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Organocatalytic Enantioselective Michael–Acetalization–Reduction–Nef Reaction for a One-Pot Entry to the Functionalized Aflatoxin System. Total Synthesis of (−)- Dihydroaflatoxin D_2 and (−)- and (+)-Microminutinin

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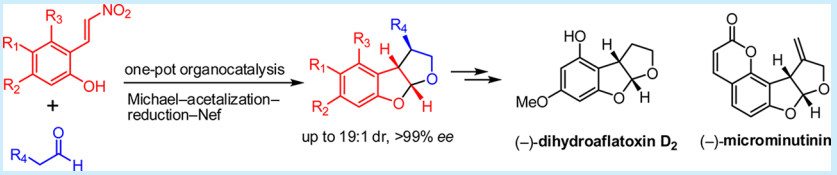
Supporting Information



ABSTRACT: An efficient method has been developed for the enantioselective synthesis of the aflatoxin system with multiple stereocenters via a sequence of organocatalytic Michael–acetalization–reduction–Nef reactions that proceed with high enantioselectivities (90–99% ee). The one-pot reaction sequence provides a facile entry to the aflatoxin system, including dihydroaflatoxin D_2, which includes a formal total synthesis of aflatoxin B_2. The first total synthesis of (−)- and (+)-microminutinin was also achieved via this protocol.

For more than a half century, aflatoxins,[1] a family of mycotoxins,[2] have attracted extensive synthetic attention as a result of their widespread prevalence in nature and their potent biological effects, which include toxicity, carcinogenicity, antimitoticity, antimicrobiality, and platelet-aggregating inhibition activity,[3] etc. (Figure 1).[4] Aflatoxin B_2 stands out as a prominent representative. This compound is widely known as a poisonous contaminant in improperly stored food, and many synthetic approaches to aflatoxin B_2 have been reported.[5] Most of these syntheses rely on formation of dihydro aflatoxin D_2, (±)-**1**, which contains the ABC ring core of aflatoxin B_2, which is required for the formal synthesis of (±)-aflatoxin B_2 (Scheme S1).[6] Furthermore, introduction of the D and E rings to (±)-**1** has been efficiently achieved, via a von Pechmann reaction, with a single-step annulation of the cyclopentanocoumarin ring to achieve the total synthesis. Despite the aforementioned advances, dihydroaflatoxin D_2 (**1**) (dihydro AFD_2) has been most frequently synthesized as a racemate. Most of the synthetic strategies require many steps from commercially available compounds (Scheme S1).[6] For the asymmetric approaches, Shishido et al. completed the synthesis of (+)-**1** in 15 steps using a lipase-catalyzed enantioselective acetylation (asymmetric resolution) as the key step.[7] Corey and co-workers revealed an enantioselective total synthesis of aflatoxin B_2 employing asymmetric [3 + 2]-cycloaddition as the key step. In their study, the last step of the synthesis featured a modified von Pechmann reaction of (−)-**1** with a β-bromo-α,β-enone.[8,9] Since chiral-enriched aflatoxins include a 2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran moiety, this compound is an interesting and challenging synthetic target, and an efficient synthesis of a chiral-enriched building block, e.g., **1**, and its derivatives continues to be a compelling and inspiring subject for development.[10]

In this context and in efforts to expand our interest in asymmetric organocatalytic annulations[11] with cascade reactions[12] and one-pot operations,[13] we conceived a scenario in

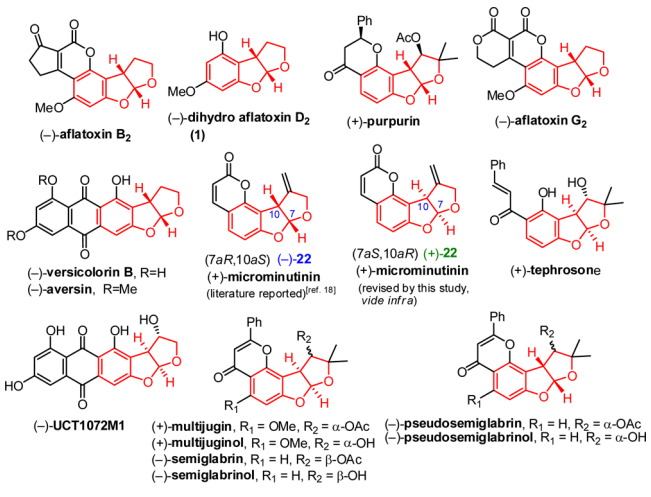


Figure 1. Selected naturally occurring compounds incorporating a tetrahydrofuro[2,3-*b*]benzofuran moiety.

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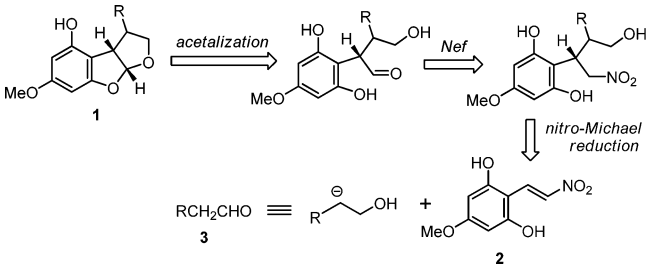
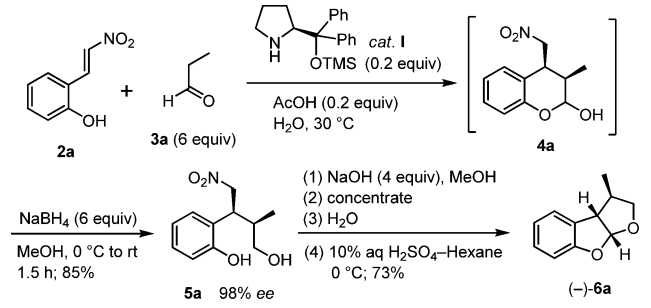
which an organocatalytic Michael–acetalization of nitroalkene (**2**) and aldehyde (**3**) followed by reduction and a Nef reaction sequence would provide an efficient platform for the construction of the functionalized aflatoxin system (Scheme 1).

Scheme 1. Retrosynthetic Analysis of 1



We tested the feasibility of this reaction sequence by treating a mixture of hydroxynitrostyrene **2a** and propanal (**3a**) in water with 20 mol % of Jørgensen–Hayashi catalyst (**I**) and acetic acid at room temperature (~30 °C) for 80 min to give hemiacetal **4a**. This was followed by cooling of the reaction mixture at ice-bath temperature and addition of MeOH and $NaBH_4$ (Scheme 2). The

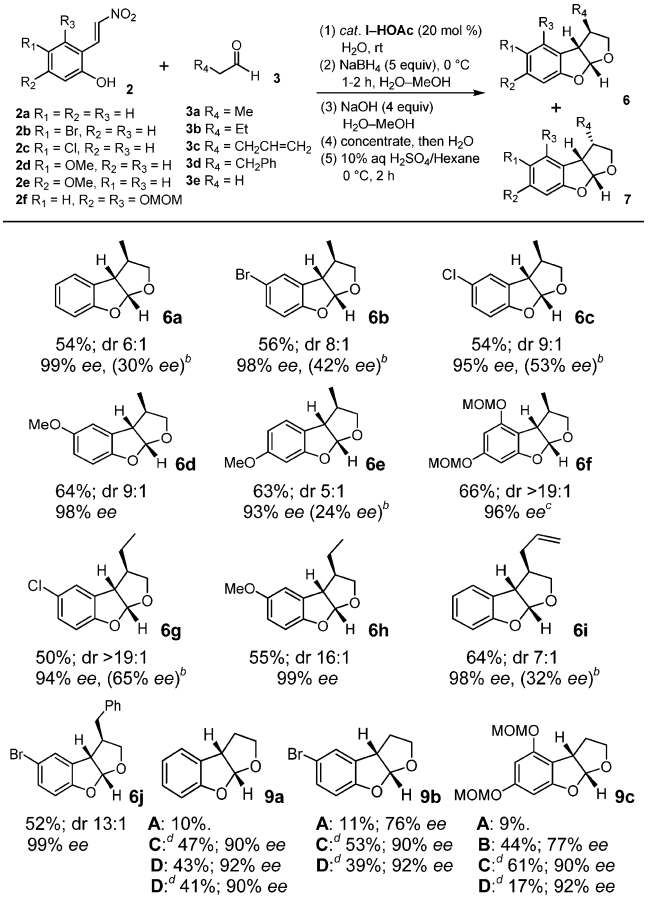
Scheme 2. Two-Pot Synthesis of (−)-6a



solution was stirred and gradually warmed to room temperature for 90 min to give an 85% yield of diol **5a** with 98% ee.[14] An aqueous solution of **5a** was treated with NaOH for 15 min and concentrated in vacuo to give a residue. The residue was diluted with water, and the solution was stirred at ice-bath temperature before the sequential addition of hexane and 10% aqueous H_2SO_4 solution. Subsequently, the solution was stirred at ice-bath temperature for 1.5 h, and this followed by a regular workup and silica gel chromatography purification to afford the product (−)-**6a** in 73% yield.

Additionally, the four-step reaction sequence for the synthesis of (−)-**6a** was advanced using a one-pot synthesis to give (−)-**6a** in 54% yield (dr 6:1) with 99% ee of the major diastereomer (Scheme 3). With a suitable reaction procedure in hand, a series of hydroxynitrostyrenes **2** and aldehydes **3** were applied with the optimal conditions for the Michael–acetalization–reduction–Nef reaction (Scheme 3). The outcome was promising with the yields ranging from 47% to 66% yields after the one-pot, four-step reaction sequence, and the enantioselectivities of the major diastereomeric products were 90–99% ee (Scheme 3), while relatively low ee was observed in the minor diastereomeric products. Satisfyingly, the diastereomeric ratios of those examples are high, ranging from >19:1 to 5:1. Moreover, in the separate reactions for the synthesis of **6c**, after the $NaBH_4$ reduction, the intermediate diol **5c** was isolated, and this was followed by treatment with an aqueous H_2SO_4 solution, affording the **6c** and

Scheme 3. Examples of the One-Pot Michael–Acetalization–Reduction–Nef Reaction[a]



[a]Unless otherwise noted, for the first-step Michael–acetalization, the reactions were performed with **2** (1 equiv) and **3** (6 equiv) with 20 mol % of catalyst I and HOAc "on H_2O" at ambient temperature (~20–25 °C), Method A. Isolated yield is shown for **6** and **7** or **9**; dr, determined by the crude ^1H NMR; ee of **6**, determined by HPLC with Chiralpak IC. [b]ee of the **7** in parentheses. [c]ee determined with Chiralpak IF. [d]Reaction in the absence of acetic acid. Method B: The first step of the reaction was conducted in MeOH. Method C: The first-step reaction was conducted in MeOH–dioxane (2:1). Method D: The first-step reaction was conducted in dioxane.

7c in 37 and 5% yields, respectively, accompanied by formation of γ-lactone (+)-**8** (11% yield), vide infra. It is worth noting that this lactone type of side product (+)-**8** was not observed in the one-pot synthesis of **6c** and was not observed in the other examples of the syntheses of **6** in either the one-pot or the stepwise synthesis.

Despite the success in the preceding cascade one-pot examples, the reaction of **2a** and acetaldehyde (**3e**), where R_4 = H, performed under "on-water" conditions, gave a low yield in the first Michael–acetalization process (~20% yield) and produced only a 10% yield of the adduct **9a** (Scheme 3, Method A). This obstacle resulted a low yield for the first-step Michael–acetalization reaction of **2a** and **3e**. A few factors hampered success in the Michael–acetalization reaction of **3e** with hydroxynitrostyrene **2a**, including (a) the high solubility of acetaldehyde in water, which led to a homogeneous solution media during the reaction process, and deterioration of the enamine formed in the first-step process; (b) the ease of the self-aldol and the self-polymerization of the acetaldehyde; (c) the facile formation of the side product, affording alcohol **10** after

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$NaBH_4$ reduction, which arose from the Michael−aldol−oxa-Michael cascade of hydroxynitrostyrene with 2 equiv of acetaldehyde (Figure 2);[15] and (d) the relatively low

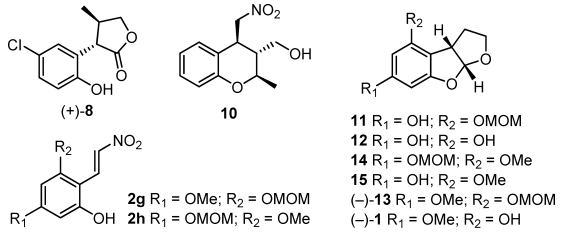


Figure 2. Other examples of prepared products.

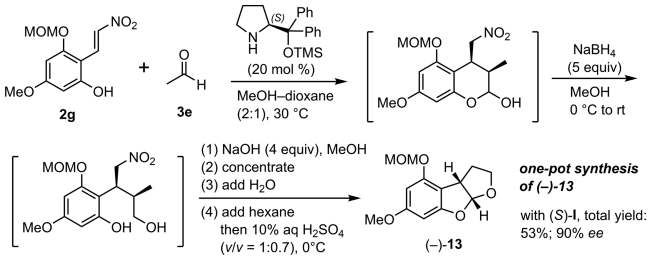
enantioselectivity of **2a** and **3e** in most organic solvents, as compared to the reaction with other alkylaldehydes **3a**−**d**.[16] Extensive studies were then performed in the first step of the Michael−acetalization of **3e** and **2a** at various reaction conditions.[6] Select reaction methods, e.g., methods B−D, are presented in Scheme 3. Reaction of **2a** and acetaldehyde (**3e**) in dioxane, followed by the one-pot reaction sequence, gave a 43% yield of **9a** with 92% ee (Scheme 3, method D). The yield of **9a** could be increased to 47% by conducting the first-step Michael−acetalization of **2a** and **3e** in MeOH−dioxane (2:1), although the enantioselectivity was slightly reduced to 90% (Scheme 3, method C). Similarly, the best results of the reaction media in producing **9b** and **9c** were found to be using the combination of the MeOH−dioxane (2:1) in the first-step Michael−acetalization (Scheme 3, method C). In addition, in the separated experiments, we found that addition of acetic acid in the first Michael−acetalization step was not critical. The reaction with the catalyst alone gave similar yields and stereoselectivities (Scheme 3, footnote d). To account for the outcome of this multiple step transformation, a conceivable mechanism was proposed as shown in Scheme S2.[6]

Selective hydrolysis of **9c** with 3 N aqueous HCl solution afforded 54% yield of alcohol **11** and 42% yield of diol **12** (Figure 2). After methylation of alcohol **11** with Me_2SO_4 and K_2CO_3 in acetone, **13** was obtained in 64% yield. Deprotection of (−)-**13** with a 3 N HCl aqueous solution yielded 84% of (−)-**1**, dihydroaflatoxin D_2, which constituted a formal synthesis of aflatoxin B_2, vide supra. The structure of (±)-**6b**[17] and the absolute configuration of (+)-**8** and (−)-**1** was revealed by single-crystal X-ray analysis.[6]

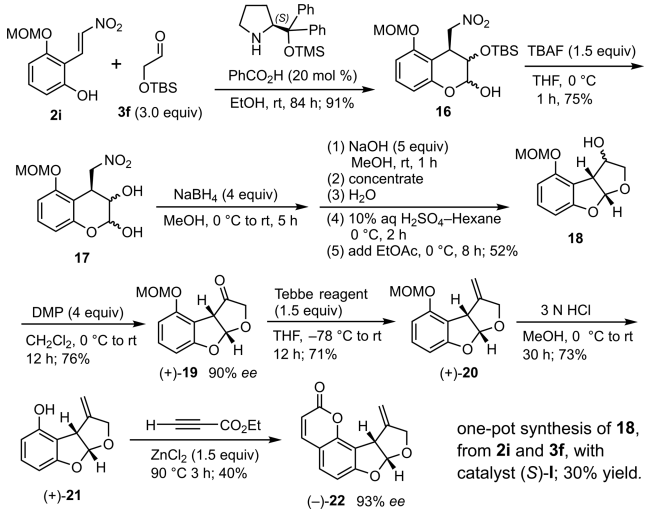
In addition, the reaction of a mixture of **2g** and **2h**[6] (~1.2:1 ratio) and acetaldehyde mediated by (*S*)-**I**, after the one-pot process, gave 56% yield of **13** and **14** (~1.2:1 ratio) (Figure 2). Deprotection of **14** with a 6 N HCl aqueous methanol solution provided a 97% yield of **15** (Figure 2). Later, the one-pot synthesis of (+)-**13** and (−)-**13** was achieved from the reaction of nitroalkene **2g**[6] and acetaldehyde by catalyst (*S*)-**I** or (*R*)-**I**, respectively (Scheme 4). As a result, in the one-pot synthesis, (−)-**13** was isolated in 53% yield with 90% ee, and (+)-**13** was isolated in 54% yield with 90% ee.

We next looked to demonstrate the utility of this methodology in the total synthesis of microminutinin (Scheme 5).[18] On the basis of the absolute configuration of (+)-microminutinin present in the literature (Figure 1) and our aforementioned results, catalyst (*S*)-**I** was selected for the reaction with nitrostyrene **2i**[6] and commercially available aldehyde **3f** (3 equiv) in 95% EtOH to give adduct **16** (91% yield), followed by the deprotection of the OTBS group with TBAF (75% yield) and the one-pot reduction−Nef reaction to give the alcohol **18** in 52% yield. Oxidation of **18**

Scheme 4. One-Pot Process for the Synthesis of (−)-13



Scheme 5. Total Synthesis of Microminutinin (−)-22



with Dess−Martin periodinane in CH_2Cl_2 gave a 76% yield of ketone (+)-**19** with an ee of 90%. Treatment of (+)-**19** with Tebbe reagent, $(C_5H_5)_2TiCH_2ClAl(CH_3)_2$, in THF at −78 °C to rt for 12 h afforded (+)-**20** in 71% yield. Deprotection of the MOM protecting group of (+)-**20** with a 3 N aqueous HCl solution in methanol gave a 73% yield of (+)-**21**. Coumarin synthesis was achieved by heating (+)-**21**, ethyl propiolate, and $ZnCl_2$ at 90 °C for 3 h to undergo the Pechmann-type condensation reaction to produce (−)-**22** in 40% yield with 93% ee. It is noteworthy that the specific optical rotation sign of the synthetic (−)-**22** is opposite to the naturally occurring isolated (+)-microminutinin (Figure 1). In addition, since the absolute configuration of the tetrahydrofuro[2,3-*b*]benzofuran, i.e., (−)-**22**, synthesized by (*S*)-**I** was confirmed by our foregoing synthetic evidence, the original absolute configurational assignment of natural product (+)-microminutinin as 7a*R*,10a*S* is wrong, and the correct stereochemistry of natural occurring (+)-microminutinin is 7a*S*,10a*R*, (Figure 1). In particular, the tetrahydrofuro[2,3-*b*]benzofurans with such an absolute configuration (7a*S*,10a*R*) were also observed in naturally occurring substances, for example, (−)-semiglabrin,[19] UCT1072M1, and (+)-tephrosone. Moreover, both (+)-multijugin and (−)-enantiomultijugin have been isolated from different natural sources (Figure 1).[20] Furthermore, the specific optical rotation of naturally occurring (+)-microminutinin has been reported to be $[\alpha]_D$ +59[18a] and $[\alpha]_D$ +81.[18b] The data may be underestimated since our synthetic (+)-microminutinin[21] and (−)-microminutinin gave values of +321.9 and −329.6, respectively. In addition, the specific optical rotation of naturally occurring 6-methoxymicrominutinin was separately reported to be $[\alpha]_D$ +336[18a] and $[\alpha]_D$ +113.[18b] That these data are not equal or

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opposite supports their enantiomeric purity and relationship. On the basis of these findings, it is possible that some of these naturally occurring substances are not present in the enantiomerically enriched compounds but rather as mixtures of the enantiomers.[22]

In summary, we have developed an enantioselective synthesis of the aflatoxin system via a sequence of asymmetric Michael−acetalization−reduction−Nef reaction with high enantioselectivities (90−99% ee). The structures and absolute configurations of the products (±)-**6b**, (+)-**8**, and dihydroaflatoxin D_2, (−)-**1**, have been unambiguously confirmed by single-crystal X-ray crystallographic analyses. The multiple-step reaction sequence can be conducted with only a one-step purification, constituting a one-pot synthesis strategy. The process provides an efficient and expedited synthesis of dihydroaflatoxin D_2 that constitutes a formal total synthesis of aflatoxin B_2. Our synthetic method culminated in the first total synthesis of (+)- and (−)-microminutinin and led to a revision of the absolute configuration of naturally occurring microminutinin. The results not only provide a seminal example of the total synthesis of these types of natural products but also permit assignment of the absolute configuration of these naturally occurring compounds for which there had previously been insufficient evidence to draw a conclusion; in particular, the ambiguity of the absolute configuration of some *Tephrosia* flavones existing in the literature has puzzled investigators for decades. Given the prevalent occurrence of the aflatoxins and their analogues in nature and their biological significances, this efficient and asymmetric process could provide an effective protocol for related natural product syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01473.

Experimental procedures and characterization data (PDF)
X-ray crystallographic data for compound (±)-**6b** (CIF)
X-ray crystallographic data for compound (+)-**8** (CIF)
X-ray crystallographic data for compound (−)-**1** (CIF)

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Notes

The authors declare no competing financial interest.

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