **51** by acylation, iodization, and Stille coupling. The C-ring was then successfully constructed by [3,3]- σ rearrangement. Finally,

the formal synthesis of aflatoxin B_1 was successfully achieved through eight steps including deacylation and cyclization.

5.2 Stereoselective Formal Total Synthesis of Aflatoxin B_2 by Shishido Group

In 1997, Shishido's group (Bando and Shishido, 1997) used the lipase-mediated asymmetric acetylation of prochiral diol compounds as the key strategy to accomplish the asymmetric formal synthesis of aflatoxin B_2 , as shown in Figure 13A. The coupling product was obtained from iodide **108** via Heck reaction. After ozonation and NaBH_4 reduction, the diol **110** was obtained. After screening with a large number of lipases, the authors found that the lipase AL mediated the transfer of the ester group from *Achromobacter* sp., resulting in high yield with an *ee* of 89%. Compound **111** was then transformed into cyanide **112** by the introduction of a methyl sulfonyl group, cyanogen substitution, and deacylation. Subsequently, the B-ring was constructed via the oxidation of alcohol, the deprotection of phenol, and tandem cyclization. The benzylation of phenolic OH group, homeopathic reduction to alcohol after hydrolysis of

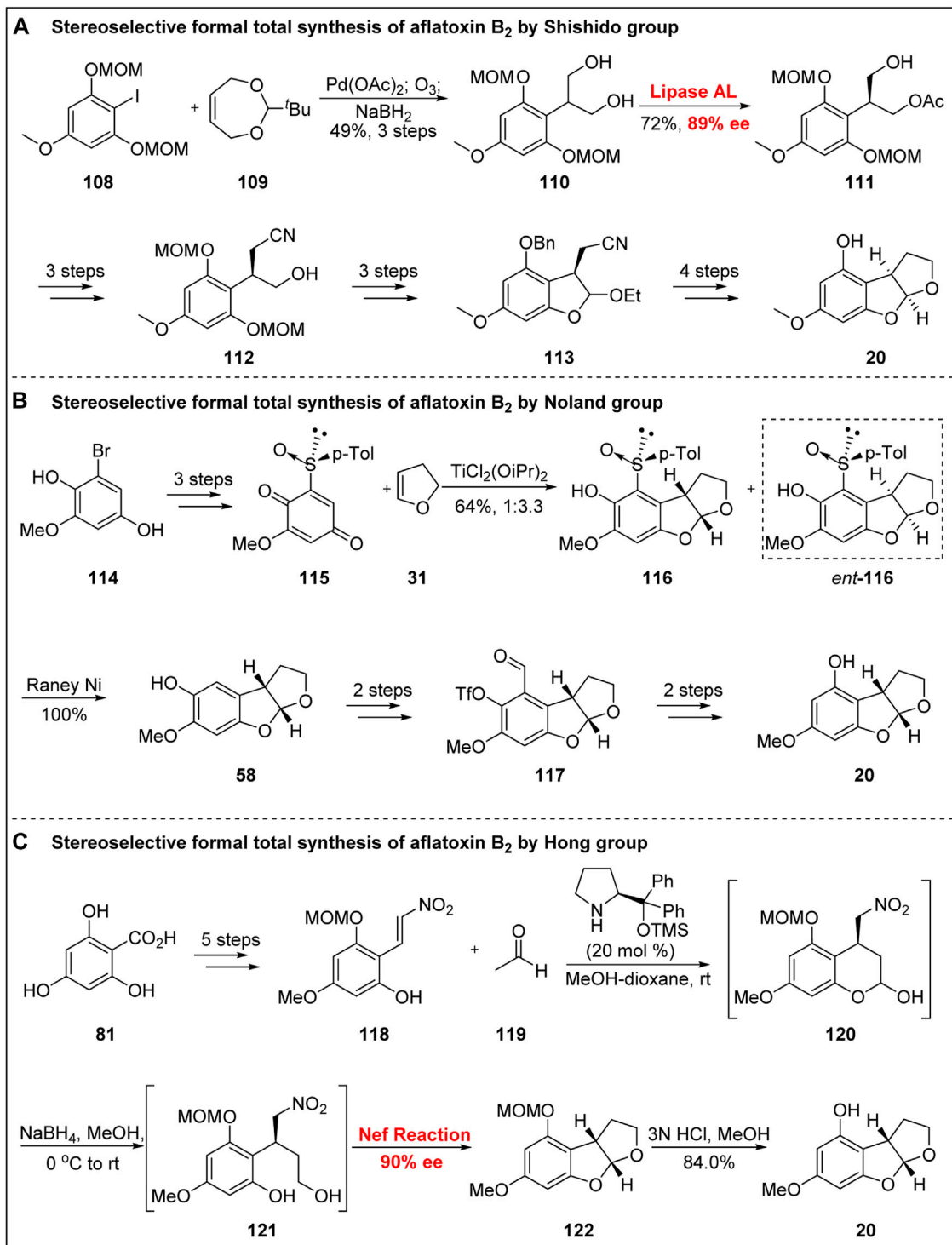
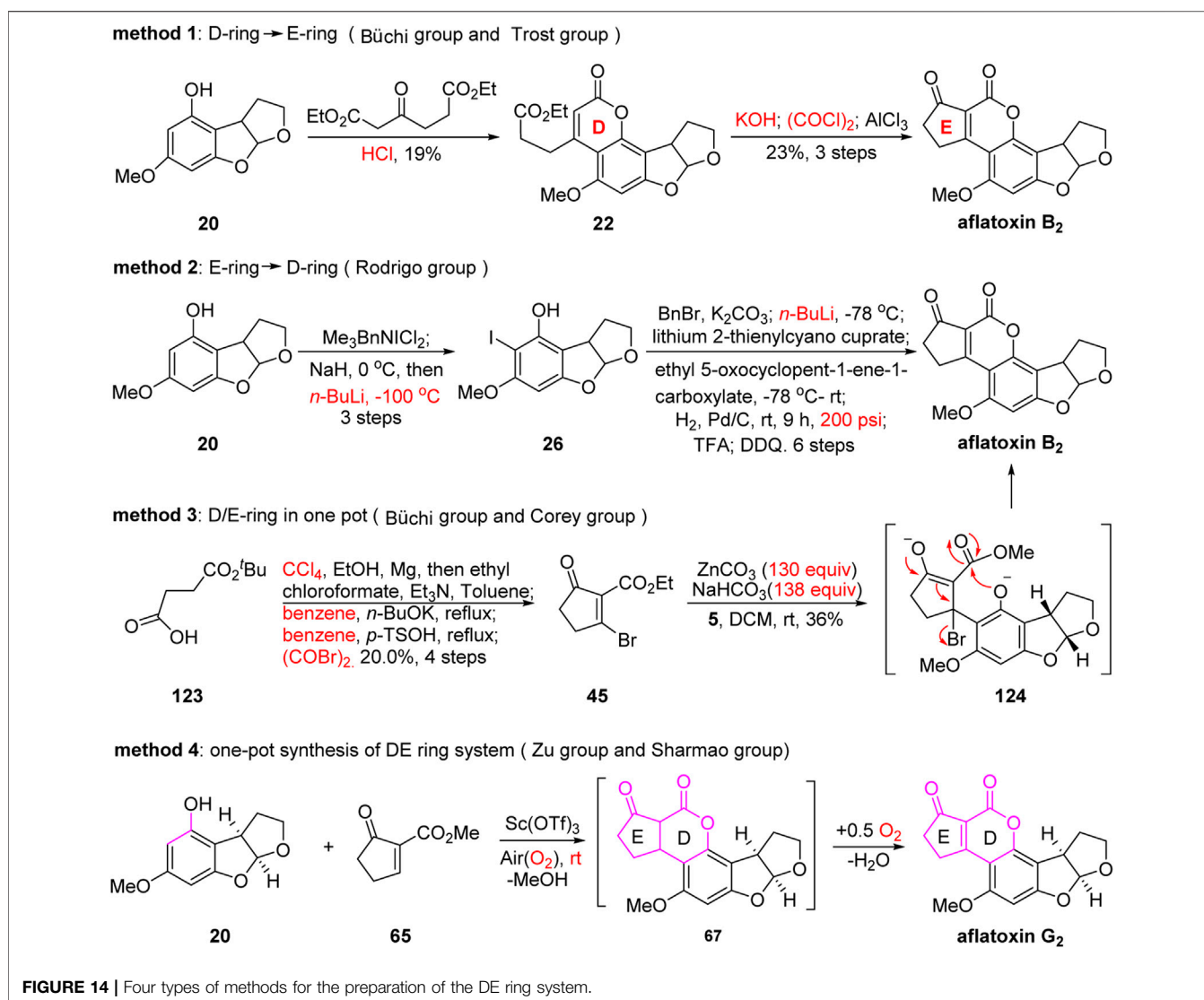


FIGURE 13 | Stereoselective formal total synthesis of aflatoxin B₂.

cyanide. Next, under the action of TsOH, the C-ring was obtained through intramolecular cyclization. Finally, the asymmetric formal synthesis of aflatoxin B₂ was realized via debenzoylation.

In 2000, Noland's group (Noland and Kedrowski, 2000) reported the asymmetric formal synthesis of aflatoxin B₂ using

chiral sulfoxide, as shown in **Figure 13B**. Based on the method developed by Andersen's group (Andersen et al., 1964), a compound containing a sulfoxide subsidiary was synthesized from the known intermediate **114** after MOM protection. Under the action of CAN, the quinone sulfoxide intermediate



115 was obtained by oxidative demethylation. Under the catalysis of the Lewis acid $\text{TiCl}_2(\text{OiPr})_2$, compounds **116** and ent-**116** were obtained in a ratio of 1:3.3, and the construction of the ABC tricyclic skeleton was realized. The sulfoxide auxiliary group was then removed by Laney nickel. After Duff reaction, the formylation product was obtained, and the phenol was esterified.

The functional group transformation of **117** was performed by Baeyer–Villiger oxidation, saponification, and reduction under the action of Laney nickel to obtain the precursor **20**. Notably, their synthetic strategy and particularly the late functional group transformation provided important ideas and inspiration for the asymmetric total synthesis of aflatoxin B_2 by Corey's group (Zhou and Corey, 2005).

In 2017, Hong's group (Huang et al., 2017) reported the concise formal total synthesis of (-)-aflatoxin B_2 based on the synthesis of an advanced intermediate of **20** in seven steps using an organic-catalyzed tandem one-pot reaction (Figure 13C). Starting from benzoic acid **81**, the key precursor **118** was obtained by using acetone to protect the

carboxyl group and its o-phenol OH followed by selective methylation, MOM protection, reductive deprotection using DIBAL-H, and aldol reaction. Subsequently, using the organic catalytic tandem one-pot reaction developed by their own group, Hong's group obtained the BC double-ring skeleton with excellent enantioselectivity. The specific sequence of the tandem reaction was as follows: first, under the action of Jørgensen catalyst and in the presence of acetic acid, the hemiacetal **120** was obtained with high *ee*; second, under the action of NaBH_4 , diol **121** was generated; finally, the BC double ring was constructed by Nef reaction. Subsequently, the asymmetric synthesis of **20** was completed by the removal of MOM.

6 SUMMARY AND OUTLOOK

Given the broad implications that aflatoxins have for public health, considerable progress has been made in the total

synthesis of aflatoxins since the 1960s. During the past 55 years, three enantioselective total syntheses have been described, including the first asymmetric total synthesis of aflatoxin B₁ and B₂ by the groups of Trost and Corey, and the second asymmetric total synthesis of aflatoxin B₂ by the group of Zu. These works represent wonderful progress in the total synthesis of aflatoxins in terms of elegance, efficiency, and environmental friendliness.

Most reported studies have focused on four types of methods. Taking the preparation of the DE ring system as an example (Figure 14), in 1966, the group of Büchi assembled the DE ring system via Pechmann condensation and Friedel–Crafts acylation in four consecutive steps with an extremely low overall yield (4.4% yield). Later, in 1971, Büchi's group used a brominated five-membered cyclic ketone or six-membered lactone in the presence of ZnCO₃ (130 equiv.) and NaHCO₃ (138 equiv.) to successfully obtain the DE ring system in one step. However, it should be noted that the preparation of the brominated ketone or lactone requires four or five steps along with CCl₄ and benzene as solvents, which is not ideal. In 1990, the group of Rodrigo assembled the DE ring system using a very different strategy from Büchi's. Rodrigo's approach involved transmetalation and addition with nine tedious consecutive steps, and both low temperature (−100°C) and high pressure (200 psi) were required. In 2019, the group of Zu developed a new Sc(OTf)₃-promoted, green, facile, and economic single-pot strategy to synthesize the DE ring system of aflatoxins.

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- In brief, economic, facile, and green processes are being advanced as effective ways to not only form the key structural motifs of aflatoxins but also to circumvent tedious purification steps and promote environmental sustainability. Given the vital importance of this topic, the organic chemistry community should continue to invest efforts in developing new methods for the efficient total synthesis of aflatoxins.

AUTHOR CONTRIBUTIONS

LY conceived the review. LY collected the literatures. ZW and LY wrote the manuscript. ZW edited the manuscript. All authors read and approved the final version of the manuscript.

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