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Synthesis of Octahydroperylene, the Framework of Altertoxin III

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Routes to the framework of perylenequinone-derived mycotoxins of the dihydroanthracene type are described. Starting with anthracene derivatives, attachment of C_3 units at positions 9 and 10 and twofold cyclization would furnish the required pentacycle. Heck-type couplings, S_N2 additions of enolates, alkynyl and allyl additions turned out to be not successful, while addition of a Grignard reagent prepared from acetal-protected 3-bromopropionaldehyde to anthraflavic acid methyl ester, subsequent acetal cleavage, and Birch reduction furnished octahydroperylene in only four steps.

Introduction

Natural products derived from perylenequinone and thus from the aromatic pentacycle perylene can be assorted into two major classes, where representatives of the first one generally show intact, fully conjugated perylenequinone moieties.[1] Typical natural products of this type are cercosporin[2] or the elsinochromes (Figure 1),[3] where a number of total syntheses have been presented for this class of natural products.[2d,4] Members of a second class of perylenequinone-derived natural products do not show full conjugation in the carbon core; they are partially reduced to di-, tetra-, and hexahydroperylenequinones. Furthermore, they are not augmented by additional carbon substituents and the twenty carbon atoms of the parent perylene are thus only complemented by an optional presence of *O*-alkyl groups, especially of methoxy groups. These compounds are most generally fungal metabolites and their toxicity is thus of relevance when the respective fungi invest food or feed. No total synthesis has been presented so far for any of these compounds, although we noted some efforts in this direction made in the Krohn group.[5] Mycotoxins of this type can be categorized in some sub-classes:[6] Most of them either belong to the biphenyl type, in which two stacked, fully intact benzene rings are present (e.g., altertoxin I), or to the dihydroanthracene type, where two diagonally arranged benzene rings are present (e.g., altertoxin III, alterlosin II, or stemphyperylenol). An overview on this class of compounds has been published only recently.[7]

In this manuscript we describe our efforts on the synthesis of the altertoxin III framework, i.e., of the core of the dihydroanthracene-derived toxins. Our synthetic approaches towards the altertoxin I core are summarized in a further publication.[8]

Results and Discussion

Retrosynthetic analysis of the altertoxin III framework (**A**) includes a Birch-type reduction of tetrahydroperylenequinone **B** (Scheme 1). This should be accessible by intramolecular Friedel-Crafts-type reaction of a suitable precursor **C**, e.g., of an aldehyde, a carboxylic ester, or of more activated substrates like acyl halides. These intermediates could be traced back to aromatic electrophiles **D**, from which they are accessible, e.g., by Heck reaction. Anthracene derivatives **D** could be obtained from anthraquinones **E** (route A). Alternatively, intermediates **C** could be synthesized from anthracenes **F**, where substituents R could be any moiety (above all C_3 units) allowing transformation into **C**, e.g., allyl groups or (unsaturated) propanoates (route B). Introduction of these substituents R should be possible by Grignard addition to anthraquinones **E** and subsequent reduction of the intermediate diols **G**.

According to the retrosynthetic scheme (route A), we at first envisioned Heck coupling of anthracene-derived electrophiles **D** with acrylates. We tested this sequence with the parent anthracene **1**, which was brominated at 9,10-positions (→**2**) following a published procedure,[9] and subsequently coupled with methyl acrylate using palladium(II) acetate as catalyst and imidazole-derived NHC ligand IMes[10] to the known diester **3** (Scheme 2).[11] To get access to 2,6-dihydroxyanthracene derivatives **6** we at first protected commercially available 2,6-dihydroxyanthraquinone (anthraflavic acid, **4**) with the methyl[12] and the hexyl group.[13] The latter was used to improve solubilities of the respective products.[8,12] Further protective groups (MOM, Bn, TBDMS, TPS) were tested, but turned out to be less suitable. The respective transformations are not included herein. Subsequent reduction of protected anthraquinones **5**

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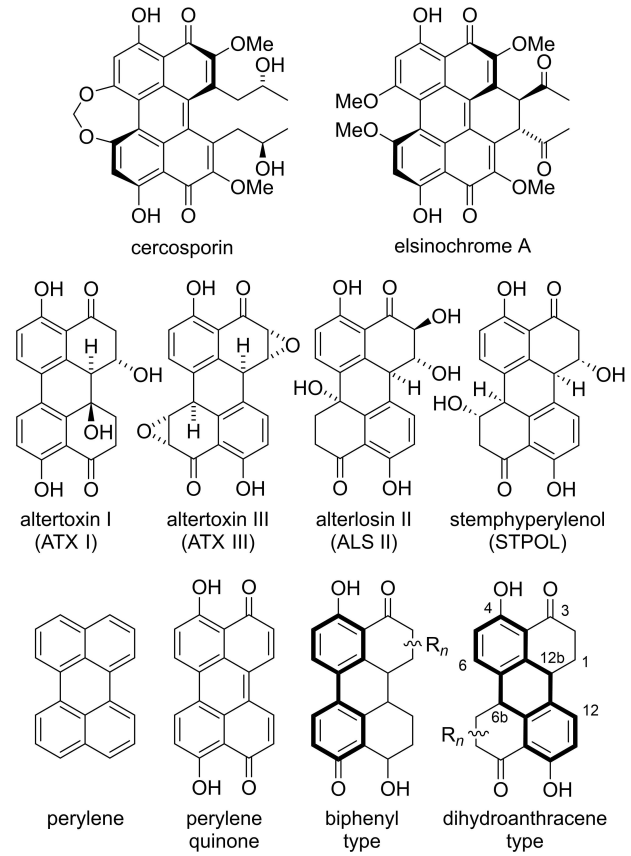
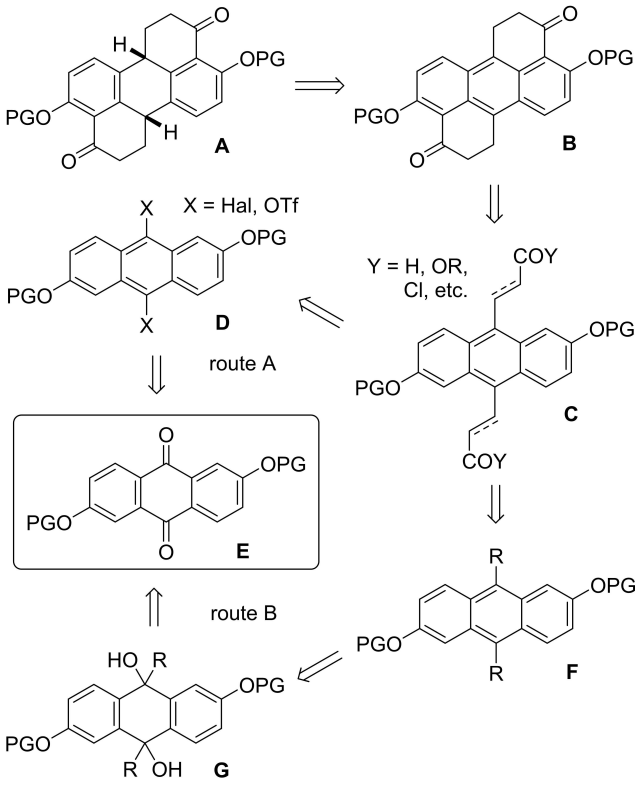
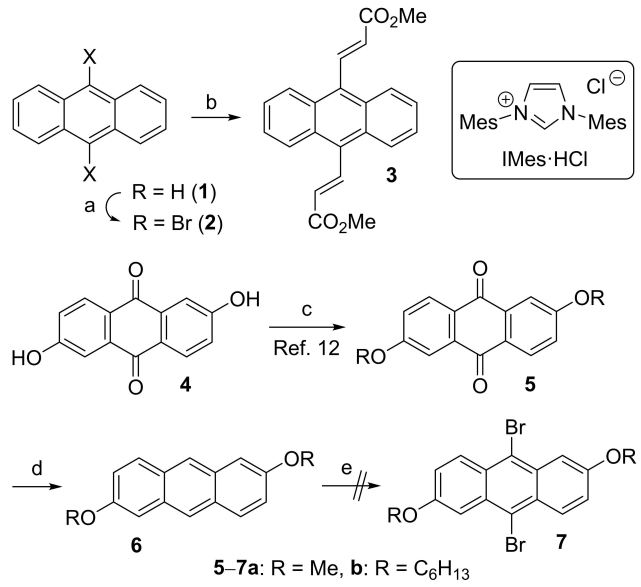


Figure 1. A selection of perylenequinone-derived natural products.



Scheme 1. Retrosynthetic analysis for the altertoxin III framework.

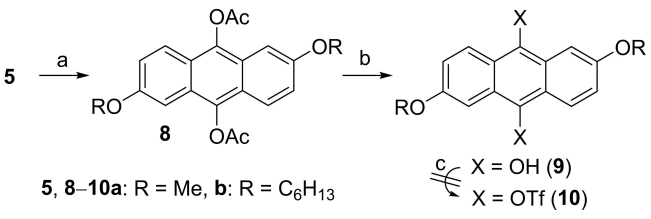


Scheme 2. Heck coupling of anthracene derivatives. Conditions: a) NBS, $LiClO_4/SiO_2$ (1:4), CH_2Cl_2, rt, 30 min, quant.; b) methyl acrylate, $Pd(OAc)_2$, IMes·HCl, K_2CO_3, DMF, 120 °C, 65 h, 65%; c) R = Me, **5a**: Me_2SO_4, K_2CO_3, acetone, 75 °C, 8 h, 78%; R = C_6H_{13}, **5b**: $C_6H_{13}Br$, K_2CO_3, DMF, 90 °C, 20 h, 92%; d) $NaBH_4$, iPrOH, 90 °C, 16 h, R = Me, **6a**: 90%, R = C_6H_{13}, **6b**: 29%; e) e.g., Br_2, HOAc, rt, 1 h or NBS, DMF, 0 °C→rt, 16 h.

with sodium borohydride ($NaBH_4$)[12] furnished the anthracenes **6**. Unfortunately, these could not be cleanly brominated in 9,10-positions. The activating properties of the alkyloxy groups promoted *ortho* brominations and unusable mixtures of isomers were obtained with various tested protocols.

Triflates have repeatedly been used in Heck reactions as alternatives for the respective halogenated electrophiles.[14] For their preparation, we started with a reductive acylation of the protected anthraflavic acids **5** with zinc and acetic anhydride (Scheme 3).[15] The thus obtained diacetates **8** were saponified (→**9**)[16] and should then be transformed into the respective bis(triflates) **10**. Unfortunately, a tested protocol, which turned out to be successful for the transformation of hydroquinone and other aromatic diols,[17] did not furnish the bis(triflates), even with increased reaction temperatures and/or prolonged reaction times.

Since we were not successful in adopting Heck reactions for our endeavor, we followed alternative routes, which are summarized as route B in retrosynthetic Scheme 1. Grignard



Scheme 3. Triflates as precursors for Heck couplings. Conditions: a) R = Me, **8a**: Zn, Ac_2O, NaOAc, 150 °C, 4 h, 96%; R = C_6H_{13}, **8b**: Zn, Ac_2O, pyridine, 130 °C, 4 h, 91%; b) K_2CO_3, NaOAc, MeOH; R = Me, **9a**: rt, 1 h, 88%; R = C_6H_{13}, **9b**: 70 °C, 2 h, 84%; c) Tf_2O, pyridine, CH_2Cl_2, 0 °C→rt, 2–24 h.

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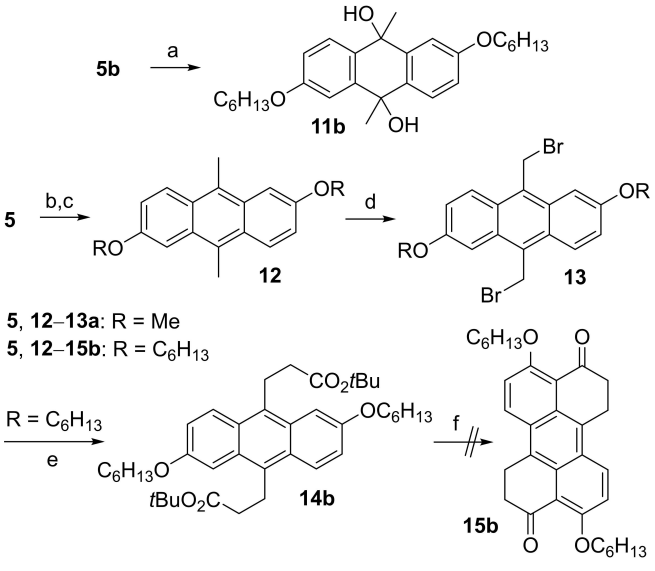
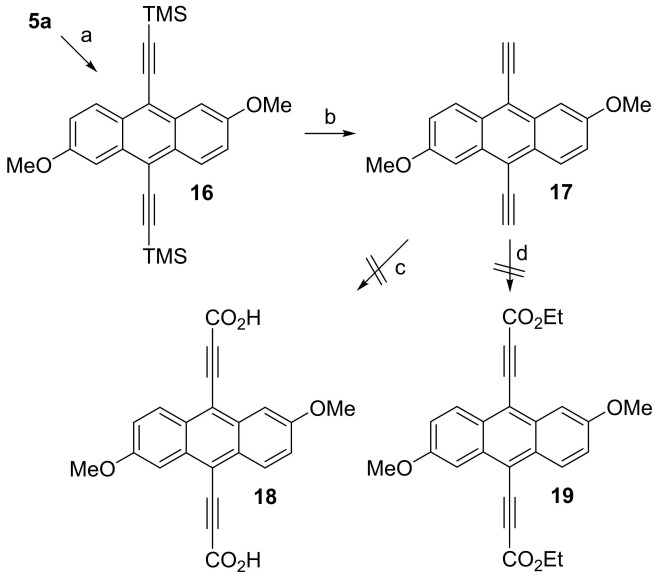
additions to anthraquinones have repeatedly been investigated[18] and were considered applicable for the introduction of suitable substituents in positions 9 and 10 of anthracenes. To test, whether these reactions can be applied to anthraflavic acids **5**, we adapted a published protocol[18b] and used a simple methyl Grignard reagent as nucleophile (Scheme 4). However, no product was obtained with hexyl-protected anthraquinone **5b**, neither with an excess of the Grignard reagent, nor with prolonged reactions times. Nevertheless, utilization of an ate complex, formed by mixing methyl magnesium bromide and methyl lithium,[19] led to a clean reaction and dialcohol **11b** was obtained with 87% yield. As the diol turned out to be quite unstable, we did not isolate the Grignard adducts in further reactions, but immediately reduced these to the respective 9,10-disubstituted anthracenes. This could be achieved with triethylsilane in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$)[20] to yield methyl-protected anthracene **12a**, albeit containing some impurities. This method did neither furnish clean product, when hexyl-protected derivative **5b** was reacted, while the alternative utilization of tin(II) chloride in acetic acid[21] delivered pure **12b** with 67% yield. In the following Wohl-Ziegler dibromination we faced well-known solubility problems.[12] No bromination of methyl-protected derivative **12a** was achieved with *N*-bromosuccinimide (NBS) and azobis(isobutyronitrile) (AIBN),[22] while a clean formation of **13b** (72%) was observed for the hexyl-protected anthracene **12b**. From this a suitable C_3 substituent could be built by nucleophilic substitution with an acetate enolate. Reaction of **13b** with *tert*-butyl acetate, deprotonated with lithium diisopropylamide (LDA), furnished diester **14b** with 64% yield.[23] Electrophilic aromatic substitutions (especially their intramolecular variations) of *tert*-butyl carboxylates are well established with a variety of acidic or otherwise activating conditions. Nevertheless, neither a cyclization using Eaton's reagent (P_2O_5 in $MeSO_3H$),[24] which gave good results in the synthesis of the altertoxin I framework,[8] nor in situ formation of a mixed anhydride with trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA)[25] furnished tetracycle **15b**. Saponification[26] or acidic cleavage[27] of the ester and subsequent activation with TFAA/TFA[28] or with $BF_3{\cdot}OEt_2$[29] was neither successful.

Ethynyl groups could similarly be introduced as Grignard reagents (Scheme 5). We planned subsequent extensions to propiolic acid or propiolates by reaction with carbon dioxide or its respective derivatives. The triple bonds were expected to be easily reduced to *E* or *Z* double bonds or even to single bonds in the respective propionates. Reaction of methyl-protected anthraflavic acid **5a** with lithiated (trimethylsilyl)acetylene[30] and subsequent reductive aromatization with tin(II) chloride furnished dialkynylanthracene **16**, which was desilylated to **17** using a standard protocol (K_2CO_3, MeOH).[31] Unfortunately, neither reaction of the lithiated terminal alkynes with carbon dioxide (→**18**) nor with ethyl chlorocarbonate (→**19**)[32] could be achieved with this substrate. Since other approaches in-between turned out to be more successful, we ceased our efforts in this context. Nevertheless, dialkynes **16** and **17** could be of significant interest for the synthesis of electronic devices and of molecular rods.[33]

The allyl group was identified as a further suitable substituent, which might be transferred into a propionate moiety through hydroboration and subsequent oxidation of the alcohol. To facilitate ^{1}H NMR analysis, we at first tested allyl additions with the methyl-protected anthraquinone **5a** (Scheme 6). Utilization of allyl magnesium bromide (purchased



Scheme 4. Synthesis and attempted cyclization of biscarboxylate **14**. Conditions: a) MeMgBr, MeLi, THF, −78 °C, 1.5 h, then **5a**, −78 °C→rt, 16 h, 87%; b) R = Me, **11a**: MeMgBr, toluene, 100 °C, 16 h; R = C_6H_{13}, **11b**: MeLi, MeMgBr, THF, −78 °C→rt, 18 h, 87%; c) R = Me, **12a**: Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 1 h, 12% (2 steps); R = C_6H_{13}, **12b**: $SnCl_2$, HOAc/THF (1:1), reflux, 5 h, 67% (2 steps); d) NBS, AIBN, CCl_4, reflux, 20 h; R = Me: no conversion; R = C_6H_{13}, **13b**: 72%; e) AcO*t*Bu, LDA, THF, −78 °C→rt, 17 h, 64%; f) see text.



Scheme 5. Attempted synthesis of anthracene-derived acetylene carboxylates. Conditions: a) TMS-acetylene, BuLi, THF, −78 °C, 1.5 h, then **5a**, −78 °C→rt, 16 h, then $SnCl_2$, HOAc/THF (1:1), reflux, 5 h, 47%; b) K_2CO_3, MeOH/CH_2Cl_2 (1:1), 20 h, 78%; c) BuLi, THF, −78 °C, 1.5 h, then CO_2, −78 °C to rt, 16 h; d) BuLi, THF, −78 °C, 1.5 h, then $ClCO_2Et$, −78 °C→rt, 16 h.

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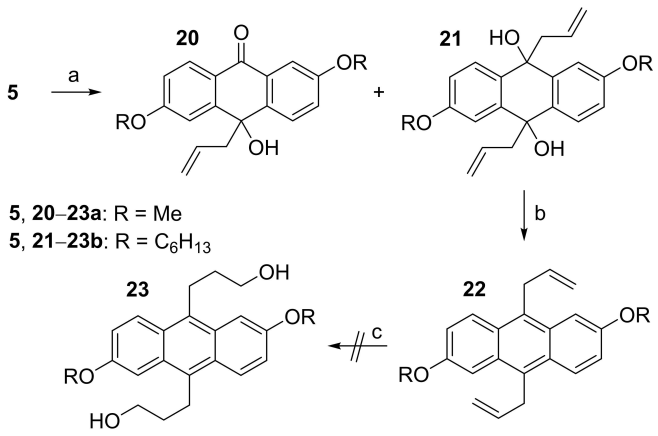


Scheme 6. Alcohols **23** as precursors for Friedel-Crafts acylations. Conditions: a) see Table 1; b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C→rt, 1 h, quant.; c) see text.

as 1 M solution in Et_2O) led to no allyl adduct at all when the reaction was performed in diethyl ether,[18a] tetrahydrofurane,[18b] or toluene,[4] at temperatures ranging from 0 to 70 °C, and with reaction times prolonged to even 72 h (Table 1). Some conversion was observed when the reaction was performed in boiling toluene, but yield of diallyl adduct **21 a** did not exceed 12%. Similar observations were made when hexyl-protected anthraflavic acid **5 b** was reacted with these conditions: Only a poor 20% yield of **21 b** was obtained when the reaction was performed in toluene at 110 °C and other conditions were even less successful. It could be mentioned that even with over-stoichiometric amounts of the Grignard reagent we always observed diol **21** together with unreacted starting material **5**, mono adduct was not observed at all. This might be possibly due to a kinetically hindered reaction of **5**, while adduct **20** reacted significantly faster.

We thus used indium-mediated Barbier-type reactions, which are known to be well suited for the allylation of carbonyl groups.[35] A published protocol for the mono-allylation of anthraquinones with allyl bromide, indium, and sodium iodide[36] similarly furnished mono-allylated product **20 a** in up to 70% yield. Contrary to the addition of Grignard reagents, no double allylation was observed even with 4.2 equivalents of the indium reagent. Increasing the temperature from room temperature to 100 °C and prolonging the reaction time to 72% led to the formation of diallyl adduct **21 a**, but only with a poor yield of 15%.

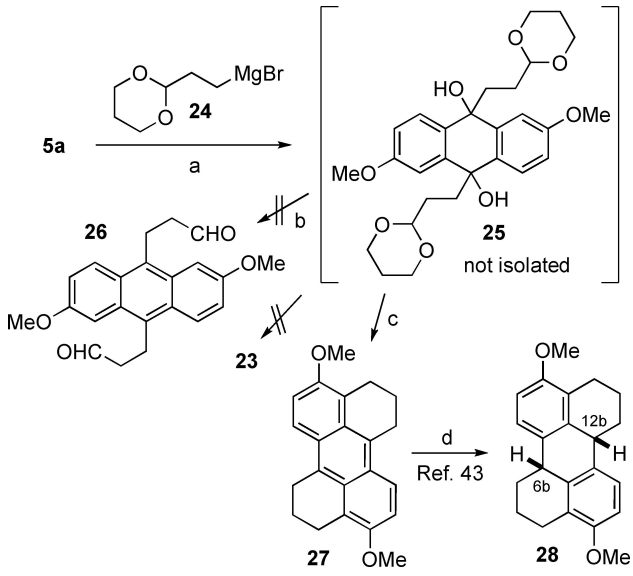
We used the small amounts of **21 a** and **b** obtained to investigate the further course of the proposed reaction scheme. Reductive aromatization with the proven combination of triethylsilane and boron trifluoride furnished **22 a** and **b**, respectively, with quantitative yields. Unfortunately, a hydroboration (with subsequent oxidative work-up) to **23** could not be achieved, neither with borane dimethyl sulfide complex ($BH_3{\cdot}SMe_2$)[37] nor with 9-borabicyclo[3.3.1]nonane (9-BBN),[38] although numerous variations of the conditions were tested. Further efforts on this route were thus not made.

We finally decided to use Grignard reagents, which already contain a (protected) carbonyl group, which can be used in the due course. Reaction of methyl-protected anthraflavic acid **5 a** with Grignard reagent **24** lead to a product mixture, where ^1H NMR-spectroscopic analysis suggested formation of adduct **25** (Scheme 7). We expected that Lewis acid-catalyzed reductive aromatization would concomitantly lead to a cleavage of the acetal groups and thus to a liberation of the aldehyde functions. We thus chose reaction conditions, which had been reported to be similarly applicable for the cleavage of acetals. Nevertheless, neither utilization of tin(II) chloride with hydrochloric[39] or acetic acid,[40] nor of potassium[41] or sodium iodide[42] together with the respective dihydrogenphosphate salt and acetic acid led to the formation of aldehyde species. Since we suspected a reduction of the intermediately formed carbonyl groups, we intended to enforce this transformation and again used

Table 1. Allyl addition to anthraquinones **5**.

Starting material	Conditions	Product (yield [%])
5 a	allylMgBr, Et_2O, THF, or toluene, 0–70 °C, 3–72 h	(–)
5 a	allylMgBr, toluene, 110 °C, 16 h	**21 a** (11)
5 a	allylMgBr, toluene, 130 °C, 65 h	**21 a** (12)
5 a	allylBr, In, NaI (4.2 equiv.), DMF, rt, 16 h[a]	**20 a** (70)
5 a	allylBr, In, NaI (2.1 equiv.), DMF, 100 °C, 72 h[b]	**21 a** (15)
5 b	allylMgBr, Et_2O, THF, or toluene, rt, 16 h	(–)
5 b	allylMgBr, THF, 70 °C, 6 h	(–)
5 b	allylMgBr, toluene, rt, 16 h	(–)
5 b	allylMgBr, toluene, 110 °C, 16 h	**21 b** (20)

[a] 2.1 equivalents, temperatures ranging from rt to 60 °C, and reaction times from 16 to 72 h gave lower yields of **21 a** in the range of 39–49%; [b] only traces of **20 a** and **21 a** were observed after 16 h.



Scheme 7. Acetals and aldehydes as precursors for Friedel-Crafts-type reactions. Conditions: a) **24**, toluene, 100 °C, 16 h; b) see text; c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C→rt, 1 h, **27**: 22% (2 steps from **5 a**); d) Ref. [43] Li, NH_3 (l), THF, −33 °C, 1 h.

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triethylsilane with boron trifluoride as reductive reagent combination. We were delighted to see that neither diol **23** nor any other similar intermediate had been formed; instead we isolated pentacycle **27** in an acceptable yield (22% over two steps from **5a**). This product has obviously been formed by double intramolecular Friedel-Crafts-type cyclization of an intermediate like **23** or **26**, where reductive dihydroxylation happened at any stage of the sequence.

As reported previously by us,[43] anthracene-derived pentacycle **27** can be transferred with Birch conditions to octahydroperylene **28**, the framework of all perylenequinone-derived toxins of the dihydroanthracene type. The herein achieved *cis*-arrangement at positions 6b and 12b is that present in these natural products.

Conclusions

We finally achieved the synthesis of the *cis*-configured octahydroperylene core present in altertoxin III and various further perylenequinone-derived mycotoxins starting from anthraflavic acid (**4**) in only four steps, where the last step has already been published previously by us. We had to realize that quite a number of promising alternative approaches turned out to be not successful. On the other hand, the therein obtained intermediates seem to be of significant synthetic value and alkynyl derivatives like **16** and **17** might be additionally useful, e.g., for the synthesis of electronic devices and of molecular rods.

Experimental Section

4,10-Dimethoxy-1,2,3,7,8,9-hexahydroperylene (27): Adapting a published protocol,[44] Mg (500 mg, 20.6 mmol) and a catalytic amount of I_2 were heated under an argon atmosphere and stirred overnight. Anhydrous THF (10 mL) was added and a fraction of a solution of 2-(2-bromoethyl)-1,3-dioxane (0.6 mL of a total of 2.10 mL, 3.01 g, 15.4 mmol) in anhydrous THF (4 mL) was added. The mixture was stirred at rt until the reaction started and the rest of the bromide solution was added dropwise within 20 min. Meanwhile, the reaction flask was occasionally lowered into a water bath to avoid boiling of the reaction mixture. After completion of the addition, the mixture was stirred for a further 2 h at rt. The thus obtained Grignard reagent was added dropwise within 30 min under an argon atmosphere to a solution of anthraquinone **5a** (408 mg, 1.52 mmol) in anhydrous toluene (120 mL). The mixture was heated for 18 h to 90 °C and cooled to rt. 1 M aqueous HCl (75 mL) was added and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (2×50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated at reduced pressure to yield crude intermediate **25**, which was reacted without further purification by adaption of a published protocol:[20] Et_3SiH (0.65 mL, 473 mg, 4.07 mmol) was added dropwise under an argon atmosphere to a cooled (0 °C) solution of the crude product in anhydrous CH_2Cl_2 (15 mL) and the mixture was stirred for 10 min at this temperature. $BF_3{\cdot}OEt_2$ (0.52 mL, 588 mg, 4.14 mmol) was added dropwise and the mixture was stirred for 1 h at rt. 1 M aqueous $NaHCO_3$ solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with H_2O (2×20 mL) and brine (20 mL), dried (Na_2SO_4), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/CH_2Cl_2 2:1) to yield **27** as a yellow crystalline solid (106 mg, 0.333 mmol, 22%). $R_f = 0.39$ (cyclohexane/CH_2Cl_2 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.16$ (quint, $^3J = 6.4$ Hz, 4 H, 2-H_2, 8-H_2), 3.14 (t, $^3J = 3.4$ Hz, 4 H, 3-H_2, 9-H_2 or 1-H_2, 7-H_2), 3.50 (t, $^3J = 6.1$ Hz, 4 H, 1-H_2, 7-H_2 or 3-H_2, 9-H_2), 3.98 (s, 6 H, 2×OCH_3), 7.34 (d, $^3J = 9.6$ Hz, 2 H, 5-H, 11-H), 8.08 ppm (d, $^3J = 9.6$ Hz, 2 H, 6-H, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.6$ (2×CH_2), 23.8 (2×CH_2), 27.1 (2×CH_2), 57.1 (2×CH_3), 114.9 (2×CH) 120.8 (2×C), 122.8 (2×CH), 125.6 (2×C), 127.3 (2×C), 128.8 (2×C), 150.7 ppm (2×C); IR (ATR): $\tilde{\nu} = 3257$ (vw), 2928 (w), 2859 (w), 2829 (w), 1679 (vw), 1615 (m), 1426 (w), 1246 (m), 1108 (m), 1021 (m), 875 (w), 796 (m), 615 cm^{-1} (w); MS (FAB): *m/z* (%): 319 (36) $[M+1]^+$, 318 (100) $[M]^+$, 317 (31) $[M-1]^+$; HRMS (FAB): *m/z* calcd for $C_{22}H_{22}O_2$: 318.1614; found: 318.1612.

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [45–48]).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: perylenequinones · mycotoxins · total synthesis · Grignard addition · anthracene derivatives

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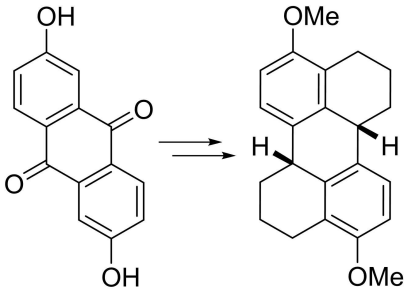
RESEARCH ARTICLE

The *cis*-configured octahydroperylene core, present in perylenequinone-derived mycotoxins like altertoxin III was synthesized from anthraflavic acid in four steps.



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