Total Synthesis of 4-Azaeudistomin Y_1 and Analogues by Inverse-Electron-Demand Diels–Alder Reactions of 3-Aminoindoles with 1,3,5-Triazines

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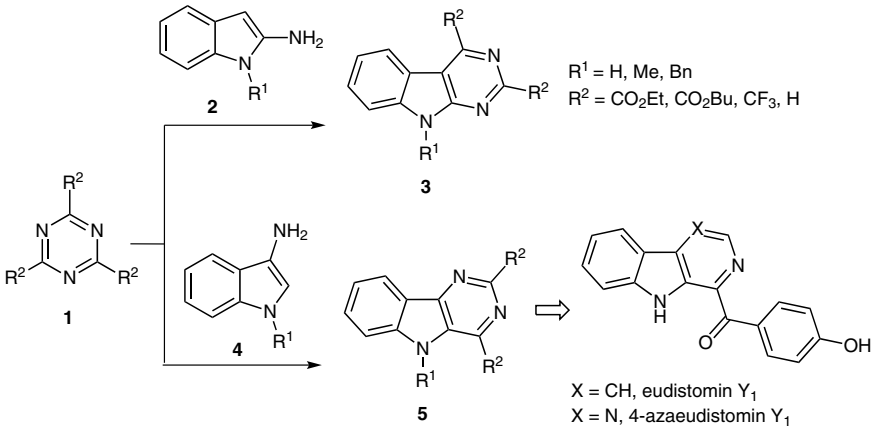
Abstract: A new inverse-electron-demand Diels–Alder (IDA) reaction of 3-aminoindoles as dienophiles was developed for the efficient preparation of 4-aza-β-carbolines in high yields. Because N^1-unprotected 3-aminoindoles show poor thermal stability, a one-pot protocol was developed that combines the removal of *tert*-butoxycarbonyl protecting groups with the IDA reaction. This protocol, using *tert*-butyl 1*H*-indol-3-ylcarbamates as reactants, gave the corresponding IDA products in excellent yields. The new IDA methodology was used in a total synthesis of 4-azaeudistomin Y_1, which was obtained in 57% overall yield in four steps. Moreover, the chemistry is suitable for the rapid preparation, through either Friedel–Crafts acylation or amide-formation reactions, of analogues that are useful for exploring structure–activity relationships at the C_1-position.

Key words: indoles, Diels–Alder reactions, heterocycles, total synthesis

Eudistomins are a group of β-carboline natural products with interesting biological activities.[1] For example, eudistomins D, G, H, I, K, N, and O exhibit antiviral activities[2] and eudistomins Y_1–Y_7 show antibacterial activities.[3] Consequently, a number of efforts to synthesize eudistomins and their analogues have been reported,[4–9] and these have led to the synthesis of several eudistomins.[4,5,7] We became interested in eudistomins and we planned to investigate the structure–activity relationships of eudistomin analogues with modifications of the β-carboline core. However, few methods for generating variations of the β-carboline core have appeared in the literature. Drug-discovery programs often begin with natural products as lead substances that are subjected to optimization to produce drug candidates with the desired potency and physical properties.[10–12] One common strategy is to replace a ring carbon atom with a nitrogen, which can increase aqueous solubility, modulate the octanol–water partition coefficient log *P*, and increase selectivity toward a desired target. We envisioned a series of 4-aza-β-carboline analogues of eudistomin Y_1 as potential antibacterial agents, but we needed to develop a new method for preparing this new heterocyclic scaffold.

The inverse-electron-demand Diels–Alder (IDA) reaction of nonaromatic electron-rich dienophiles is a proven technique for preparing various heterocycles.[13,14] The use of electron-rich aromatic heterocycles as dienophiles has also been established as a productive method for synthesizing fused heterocycles through IDA reactions.[15–24] Both experimental and theoretical studies have shown that the position of a strongly electron-donating group (e.g., an amino group) dictates the regiochemical outcome of the reaction.[25,26] We recently reported that 2-aminoindoles participate in IDA reactions with 1,3,5-triazines to give 3-aza-α-carbolines regiospecifically.[27] We therefore hypothesized that IDA reactions of 3-aminoindoles with 1,3,5-triazines should produce 4-aza-β-carbolines



Scheme 1 IDA reactions of aminoindoles with 1,3,5-triazines

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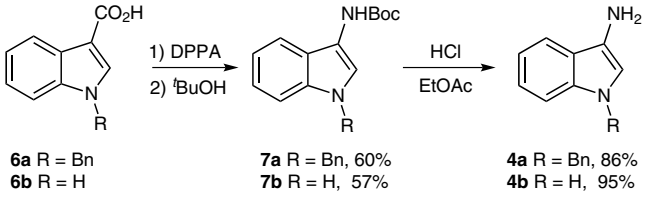
(Scheme 1). The 4-aza-β-carbolines obtained from IDA reactions of 3-aminoindoles and 1,3,5-triazines might be used to prepare 4-azaeudistomin Y_1 (Scheme 1). Moreover, such a new methodology might also allow the efficient synthesis of analogues of 4-azaeudistomin Y_1. Here, we report the development of a new IDA reaction using 3-aminoindoles as dienophiles, and the application of this new method in the total synthesis of 4-azaeudistomin Y_1 and its analogues.

3-Aminoindoles **4a** and **4b** were prepared from the corresponding 3-indolecarboxylic acids by a two-step sequence involving a Curtius rearrangement and subsequent removal of the *tert*-butoxycarbonyl (Boc) protecting group (Scheme 2). Treatment of the resulting indolecarboxylic acids **6a** and **6b** with diphenylphosphoryl azide in *tert*-butyl alcohol gave indoles **7a** and **7b** in moderate yields.[28,29] Subsequent removal of the Boc group by treatment with hydrogen chloride in ethyl acetate gave the corresponding 3-aminoindoles **4a** and **4b** as their hydrochloride salts, which could be used without purification in subsequent reactions.

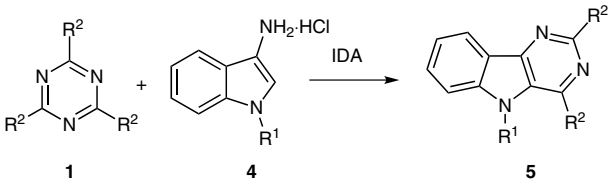


Scheme 2 Synthesis of 3-aminoindoles **4a** and **4b**

To test the concept of using 3-aminoindoles **4a** and **4b** as dienophiles in IDA reactions, we selected the *S*[2],*S*[4],*S*[6]-triethyl 1,3,5-triazine-2,4,6-tricarbothioate (**1a**; Table 1)[30] as a reactant for our initial investigations because this compound has better solubility than the commonly used triethyl 1,3,5-triazine-2,4,6-tricarboxylate (**1b**). The reaction of indole **4a** with triazine **1a** in *N*,*N*-dimethylformamide under mild thermal conditions gave an excellent yield of the desired IDA product **5a** (Table 1, entry 1). Increasing the temperature shortened the reaction time but gave a lower yield (entry 2), probably as a result of partial decomposition of the highly electron-rich 3-aminoindole **4a** at the higher temperature. We therefore explored the scope of the IDA reaction of 3-aminoindoles with other 1,3,5-triazines (entries 3–7). Electron-deficient triazines **1b** and **1c** were also good substrates for this reaction, giving good-to-high yields of the corresponding IDA products, whereas triazines **1d** and **1e** did not give the expected products, probably because they are insufficiently electron-deficient to function as dienes in the IDA reaction. Finally, the N^1-unprotected 3-aminoindole **4b** was also shown to act as a dienophile, although it gave only a moderate yield of the IDA product, probably as a result of its poor thermal stability.

Having developed a robust method for preparing the desired 4-aza-β-carboline **5b**, we next examined its conversion into 4-azaeudistomin Y_1 (Scheme 3). The ester group at the C_1-position of **5b** was functionalized by reduction with sodium borohydride to give a high yield of the desired alcohol **8b**. Oxidation of the primary alcohol group to an aldehyde group with 1-hydroxy-1λ[5],2-benziodoxol-1,3-dione (IBX)[31,32] followed by a Grignard addition gave secondary alcohol **11b**, which was subsequently oxidized to give the dibenzyl-protected form of 4-azaeudistomin Y_1 **12b**. Unfortunately, all attempts to remove the two benzyl protecting groups [for example, by treatment with hydrogen in the presence of palladium/carbon,[33] with trifluoroacetic acid,[34] or with aluminum(III) chloride][35] failed to give the desired 4-azaeudistomin Y_1.

Table 1 IDA Reactions of 3-Aminoindoles with 1,3,5-Triazines

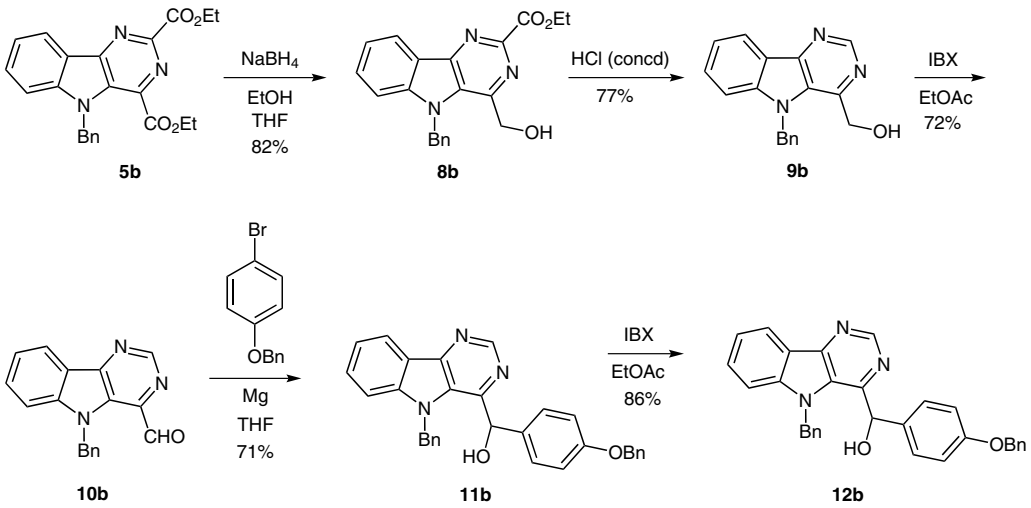


1 4 5

Entry[a]	Indole	R^1	Triazine	R^2	Time (h)	Product	Yield (%)
1	**4a**	Bn	**1a**	COSEt	12[b]	**5a**	92
2	**4a**	Bn	**1a**	COSEt	7[b,c]	**5a**	80
3	**4a**	Bn	**1b**	CO_2Et	13	**5b**	85
4	**4a**	Bn	**1c**	CO_2Bn	8	**5c**	92
5	**4a**	Bn	**1d**	4-BrC_6H_4	48	**5d**	0[d]
6	**4a**	Bn	**1e**	OMe	48	**5e**	0[d]
7	**4b**	H	**1b**	CO_2Et	14[e]	**5f**	44

[a] All reactions were conducted using the indole (1 equiv) and triazine (2 equiv) in DMF at 50 °C.
[b] Indole (2 equiv) and triazine (1 equiv) were used.
[c] The reaction was conducted at 80 °C.
[d] Only traces of the products were detected by LC/MS.
[e] The reaction was conducted in DMSO.

Because the N^1-benzyl group proved to be unexpectedly stable toward various deprotection strategies, we decided to investigate the conversion of the N^1-unprotected β-carboline **5f** into 4-azaeudistomin Y_1. However, the initial IDA reaction of 1*H*-indol-3-amine (**4b**) gave only a moderate yield of compound **5f** (Table 1, entry 7). We therefore attempted to optimize this reaction to generate larger amounts of the N^1-unprotected β-carboline with a greater efficiency. We hypothesized that the lower yield of the IDA reaction of 1*H*-indol-3-amine (**4b**) was probably due to its poor stability (highly electron-rich nature) under the thermal reaction conditions. One approach to solving this problem might be to generate the reactive species in situ, a technique that has already been successfully applied in several IDA reactions.[18,36] Previously, we demonstrated that 2-aminofurans generated in situ from their Boc-protected analogues participate in IDA reactions with 1,3,5-triazines and give the desired IDA products in high



Scheme 3 Initial attempt at a total synthesis of 4-azaeudistomin Y_1

yields.[24] We therefore decided to investigate the IDA reactions of Boc-protected aminoindoles under conditions suitable for in situ removal of Boc groups that were reported previously,[24] and our results are summarized in Table 2.

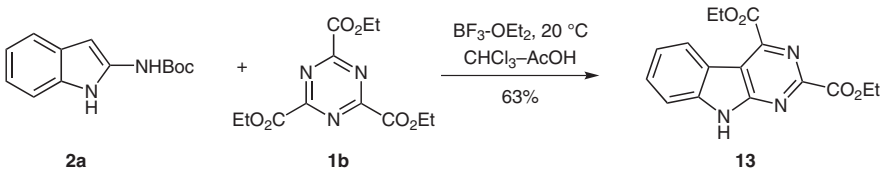
Table 2 IDA Reactions of *tert*-Butyl 3-Amino-1*H*-indole-1-carboxylate (**7b**) with 1,3,5-Triazine **1b**

Entry[a]	Ratio **7b**/**1b** (equiv)	Lewis Acid (equiv)	Time	Yield[b] (%)
1	1:2	$BF_3{\cdot}OEt_2$, (6)	1 h	95
2	2:1	$BF_3{\cdot}OEt_2$, (6)	1 h	71
3	1:1	$BF_3{\cdot}OEt_2$, (6)	1 h	69
4	1:2	$BF_3{\cdot}OEt_2$, (0.1)	4 d	trace[c]
5	1:2	none	4 d	0[c]

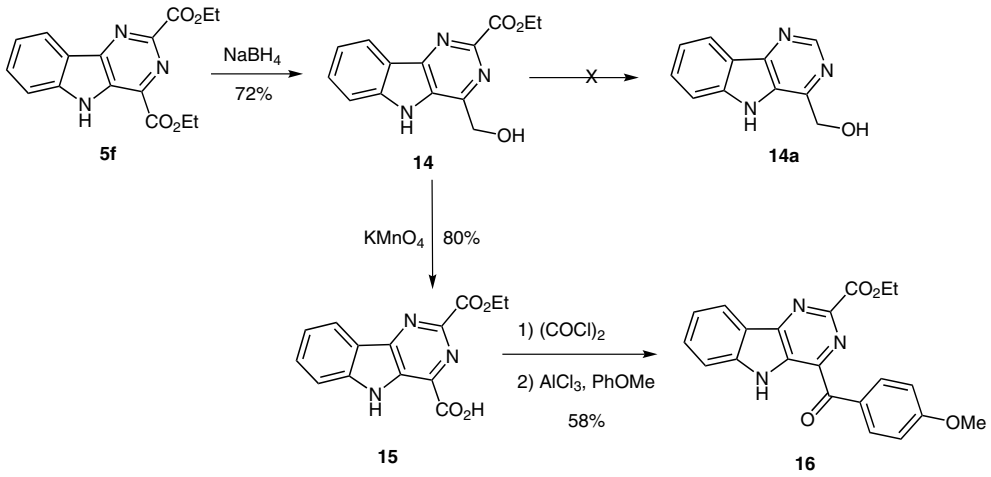
[a] All reactions were conducted on 0.5 mmol scale of the limiting reagent in 3:1 $CHCl_3$–AcOH (4 mL) under N_2 at 20 °C.
[b] Yield of isolated product.
[c] Unreacted indole **7b** remained.

The reaction of indole **7b** with an excess of triazine **1b** under our previously reported conditions[24] (Table 2, entry 1) gave an excellent yield of the desired IDA product **5f**. It is likely that the presence of an excess of the triazine **1b** ensured speedy capture of the reactive and less-stable 3-aminoindole generated in situ, thereby resulting in an excellent yield of the IDA product. To confirm this hypothesis, we used the triazine **1b** as the limiting reagent (entries 2 and 3) and, under otherwise identical conditions, the IDA product **5f** was obtained in lower yields. This result suggests that the rate-limiting step is the IDA reaction step rather than the Boc deprotection step, and that some degree of decomposition of the 1*H*-indol-3-amine probably occurred. To investigate whether an excess of the Lewis acid is required, we conducted the reaction in the presence of either a catalytic amount of boron trifluoride etherate (entry 4) or in the absence of the Lewis acid (entry 5). A catalytic amount of Lewis acid gave only a trace of the IDA product, whereas none was formed in the absence of the Lewis acid; unreacted indole **7b** remained under both sets of conditions. These results show that the Boc-protected 3-aminoindole is not sufficiently electron rich to participate in IDA reactions with 1,3,5-triazines and that the in situ removal of the Boc group requires the presence of an excess of boron trifluoride etherate. Therefore, the optimal conditions for the one-pot Boc-removal–IDA reaction of *tert*-butyl 3-amino-1*H*-indole-1-carboxylate (**7b**) are those shown in entry 1 of Table 2.

Because of the electronic and steric differences between 2-aminoindoles and 3-aminoindoles, a comparison of the two systems under the same reaction conditions might provide insights into their IDA reactions. We therefore treated indole **2a** with triazine **1b** under the optimal conditions for the protected 3-aminoindole **7b**. The reaction took 46 hours to complete and gave a 63% yield of the desired IDA product **13** (Scheme 4). These results suggest that 1*H*-indole-2-amine is less reactive than 1*H*-indole-3-amine toward the IDA reaction with triazine **1b**. The lon-



Scheme 4 Comparative reactivity of a 2-aminoindole derivative



Scheme 5 Elaboration of compound **5f** to 4-azaeudistomin Y_1

ger reaction time probably contributed to the lower yield of the IDA product **13**.

Having established that the key intermediate **5f** could be efficiently prepared by our newly developed method, we examined its conversion into 4-azaeudistomin Y_1 by the synthetic sequence shown in Scheme 5. Selective reduction of **5f** with sodium borohydride gave the alcohol **14** as the major product in good yield. To establish the regiochemistry of product **14** unambiguously, we performed an X-ray crystal structure determination (Figure 1), which confirmed that the hydroxymethyl group is attached at the C_1-position.[37]

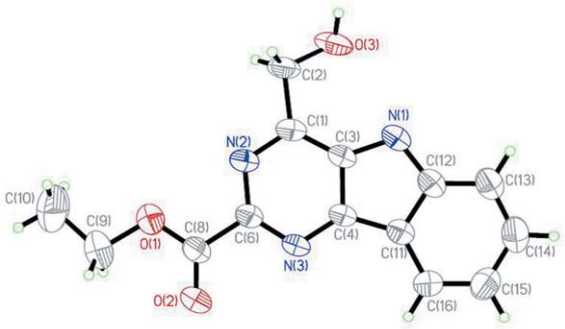


Figure 1 X-ray crystal structure of IDA product **14**[37]

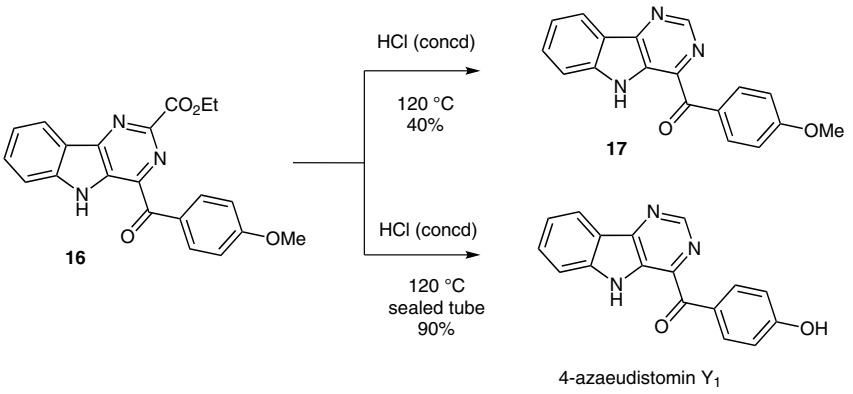
However, removal of the C_3-ester group by using the conditions shown in Scheme 3 (concentrated hydrochloric acid)[38] failed to give the desired product **14a**. Attempts to perform a two-step decarboxylation through hydrolysis of compound **14** to the carboxylic acid followed by decarboxylation by treatment with acetic anhydride and acetic acid[18] or with copper(II) oxide, quinoline, and acetic acid[39] were also unsuccessful (Scheme 5). We therefore hypothesized that installation of the desired moiety at the C_1-position, followed by global deprotection under strongly acidic conditions might result in the desired removal of the C_3-ester group.

Oxidation of alcohol **14** with potassium permanganate gave the carboxylic acid **15**, which is already in the desired oxidation state for 4-azaeudistomin Y_1. To introduce the aroyl group at the C_1-position, we chose to use a Friedel–Crafts acylation reaction[40,41] instead of the previous two-step sequence (Grignard addition followed by oxidation; Scheme 3). Conversion of carboxylic acid **15** into the corresponding acyl chloride by treatment with oxalyl chloride in the presence of catalytic amount of *N*,*N*-dimethylformamide, followed by a Friedel–Crafts reaction with anisole in the presence of aluminum(III) chloride gave keto ester **16** in 58% yield (Scheme 5). All attempts to couple compound **15** with phenol directly failed to give the desired Friedel–Crafts product, and only the phenyl ester product was obtained.

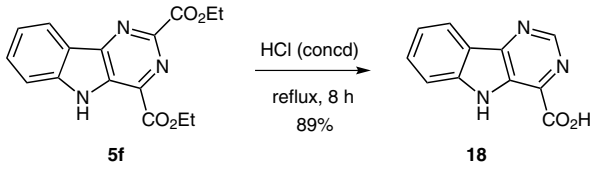
To prepare 4-azaeudistomin Y_1 from compound **16**, it was necessary to remove the C_3-ester group and the methyl group from the phenyl ether. Application of the Von Strandtmann conditions[38] produced compound **17** in 40% yield (Scheme 6). We also attempted a two-step procedure involving hydrolysis followed by decarboxylation with acetic anhydride–acetic acid,[18] but decarboxylation was not achieved. To prevent escape of hydrogen chloride from the reaction system under the Von Strandtmann conditions, we conducted the reaction in a sealed steel bomb reactor. To our delight, the ester and methyl groups were both removed, and 4-azaeudistomin Y_1 was obtained in 90% yield (Scheme 6). This completed a total synthesis of 4-azaeudistomin Y_1 in five steps and 28% overall yield.

Given that compound **5f** has a similar electronic configuration to compound **16**, it was possible that one of the two ester groups might be eliminated selectively. Treatment of compound **5f** with concentrated hydrochloric acid indeed led to a clean removal of the C_3-ester group. Moreover, the C_1-ester group was also hydrolyzed under the reaction conditions, leading to the desired carboxylic acid **18** in excellent yield (Scheme 7).

We had therefore developed an efficient two-step sequence involving an IDA reaction and subsequent



Scheme 6 Synthesis of 4-azaeudistomin Y_1 and an *O*-methoxy analogue



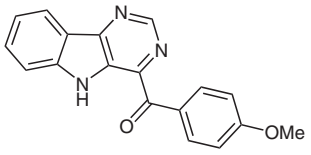
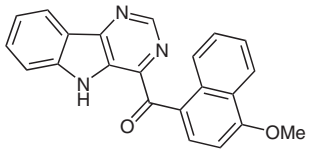
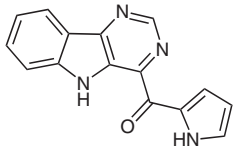
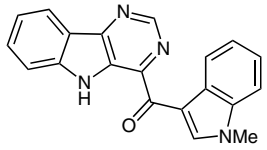
Scheme 7 Synthesis of 5*H*-pyrimido[5,4-*b*]indole-4-carboxylic acid

deesterification for converting triazine **1b** into the acid **18**, an excellent intermediate for the total synthesis of 4-azaeudistomin Y_1 and its analogues. Conversion of compound **18** into the corresponding acyl chloride, followed by Friedel–Crafts reaction with anisole gave the ketone **17** in good yield (Table 3, entry 1). We then examined the expansion of the scope of the Friedel–Crafts acylation to give the 4-azaeudistomin Y_1 analogues **19a–c** in a single step (entries 2–4).

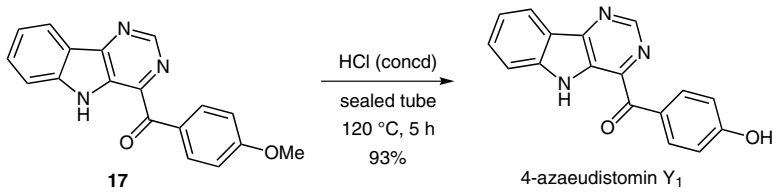
As evident in Table 3, both electron-rich aromatic (entries 1 and 2) and heteroaromatic (entries 3 and 4) compounds are good substrates for the Friedel–Crafts reaction with compound **18**. A library of C_1-analogues of 4-azaeudistomin Y_1 could therefore be readily prepared. The availability of compound **17** should also enable us to improve our total synthesis of 4-azaeudistomin Y_1. Treatment of compound **17** with concentrated hydrochloric acid[38] at 120 °C gave 4-azaeudistomin Y_1 in 93% yield (Scheme 8). Thus, 4-azaeudistomin Y_1 was synthesized in 57% overall yield in four steps starting from the commercially available triazine **1b**.

In summary, 3-aminoindoles were used as productive dienophiles in IDA reactions with 1,3,5-triazines to give the corresponding 4-aza-β-carbolines. One problem with using 3-aminoindoles as a dienophiles is their poor stability,

Table 3 Friedel–Crafts Reactions of Compound **18**

Entry	ArH	Product	Yield (%)
1	PhOMe	 **17**	73
2	1-methoxynaphthalene	 **19a**	78
3	pyrrole	 **19b**	65
4	1-methyl-1*H*-indole	 **19c**	79

which contributed to the moderate yields initially observed for the IDA reactions. To alleviate this problem, we developed a one-pot protocol involving Boc-removal



Scheme 8 Improved total synthesis of 4-azaeudistomin Y_1

from *tert*-butyl 3-amino-1*H*-indole-1-carboxylate as a reactant with a subsequent IDA reaction to give the corresponding IDA products in excellent yields. The new IDA method was applied to the total synthesis of 4-azaeudistomin Y_1, which was obtained in 57% overall yield in four steps. Moreover, the chemistry that we have established is suitable for the rapid generation of analogues (either through Friedel–Crafts acylation or amide-formation reactions) that are useful for exploring structure–activity relationships pertaining to the C_1-position.

Triazines **1b**, **1d**, and **1e** were purchased (Aldrich) and used without further purification. Triazines **1a** and **1c** were synthesized as described in the literature.[21] THF was distilled from sodium/benzophenone. Et_3N and *t*-BuOH were distilled from CaH_2. CH_2Cl_2 and EtOH were dried with $MgSO_4$ and Na_2SO_4. Other commercial reagents were used as received without additional purification. Melting points were measured with a SGW X-4 apparatus. Mass spectra and HPLC (ELSD) data was recorded on an Agilent 1100 LC/MS system using a 4.6 × 50 mm column (C-18 AQ+, 5 μm) with elution by a 5–95% (v/v) linear gradient of MeCN in H_2O containing 0.035% TFA over 5 min at a flow rate of 3.5 mL/min. Anal. TLC was performed on 2.5 × 5 cm plates coated with a 0.25-mm thickness of silica gel GF_{254}. Column chromatography was performed on silica gel G (200–300 mesh). NMR spectra were recorded on a Varian 300 MHz spectrometer. ^{1}H NMR spectra (300 MHz) shifts are referenced to TMS as internal standard. ^{13}C NMR spectra (75 MHz) were determined with complete proton decoupling. High-resolution mass spectrometric analyses and elemental analyses were carried out at Jilin University.

tert-Butyl (1-Benzyl-1*H*-indol-3-yl)carbamate (7a)

Et_3N (1.7 mL, 11.90 mmol) and DPPA (3.275 g, 11.90 mmol) were added to a soln of 1-benzyl-1*H*-indole-3-carboxylic acid[42] (2.990 g, 11.90 mmol) in THF (40 mL) under N_2 at r.t. After 48 h, the solvent was removed under reduced pressure, *t*-BuOH (40 mL) was added, and the mixture was refluxed for 5 h under N_2. The solvent was removed under reduced pressure, and the residue was purified by chromatography [silica gel, PE–EtOAc (10:1)] to give a white solid; yield: 2.302 g (60%); mp 165–167 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.45 (m, 2 H), 7.29–7.21 (m, 4 H), 7.19–7.04 (m, 4 H), 6.44 (s, 1 H), 6.24 (s, 2 H), 1.51 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 134.2, 128.6, 128.5, 128.4, 127.4, 126.7, 126.6, 122.1, 118.7, 118.0, 116.7, 114.5, 109.6, 49.9, 28.3.

MS (ESI): *m/z* = 345 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.60; H, 6.92; N, 8.70.

tert-Butyl 1*H*-Indol-3-ylcarbamate (7b)

Et_3N (0.9 mL, 6.21 mmol) and DPPA (1.707 g, 6.21 mmol) were added to a soln of 1*H*-indole-3-carboxylic acid (1.000 g, 6.21 mmol) in THF (20 mL) under N_2 at r.t. After 48 h, the solvent was removed under reduced pressure, *t*-BuOH (20 mL) was added, and the mixture was refluxed for 5 h under N_2. The solvent was removed under reduced pressure, and the residue was purified by chromatography [silica gel, PE–CH_2Cl_2–EtOAc (200:100:30)] to give a white solid; yield: 793 mg (57%); mp 177–179 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.90 (s, 1 H), 7.45–7.42 (m, 1 H), 7.29–7.26 (m, 1 H), 7.10–7.06 (m, 2 H), 6.95 (s, 1 H), 5.78 (s, 1 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.5, 133.9, 121.2, 121.0, 118.2, 117.9, 115.3, 114.4, 111.2, 78.3, 28.3.

MS (ESI): *m/z* = 255 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.49; H, 6.97; N, 12.06.

5-Benzylpyrimido[5,4-*b*]indoles 5a–c; General Procedure

The 3-aminoindole hydrochloride (0.25 mmol) was added to a stirred soln of the appropriate 1,3,5-triazine **1** (0.50 mmol) in DMF (1 mL) under N_2 at 50 °C. When the reaction was complete, the mixture was added to H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (silica gel).

_S_^{2},_S_^{4}-Diethyl 5-Benzyl-5*H*-pyrimido[5,4-*b*]indole-2,4-dicarbothioate (5a)

Purification by column chromatography [silica gel, PE–EtOAc (100:7)] gave a yellow solid; yield: 100 mg (92%); mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 7.5 Hz, 1 H), 7.76–7.71 (m, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.51–7.46 (m, 1 H), 7.22–7.20 (m, 3 H), 6.96–6.93 (m, 3 H), 6.06 (s, 2 H), 3.15 (q, *J* = 7.5 Hz, 2 H), 3.01 (q, *J* = 7.5 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.31 (q, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 190.7, 152.5, 148.9, 144.90, 139.7, 136.5, 132.3, 128.7, 127.5, 127.2, 126.0, 123.0, 122.4, 120.5, 111.1, 49.8, 23.9, 23.7, 14.7, 14.0.

MS (ESI): *m/z* = 436 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_2S_2$: 436.1148; found: 436.1147.

Diethyl 5-Benzyl-5*H*-pyrimido[5,4-*b*]indole-2,4-dicarboxylate (5b)

Purification by column chromatography [silica gel, PE–CH_2Cl_2–EtOAc (5:5:1)] gave a yellow solid; yield: 86 mg (85%); mp 112–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 8.1 Hz, 1 H), 7.77–7.72 (m, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.48–7.47 (m, 1 H), 7.26–7.20 (m, 3 H), 6.93–6.90 (m, 2 H), 5.86 (s, 2 H), 4.59 (q, *J* = 7.2 Hz, 2 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 1.51 (t, *J* = 7.2 Hz, 3 H), 1.20 (q, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 164.0, 151.3, 147.0, 144.8, 138.9, 136.0, 132.2, 129.0, 128.4, 127.9, 126.0, 123.2, 122.3, 120.5, 110.7, 63.0, 62.7, 48.5, 14.4, 13.8.

MS (ESI): *m/z* = 404 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_4$: 404.1605; found: 404.1606.

Dibenzyl 5-Benzylpyrimido[5,4-*b*]indole-2,4-dicarboxylate (5c)

Purification by column chromatography [silica gel, PE–CH_2Cl_2–EtOAc (5:5:1)] gave a white solid; yield: 121 mg (92%); mp 156–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.1 Hz, 1 H), 7.74–7.71 (m, 1 H), 7.57–7.52 (m, 2 H), 7.50–7.45 (m, 2 H), 7.40–7.33 (m, 3 H), 7.30 (s, 5 H), 7.20–7.17 (m, 3 H), 6.88–6.85 (m, 2 H), 5.78 (s, 2 H), 5.57 (s, 2 H), 5.30 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 163.7, 151.2, 144.6, 138.2, 135.7, 135.6, 134.5, 132.1, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 127.7, 126.0, 125.9, 123.1, 122.2, 120.4, 110.6, 68.3, 67.8, 48.4.

MS (ESI): *m/z* = 528 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{33}H_{26}N_3O_4$: 528.1918; found: 528.1920.

Diethyl 5*H*-Pyrimido[5,4-*b*]indole-2,4-dicarboxylate (5f)

Triazine **1b** (297 mg, 0.5 mmol) and indole **7b** (116 mg, 0.25 mmol) were dissolved in a mixture of $CHCl_3$ (3 mL) and AcOH (1 mL) under N_2 at r.t. $BF_3{\cdot}Et_2O$ (0.4 mL) was added. After 0.5 h, the reaction

was quenched with sat. aq $NaHCO_3$ and the pH was adjusted to 6–7. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, PE–CH_2Cl_2–EtOAc (10:5:3)] to give a gray solid; yield: 149 mg (95%); mp 174–176 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 8.56 (d, *J* = 7.8 Hz, 1 H), 7.77–7.72 (m, 1 H), 7.64 (t, *J* = 7.8 Hz, 1 H), 7.48–7.43 (m, 1 H), 4.61 (q, *J* = 6.9 Hz, 4 H), 1.55–1.48 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 164.2, 151.8, 147.6, 143.2, 134.3, 132.5, 130.9, 123.4, 122.4, 120.4, 112.9, 63.1, 63.0, 14.5, 14.4.

MS (ESI): *m/z* = 314 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3O_4$: 314.1135; found: 314.1138.

Ethyl 5-Benzyl-4-(hydroxymethyl)-5*H*-pyrimido[5,4-*b*]indole-2-carboxylate (8b)

Diester **5b** (2.632 g, 6.52 mmol) was dissolved in a mixture of EtOH (20 mL) and THF (20 mL) under N_2 in an ice bath. $NaBH_4$ (247 mg, 6.52 mmol) was added in a portionwise manner. After 4 h, the reaction was quenched with H_2O (100 mL) and the pH of the mixture was adjusted to 5–6 with 5 M aq HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, CH_2Cl_2–EtOAc–MeOH (50:10:1)] to give a light-yellow solid; yield: 1.927 g (82%); mp 187–189 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (dd, *J* = 2.5, 8.1 Hz, 1 H), 7.69–7.65 (m, 1 H), 7.48–7.42 (m, 2 H), 7.28–7.26 (m, 3 H), 6.95–6.92 (m, 2 H), 5.75 (s, 2 H), 5.08 (s, 2 H), 4.59 (q, *J* = 6.3 Hz, 2 H), 1.52 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 149.0, 147.2, 145.7, 143.3, 136.9, 131.2, 129.4, 129.3, 128.0, 125.3, 122.8, 121.6, 120.5, 110.2, 62.8, 62.5, 48.4, 14.4.

MS (ESI): *m/z* = 362 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{19}N_3O_3$ (361): C, 69.79; H, 5.30; N, 11.63. Found: C, 70.02; H, 11.77; N, 5.28.

(5-Benzyl-5*H*-pyrimido[5,4-*b*]indol-4-yl)methanol (9b)

Ester **8b** (602 mg, 1.67 mmol) was dissolved in concd aq HCl (10 mL) and the mixture was refluxed for 2 h. The mixture was then cooled to r.t. and the precipitate that formed was collected by filtration and dried to give a yellow solid; yield: 372 mg (77%). This was used without purification in the next reaction.

5-Benzyl-5*H*-pyrimido[5,4-*b*]indole-4-carbaldehyde (10b)

Alcohol **9b** (372 mg, 1.29 mmol) and IBX[11] (720 mg, 2.57 mmol) were dissolved in EtOAc (10 mL), and the mixture was refluxed for 5 h, then cooled to r.t. The precipitate that formed was removed by filtration and washed with EtOAc (2 × 5 mL). The filtrate was evaporated to dryness and purified by column chromatography [silica gel, CH_2Cl_2–EtOAc (10:1)] to give a yellow viscous solid; yield: 265 mg (72%). This was used without further purification in the next reaction.

[4-(Benzyloxy)phenyl](5-benzyl-5*H*-pyrimido[5,4-*b*]indol-4-yl)methanol (11b)

1-(Benzyloxy)-4-bromobenzene[43] (346 mg, 1.31 mmol) was dissolved in THF (5 mL) under N_2, and Mg (38 mg, 1.58 mmol) and a piece of I_2 (5 mg) were added. When the reaction started, the soln was heated and refluxed for 2 h. The mixture was then was then cooled to r.t. and a soln of aldehyde **10b** (252 mg, 0.88 mmol) in THF (2 mL) was added in a dropwise manner. After 30 min, the reaction was quenched with 1 M aq HCl and the pH was adjusted to 5. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, CH_2Cl_2–EtOAc (1:1)] to give a yellow oil; yield: 295 mg (72%). This was used without further purification in the next reaction.

[4-(Benzyloxy)phenyl](5-benzyl-5*H*-pyrimido[5,4-*b*]indol-4-yl)methanone (12b)

Alcohol **11b** (265 mg, 0.56 mmol) and IBX[31] (315 mg, 1.12 mmol) were dissolved in EtOAc (5 mL) and the soln was refluxed for 2 h. The mixture was then cooled to r.t. and the precipitate was separated by filtration. The residue was washed with EtOAc (3 × 5 mL) and the organic phases were combined, evaporated to dryness, and purified by chromatography [silica gel, PE–EtOAc (4:1)] to give a yellow solid; yield: 227 mg (86%); mp 140–142 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.54 (d, *J* = 8.1 Hz, 1 H), 7.77–7.72 (m, 1 H), 7.62–7.57 (m, 3 H), 7.48–7.36 (m, 6 H), 6.55 (s, 5 H), 6.71–6.70 (m, 2 H), 5.57 (s, 2 H), 5.12 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.1, 157.9, 144.6, 143.1, 140.3, 138.7, 130.8, 130.3, 127.8, 126.1, 123.4, 123.3, 123.2, 123.0, 122.3, 122.1, 121.4, 121.3, 117.0, 116.1, 115.1, 109.2, 104.9, 64.8, 42.7.

MS (ESI): *m/z* = 470 $[M + H]^+$.

Anal. Calcd for $C_{31}H_{23}N_3O_2$ (469): C, 79.30; H, 4.94; N, 8.95. Found: C, 79.12; H, 4.93; N, 8.92.

***tert*-Butyl 1*H*-Indol-2-ylcarbamate (2a)**

Et_3N (0.9 mL, 6.21 mmol) and DPPA (1.707 g, 6.21 mmol) were added to a soln of 1*H*-indole-2-carboxylic acid (1.000 g, 6.21 mmol) in THF (20 mL) under N_2 at r.t. After 48 h, the solvent was removed under reduced pressure, *t*-BuOH (20 mL) was added, and the mixture was refluxed for 5 h under N_2. The solvent was removed under reduced pressure, and the residue was purified by chromatography [silica gel, PE–CH_2Cl_2–EtOAc (100:50:2)] to give a white solid; yield: 756 mg (52%); mp 156–157 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 7.43–7.03 (m, 4 H), 6.92 (s, 1 H), 6.74 (s, 1 H), 1.55 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 129.7, 127.3, 122.2, 114.9, 114.8, 113.6, 105.3, 79.3, 76.6, 23.1.

MS (ESI): *m/z* = 255 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.61; H, 6.99; N, 12.24.

Diethyl 5*H*-Pyrimido[5,4-*b*]indole-2,4-dicarboxylate (13)

$BF_3{\cdot}Et_2O$ (0.4 mL) was added to a soln of triazine **1b** (297 mg, 0.5 mmol) and indole **2a** (116 mg, 0.25 mmol) in a mixture of $CHCl_3$ (3 mL) and AcOH (1 mL) under N_2 at r.t. After 0.5 h, the reaction was quenched with sat. aq $NaHCO_3$ and the pH was adjusted to 6–7. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, PE–CH_2Cl_2–EtOAc (20:10:3)] to give a yellow solid; yield: 149 mg (95%); mp 201–202 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.11 (s, 1 H), 8.87 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 8.1 Hz, 1 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 4.76–4.65 (m, 4 H), 1.63–1.56 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 165.0, 158.1, 150.5, 147.1, 141.5, 130.4, 126.6, 122.3, 117.9, 115.5, 113.3, 63.3, 62.8, 14.3, 14.2.

MS (ESI): *m/z* = 314 $[M + H]^+$.

The data were consistent with those reported in the literature.[27]

Ethyl 4-(Hydroxymethyl)-5*H*-pyrimido[5,4-*b*]indole-2-carboxylate (14)

Diester **13** (555 mg, 1.77 mmol) was dissolved in a mixture of EtOH (10 mL) and THF (10 mL) cooled in an ice bath under N_2. $NaBH_4$

(134 mg, 3.54 mmol) was added in a portionwise manner. After 2 h, the reaction was quenched with H_2O (50 mL) and the pH was adjusted to 4–5 with 5 M aq HCl. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, CH_2Cl_2–EtOAc–MeOH (50:20:1)] to give a gray solid; yield: 347 mg (72%), mp >200 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.91 (s, 1 H), 8.30 (d, *J* = 6.9 Hz, 1 H), 7.81–7.68 (m, 2 H), 7.40–7.35 (m, 1 H), 5.04 (s, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.0, 151.9, 145.5, 145.0, 142.2, 130.3, 128.5, 121.3, 120.7, 119.4, 113.2, 63.3, 61.1, 14.2.

MS (ESI): *m/z* = 272 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_3$: 272.1030; found: 272.1023.

2-(Ethoxycarbonyl)-5*H*-pyrimido[5,4-*b*]indole-4-carboxylic Acid (15)

Ester **14** (460 mg, 1.7 mmol) was dissolved in H_2O (20 mL) and the soln was heated to 50 °C. $KMnO_4$ (405 mg, 2.6 mmol) was added, and the mixture was kept at 50 °C for 2 h. The mixture was then cooled to r.t. and filtered through a pad of Celite. The pH of the filtrate was adjusted to 2–3 with 5 M aq HCl, and the precipitate that separated was collected by filtration and dried to give a light-yellow solid; yield: 389 mg (80%), mp 196–198 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.23 (s, 1 H), 8.36 (d, *J* = 1.8 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 7.81–7.78 (m, 1 H), 7.47–7.44 (m, 1 H), 4.46 (q, *J* = 6.9 Hz, 2 H), 1.40 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.8, 163.6, 150.2, 146.3, 143.5, 136.7, 131.5, 129.7, 121.6, 121.4, 119.2, 113.7, 61.4, 14.2.

MS (ESI): *m/z* = 286 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3O_4$: 286.0822; found: 286.0814.

Ethyl 4-(4-Methoxybenzoyl)-5*H*-pyrimido[5,4-*b*]indole-2-carboxylate (16)

Acid **15** (389 mg, 1.36 mmol) was dissolved in CH_2Cl_2 (5 mL) under N_2 in an ice bath, and a drop of DMF was added, followed by oxalyl chloride (346 mg, 2.73 mmol). After 2 h, the mixture was evaporated to dryness. The residue was dissolved in PhOMe (10 mL) under N_2 in an ice bath and anhyd $AlCl_3$ was slowly added. The soln was stirred and allowed to warm to r.t. over 15 h and then the reaction was quenched by addition of H_2O (15 mL) in an ice bath. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography [silica gel, CH_2Cl_2–EtOAc (20:1)] to give a yellow solid; yield: 294 mg (58%); mp 190–192 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 8.84 (d, *J* = 9.3 Hz, 2 H), 8.59 (d, *J* = 8.1 Hz, 1 H), 7.74–7.71 (m, 1 H), 7.64 (d, *J* = 8.1 Hz, 1 H), 7.48–7.43 (m, 1 H), 7.04 (d, *J* = 9.3 Hz, 2 H), 4.62 (q, *J* = 7.5 Hz, 2 H), 3.93 (s, 3 H), 1.56 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 189.7, 163.7, 163.5, 150.5, 145.1, 143.8, 140.5, 133.7, 131.5, 129.0, 128.4, 121.7, 121.6, 119.4, 113.7, 113.6, 61.4, 55.6, 14.2.

MS (ESI): *m/z* = 376 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_4$: 376.1292; found: 376.1285.

4-Azaeudistomin Y_1 {(4-Hydroxyphenyl)(5*H*-pyrimido[5,4-*b*]indol-4-yl)methanone}

Ester **16** (64 mg, 0.17 mmol) was dissolved in concd aq HCl (8 mL) in a steel bomb reactor and the soln was heated at 120 °C for 5 h. The mixture was then cooled to r.t. and poured into H_2O (10 mL). The precipitate was collected by filtration, dried, and purified by chromatography [silica gel, CH_2Cl_2–EtOAc–MeOH (20:20:1)] to give a light-green solid; yield: 44 mg (90%); mp >316 °C dec.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.16 (s, 1 H), 10.60 (s, 1 H), 9.21 (s, 1 H), 8.33 (d, *J* = 8.1 Hz, 1 H), 8.29 (d, *J* = 9.0 Hz, 2 H), 7.81–7.78 (m, 1 H), 7.75–7.73 (m, 1 H), 7.42–7.37 (m, 1 H), 6.97 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.6, 162.8, 149.8, 147.6, 143.0, 141.6, 133.8, 130.9, 128.7, 127.1, 121.3, 120.8, 119.3, 115.2, 113.3.

MS (ESI): *m/z* = 290 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{11}N_3O_2$ (289): C, 70.58; H, 3.83; N, 14.53. Found: C, 70.48; H, 3.82; N, 14.49.

5*H*-Pyrimido[5,4-*b*]indole-4-carboxylic Acid (18)

Diester **5f** (620 mg, 1.98 mmol) was dissolved in concd HCl (25 mL) and the soln was reflux for 8 h. The mixture was then cooled to r.t. and precipitate that separated was collected by filtration and dissolved in H_2O (20 mL). The pH of the soln was adjusted to 6–7 with aq NH_3. The resulting precipitate was separated by filtration. The pH of the filtrate was then adjusted to 3 with 4 M aq HCl. The resulting precipitate was collected by filtration and dried to give a yellow solid; yield: 44 mg (89%); mp 264–267 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.27 (s, 1 H), 11.91 (s, 1 H), 9.17 (s, 1 H), 8.39–8.30 (m, 1 H), 7.89–7.78 (m, 1 H), 7.76–7.70 (m, 1 H), 7.48–7.33 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 154.8, 153.3, 147.9, 136.0, 134.4, 126.3, 125.7, 124.1, 118.4, 118.3.

MS (ESI): *m/z* = 214 $[M + H]^+$.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{11}H_8N_3O_2$: 214.0611; found: 214.0602.

Aryl 5*H*-Pyrimido[4,5-*b*]indol-4-yl Ketones; General Procedure

Acid **18** (70 mg, 0.33 mmol) was dissolved in $SOCl_2$ (5 mL) under N_2, and the soln was refluxed for 5 h. The mixture was then evaporated to dryness and the residue was dissolved in CH_2Cl_2 (5 mL) in an ice bath. Anhyd $AlCl_3$ (350 mg, 2.62 mmol) and the appropriate coupling agent (1.64 mmol) were slowly added. The soln was stirred and allowed to warm to r.t. When the reaction was complete, it was quenched by addition of H_2O (15 mL) in an ice bath, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (silica gel, PE–CH_2Cl_2–EtOAc).

(4-Methoxyphenyl)(5*H*-pyrimido[5,4-*b*]indol-4-yl)methanone (17)

Purification by column chromatography [silica gel, CH_2Cl_2–EtOAc (10:1)] gave a yellow solid; yield: 73 mg (73%); mp 224–226 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 9.32 (s, 1 H), 8.62–8.58 (m, 2 H), 8.44 (d, *J* = 7.5 Hz, 1 H), 7.73–7.68 (m, 1 H), 7.61–7.58 (m, 1 H), 7.44–7.39 (m, 1 H), 7.07–7.03 (m, 2 H), 3.93 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.9, 163.5, 150.0, 147.5, 143.1, 141.0, 133.4, 130.9, 128.7, 128.5, 121.3, 120.8, 119.2, 113.7, 113.3, 56.6.

MS (ESI): *m/z* = 304 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{13}N_3O_2$ (303): C, 71.28; H, 4.32; N, 13.85. Found: C, 71.17; H, 4.31; N, 13.80.

(4-Methoxy-1-naphthyl)(5*H*-pyrimido[5,4-*b*]indol-4-yl)methanone (19a)

Purification by column chromatography [silica gel, CH_2Cl_2–EtOAc (5:1)] gave a yellow solid; yield: 97 mg (78%); mp 248–250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.38 (s, 1 H), 9.23 (s, 1 H), 8.56 (d, *J* = 8.4 Hz, 1 H), 8.44–8.38 (m, 2 H), 8.18 (d, *J* = 8.1 Hz, 1 H), 7.91–7.70 (m, 4 H), 7.51–7.46 (m, 1 H), 7.20 (d, *J* = 8.1 Hz, 1 H), 4.17 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.9, 158.5, 150.1, 147.8, 143.2, 141.8, 135.1, 132.2, 131.0, 128.8, 128.3, 125.9, 125.1, 125.0, 124.9, 121.9, 121.4, 120.9, 119.3, 113.3, 103.1, 56.1.

MS (ESI): *m/z* = 354 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{15}N_3O_2$ (353): C, 74.78; H, 4.28; N, 11.89. Found: C, 74.98; H, 4.29; N, 11.93.

5*H*-Pyrimido[5,4-*b*]indol-4-yl(1*H*-pyrrol-2-yl)methanone (19b)
Purification by column chromatography [silica gel, CH_2Cl_2–EtOAc (5:1)] gave a yellow solid; yield: 56 mg (65%); mp 270–272 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.29 (s, 1 H), 12.11 (s, 1 H), 9.23 (s, 1 H), 8.32 (d, *J* = 8.1 Hz, 1 H), 7.74–7.70 (m, 1 H), 7.41–7.34 (m, 2 H), 6.38–6.36 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 179.5, 150.0, 147.7, 143.2, 141.0, 130.9, 130.6, 128.4, 127.4, 121.3, 121.2, 120.8, 119.2, 113.4, 110.8.

MS (ESI): *m/z* = 263 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{10}N_4O$ (262): C, 68.69; H, 3.84; N, 21.36. Found: C, 68.85; H, 3.83; N, 21.42.

(1-Methyl-1*H*-indol-3-yl)(5*H*-pyrimido[5,4-*b*]indol-4-yl)methanone (19c)
Purification by column chromatography [silica gel, CH_2Cl_2–EtOAc (5:1)] gave a brown solid; yield: 85 mg (79%); mp 221–224 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.20 (s, 1 H), 9.31 (s, 1 H), 9.25 (d, *J* = 0.9 Hz, 1 H), 8.56–8.52 (m, 1 H), 8.54 (d, *J* = 8.4 Hz, 1 H), 7.74–7.53 (m, 2 H), 7.40–7.36 (m, 3 H), 3.99 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 185.7, 149.9, 147.7, 143.1, 142.0, 141.6, 136.7, 128.2, 130.7, 127.3, 123.3, 122.8, 121.6, 121.2, 120.6, 119.2, 113.4, 112.9, 110.8, 33.4.

MS (ESI): *m/z* = 327 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{14}N_4O$ (326): C, 73.61; H, 4.32; N, 17.17. Found: C, 73.39; H, 4.33; N, 17.23.

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