Second-Generation, Biomimetic Total Synthesis of Chaetominine

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Received 1 July 2009

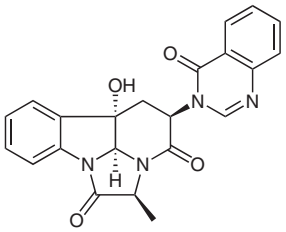
Abstract: A straightforward total synthesis of the potent anticancer agent (–)-chaetominine is reported. Central to this synthesis was a biomimetic oxidative cyclization of a tryptophanyl-alanine dipeptide, which provided a fully elaborated 1,2,3,4-tetrahydropyrido[2,3-*b*]indole. Reduction of this intermediate followed by spontaneous cyclization and installation of the side chain provided synthetic chaetominine in a nine-step sequence in 14% overall yield starting from commercially available, inexpensive starting materials.

Key words: alkaloids, total synthesis, oxidative cyclization, anticancer agents, peptides

Cancer is a leading cause of death worldwide. According to recent studies from the World Health Organization, it accounted for 7.9 million deaths (13% of all deaths) in 2007 and its incidence continues to rise.[1] Although new anticancer agents are emerging, there is still a strong need for more potent and selective drugs with fewer side effects. Natural products and natural-product-like molecules will undoubtedly play a crucial role in this area. They have been a rich source of agents of value in medicine and their role in the drug discovery and development process is undeniable. They have inspired, at various levels, the fashioning of nonnatural agents of pharmaceutical import.[2]

In the area of cancer, over the time frame from around the 1940s to 2006, of the 155 anticancer agents released, 73% were other than purely synthetic, with 47% actually being either natural products or directly derived therefrom.[3] Clearly, by building libraries around natural products, chances of finding an active compound are increased. They serve as lead agents, providing the chemist with a structural platform that can be elaborated upon or simplified to yield therapeutically valuable molecules.

With IC_{50} values of 21.0 and 28.0 nM against human leukemia K562 and colon cancer SW1116 cell lines, respectively, chaetominine (**1**) (Figure 1) most certainly falls into this category and could serve as a lead structure for the development of new anticancer agents.[4] However, the isolation of this natural product from *Chaetomium sp.* IFBE015, an endophytic fungus found on apparently healthy Adenophora axilliflora leaves, is extremely laborious (18 mg of **1** isolated from 3 kg of dehydrated fermentation batches), and this has prevented a complete understanding of its bioactivity and mode of action.



(–)-chaetominine (**1**)

Figure 1 Chaetominine (**1**)

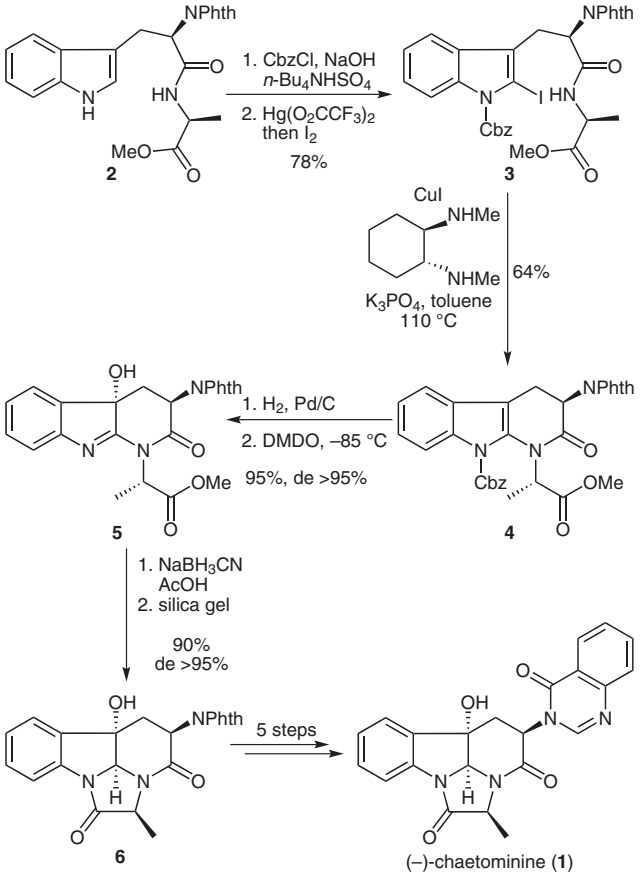
Structurally, chaetominine (**1**) possesses a unique compact tetracyclic framework built upon D-tryptophan, L-alanine, and anthranilic acid. Due to its intriguing molecular architecture and its potential as lead compound for anticancer drugs, chaetominine has attracted immediate interest from the synthetic community, and this culminated in a total synthesis by the Snider group.[5,6]

In continuation of our studies on the use of copper-catalyzed cyclization reactions for the synthesis of alkaloids,[7] we reported in 2008 the second synthesis of this natural product, based on the strategy outlined in Scheme 1.[8] Key steps include a copper-catalyzed cyclization reaction from iodinated dipeptide **3**, which allowed for the formation of the tricyclic scaffold **4**. Introduction of the two adjacent stereocenters at the ring junction was effected by consecutive diastereoselective oxidation and reduction after deprotection of the indole.

While the key cyclization proved to be efficient to construct the tricyclic core of chaetominine and the oxidation–reduction reaction sequence was highly diastereoselective, it did require protection–deprotection of the indole, as well as its iodination with mercury salts, which somehow reduced the overall efficiency of the synthesis and limited its scale-up. We report in this article a second-generation synthesis, which addresses these limitations and provides a more efficient access to synthetic chaetominine (**1**). This scalable synthetic route allowed us to access this natural product in a nine-step sequence in 14% overall yield from D-tryptophan.

The strategy of our second-generation synthesis is depicted in Scheme 2. We felt that we could considerably shorten the synthesis by constructing the pyridoindole framework of chaetominine by oxidative cyclization from dipeptide **7** in a biomimetic way. We postulated that expo-

SYNTHESIS 2009, No. 17, pp 2927–2934
Advanced online publication: 30.07.2009
DOI: 10.1055/s-0029-1216923; Art ID: C02909SS

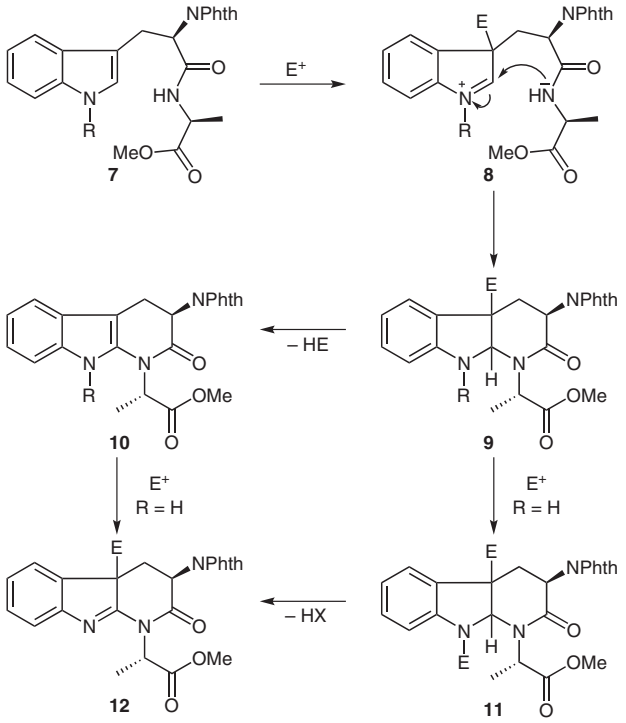


Scheme 1 First-generation synthesis of chaetominine (**1**)

sure of tryptophanyl-alanine **7** to an electrophile would result in the formation of a transient iminium ion, which would be trapped by the amide to give **9**. Subsequent elimination could then generate the aromatized tricyclic compound **10**. Alternatively, the absence of a protecting group on the aromatic amine would allow for a second reaction with the electrophile. Elimination from **11** would in this case give the functionalized imine **12**, which could also be directly formed from **10**. While similar strategies have proven to be quite successful for the preparation of pyrroloindoles[9] and for the formation of tryptophan–aniline[10] and tryptophan–imidazole linkages,[11] its use in the construction of tricyclic pyridoindoles has not been documented to date.

Provided that the reaction pathway could be controlled and that suitable levels of diastereoselectivity could be obtained, this would save us between three to five steps compared to our first-generation synthesis and would therefore provide a straightforward access to chaetominine (**1**).

With this goal in mind, the effect of various electrophiles on three different tryptophanyl-alanine derivatives **2**, **13**, and **14** was examined. We decided to protect the N-terminus of tryptophan as a phthalimide, due to concerns that other protecting groups such as carbamates might not prevent the nitrogen atom from interfering in the oxidative coupling. Accordingly, *N*-phthaloyl-D-tryptophan was

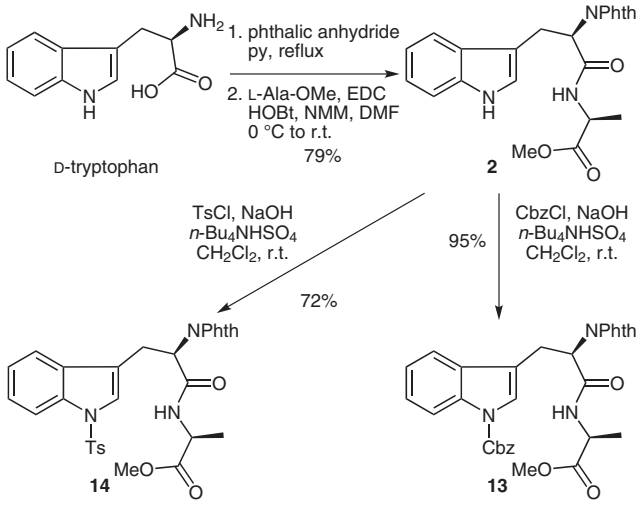


Scheme 2 Proposed oxidative cyclization process

coupled with L-alanine methyl ester under standard conditions, and the indole of the resulting dipeptide was next protected with either a tosyl group or a carbamate under phase-transfer conditions (Scheme 3).

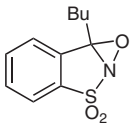
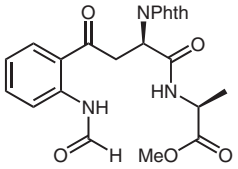
The reactivity of these substrates with oxidants was first examined. The results of these investigations of the oxidative cyclization process are collected in Table 1.

The use of dimethyldioxirane (DMDO), which proved to be the most efficient reagent in a number of related cyclization reactions,[9a–d] was rather disappointing in our case. While it failed to promote the cyclization of any substrates (Table 1, entry 1) at low temperature, extensive degradation was observed when the reaction mixtures were warmed to room temperature (Table 1, entry 2). Sac-



Scheme 3 Synthesis of cyclization substrates

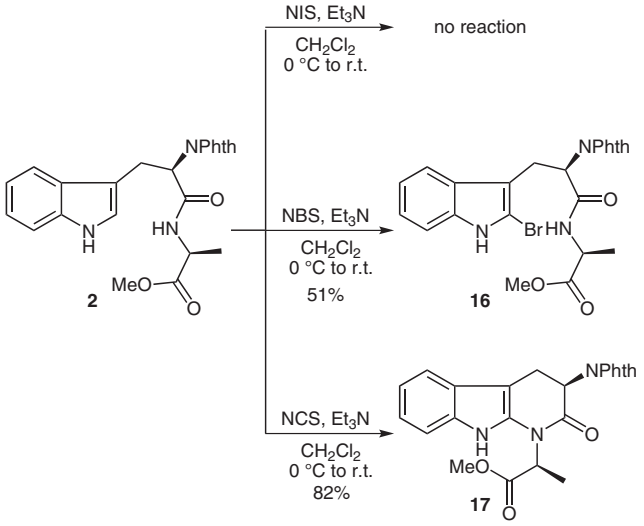
Table 1 Attempted Cyclization with Oxidants

Entry	Substrate	Electrophile	Conditions	Results
1	**2**, **13**, **14**	DMDO	CH_2Cl_2, –78 °C	no reaction
2	**2**, **13**, **14**	DMDO	CH_2Cl_2, –78 °C to r.t.	extensive degradation
3	**2**, **13**, **14**		MeOH, r.t.	no reaction
4	**13**, **14**	MCPBA	CH_2Cl_2, r.t.	no reaction
5	**2**	MCPBA	CH_2Cl_2,–40 °C to r.t.	 **15** 85%

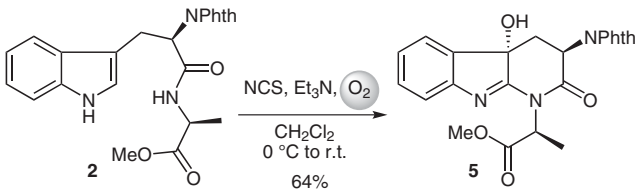
charin-derived oxaziridine[12] was equally inefficient (Table 1, entry 3) and protected substrates **13** and **14** were found to be completely inert towards *m*-chloroperoxybenzoic acid (Table 1, entry 4). A clean reaction was finally observed by treating unprotected indole **2** with *m*-chloroperoxybenzoic acid but the product of this reaction, **15**, frustratingly turned out to result from cleavage of the indole ring (Table 1, entry 5).[13]

Disappointed by these results, we next turned our attention to the use of *N*-halosuccinimides as cyclization promoters (Scheme 4). Protected substrates were mostly unreactive (data not shown), which could be attributed to the strong deactivation of the indole ring. In contrast, a dramatic difference of reactivity towards the activating agents was noted when unprotected indole derivative **2** was used as substrate. Of the halosuccinimides examined, *N*-chlorosuccinimide proved the most effective, since the long-awaited cyclized product **17** was obtained in 82% yield. We were especially surprised to isolate, in addition to this cyclized product, minor amounts of hydroxyimine **5** from the crude reaction mixture. Intrigued by this result and excited by the idea of saving one additional step, we concentrated our efforts on the optimization of this side reaction. After considerable experimentation, we eventually found that this biomimetic reaction could simply be promoted by reacting dipeptide **2** with *N*-chlorosuccinimide and triethylamine under an atmosphere of oxygen (Scheme 5). The use of this simple modification allowed the isolation of hydroxyimine **5** as a single diastereoisomer and in 64% yield.

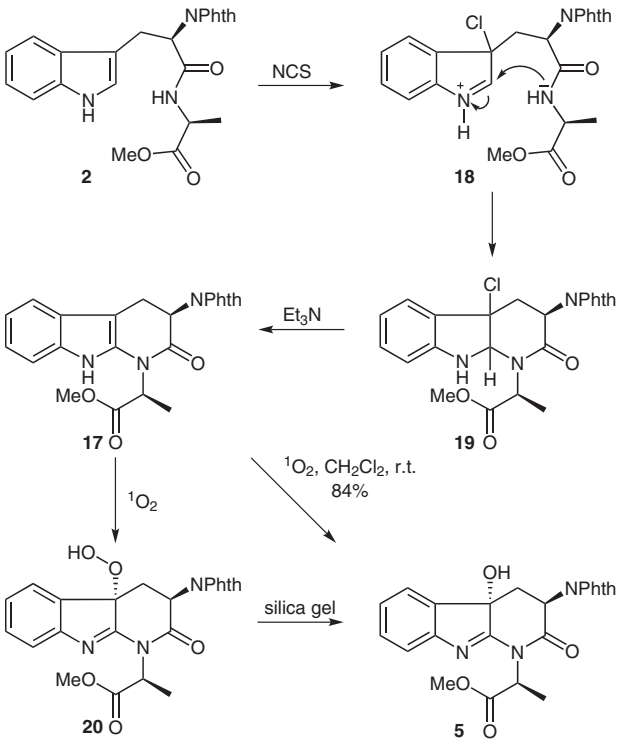
A possible explanation for this unexpected and remarkable reactivity, which saved us four steps compared to our previous synthetic route, is shown in Scheme 6. The first step involves, as mentioned above, activation of the indole to form the activated iminium ion **18**, which, after cyclization and rearomatization, gives tricyclic compound **17**. Photooxidation with oxygen[14] would then give hydroperoxide **20**, which is spontaneously reduced to hydroxyimine **5** upon purification. Experimental evidence that support this scenario are the clean conversion of **17** into an unstable mixture of **20** (characterized by mass spectrometry from the crude reaction mixture) and **5**, and the quantitative conversion of **20** into **5** upon purification on silica gel. In addition, the absence of light considerably slowed down the reaction. It is worth noting that this reaction did not require the presence of a photosensitizer, irradiation, or reductive workup.



Scheme 4 Cyclization promoted by *N*-halosuccinimides



Scheme 5 One-pot cyclization–oxidation procedure with oxygen



Scheme 6 Mechanism of the oxidative cyclization mediated by *N*-chlorosuccinimide–oxygen

Attack of oxygen from the less hindered face of **17** probably accounts for the complete diastereoselectivity of this photooxidation,[15] which is in accordance with the selectivity observed with DMDO on the same substrate during our first-generation synthesis.[8] Basic AM1 geometry optimization[16] of pyridoindole **17** shows that the phthalimide protecting group most probably also acts as an efficient directing group (Figure 2).

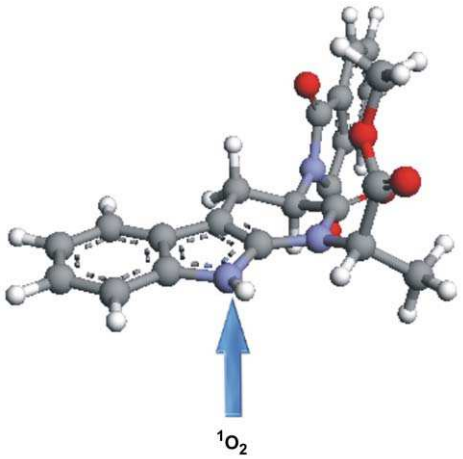
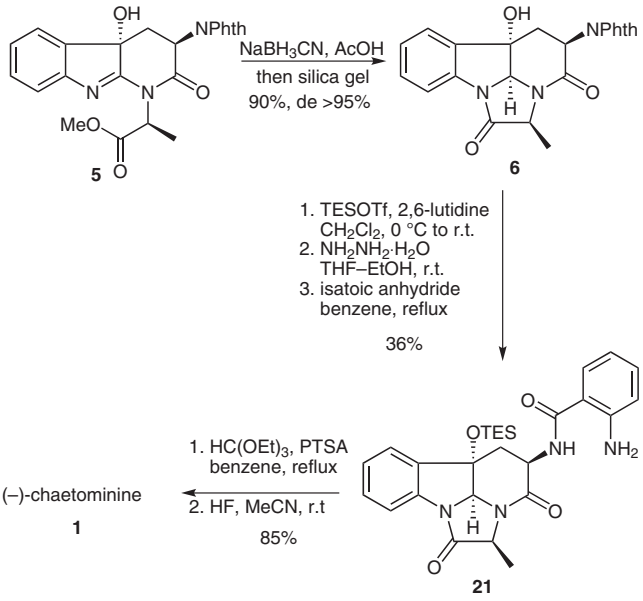


Figure 2 Diastereoselectivity of the photooxidation

Having designed a convenient and straightforward route to advanced tricyclic intermediate **5**, which was used for our first-generation total synthesis of chaetominine (**1**), we moved to the next steps of the synthesis:[8] installation of the second stereocenter at the ring junction and formation of the γ-lactam ring (Scheme 7). Following our previous strategy, imine **5** was diastereoselectively reduced with sodium cyanoborohydride, and the formation of the last ring of the compact tetracyclic chaetominine skeleton was induced by simply stirring the crude resulting amino ester with silica gel in a mixture of dichloromethane, acetone, ethanol, and aqueous ammonia. Protection of the tertiary alcohol in **6** as a triethylsilyl ether, followed by deprotection of the phthalimide with hydrazine, and further reaction with isatoic anhydride then gave amino amide **21**,[5] which was finally converted into synthetic chaetominine (**1**) by reaction with triethyl orthoformate and deprotection of the alcohol with hydrofluoric acid.[5]



Scheme 7 Completion of the synthesis

In summary, we have developed an efficient biomimetic synthesis of (–)-chaetominine in nine steps and 14% overall yield starting from D-tryptophan and L-alanine as building blocks. Central to our synthetic approach is an efficient domino process involving a diastereoselective oxidative cyclization followed by photooxidation of a tryptophanyl-alanine dipeptide, which provides a straightforward route to the chaetominine skeleton. The convergent approach reported here should be easy to apply to the synthesis of analogues for further biological testing, which will be reported in due course.

All reactions were carried out in an oven or flame-dried glassware under an argon atmosphere, except for reactions involving molecular oxygen, and standard techniques in handling air-sensitive materials were employed. All solvents were reagent grade. Benzene was freshly distilled from sodium/benzophenone under argon. MeCN, CH_2Cl_2, and DMF were freshly distilled from CaH_2. MeOH was distilled from Mg turnings and I_2. 2,6-Lutidine, NMM, and Et_3N were distilled over CaH_2. All other reagents were used as supplied. Unless otherwise noted, reactions were magnetically stirred and monitored by TLC using Merck Kieselgel $60F_{254}$ plates. Flash chromatography was performed on silica gel 60 (particle size 35–70 μm)

supplied by SDS. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H NMR spectra were recorded using an internal deuterium lock at ambient temperature on a Bruker 300 MHz spectrometer. Internal references of δ_H = 7.26 and δ_H = 2.50 were used for $CDCl_3$ and DMSO-d_6, respectively. Resonances that are either partially or fully obscured are denoted by the abbreviation 'obs' (obscured); 'app' is used for 'apparent'. ^{13}C NMR spectra were recorded at 75 MHz. Internal references of δ_C = 77.16 and δ_C = 39.52 were used for $CDCl_3$ and DMSO-d_6, respectively. Optical rotations were recorded on a Perkin Elmer 341 polarimeter at 589 nm. Melting points were recorded on a Buchi B-545. Mass spectra were obtained on an HP MS 5989B spectrometer. HRMS was carried out on an LCT Micromass-Waters spectrometer (TOF).

Phthaloyl-D-tryptophan

Phthalic anhydride (6.5 g, 44 mmol) was added to a soln of D-tryptophan (9.0 g, 44 mmol) in py (70 mL). The resulting soln was refluxed overnight and concentrated by distillation. The residue was cooled to 0 °C, treated with 6 M aq HCl (200 mL) and stirred at 0 °C for 2 h. The precipitate was filtered, washed with cold H_2O, and dissolved in EtOAc (200 mL), and the organic soln was washed with a mixture of brine and 1 M aq HCl (1:1; 200 mL), dried ($MgSO_4$), filtered, and concentrated. This gave the desired protected tryptophan as a pale brown solid, which was used without further purification in the next step.

Yield: 15.0 g (quant); mp 97 °C; $[\alpha]_D^{20}$ +187 (*c* 1.3, EtOH).

IR (film): 3390, 3047, 1778, 1711, 1388, 707 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.37 (br s, 1 H), 10.77 (s, 1 H), 7.75–7.83 (m, 4 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.06 (d, *J* = 1.9 Hz, 1 H), 7.02 (t, *J* = 7.9 Hz, 1 H), 6.92 (t, *J* = 7.9 Hz, 1 H), 5.16 (X of ABX, *J* = 9.2, 6.6 Hz, 1 H), 3.57–3.58 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.5, 167.3, 136.1, 134.8, 131.0, 127.0, 123.5, 123.4, 121.1, 118.5, 118.0, 111.5, 109.8, 52.7, 24.2.

MS (CI, NH_3 gas): *m*/*z* = 352, 335.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}N_2O_4Na$: 357.0851; found: 357.0845.

Phthaloyl-D-tryptophanyl-L-alanine Methyl Ester 2

1-Hydroxybenzotriazole (HOBt; 3.0 g, 22.2 mmol) was added to a soln of phthaloyl-D-tryptophan (6.7 g, 19.7 mmol) and L-alanine methyl ester hydrochloride (2.8 g, 20.0 mmol) in DMF (70 mL). EDC·HCl (3.8 g, 19.8 mmol) and NMM (2.8 mL, 25.5 mmol) were next added at 0 °C and the soln was stirred for 16 h while progressively warmed to r.t. The brown reaction mixture was quenched by the addition of a sat. aq soln of $NaHCO_3$ (70 mL) and diluted with EtOAc (70 mL). The aqueous layer was extracted with EtOAc (3 × 70 mL) and the combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, EtOAc–PE, 7:3); this yielded the desired dipeptide **2** as a pale yellow solid.

Yield: 6.5 g (79%); mp 99 °C; $[\alpha]_D^{20}$ +63 (*c* 0.7, $CHCl_3$).

IR (film): 3375, 2950, 1711, 1532, 1383, 1209, 717 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H), 7.72–7.77 (m, 2 H), 7.61–7.67 (m, 3 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 7.13 (app td, *J* = 7.1, 1.2 Hz, 1 H), 7.06 (app td, *J* = 8.0, 1.2 Hz, 2 H), 6.81 (d, *J* = 6.9 Hz, 1 H), 5.27 (dd, *J* = 9.0, 7.1 Hz, 1 H), 4.57 (app quint, *J* = 7.2 Hz, 1 H), 3.61–3.82 (m, 2 H), 3.67 (s, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 173.2 (rotamers), 168.5, 168.4 (rotamers), 168.2, 168.1 (rotamers), 136.4, 136.3 (rotamers), 134.2, 131.7, 127.0, 123.6, 123.2, 123.0 (rotamers), 119.8, 118.7, 111.4, 111.0, 110.9 (rotamers), 54.8, 54.7 (rotamers), 52.6, 48.6, 25.7, 25.4 (rotamers), 18.3.

ESI-MS (positive mode): *m*/*z* = 474.3, 442.2.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}N_3O_5Na$: 442.1379; found: 442.1371.

[Phthaloyl-(1-carbobenzyloxy-D-tryptophanyl)]-L-alanine Methyl Ester 13

n-Bu_4NHSO_4 (441 mg, 1.3 mmol) and freshly finely powdered NaOH (2.7 g, 67.5 mmol) were successively added to a soln of **2** (5.6 g, 13.3 mmol) in anhyd CH_2Cl_2 (170 mL). The resulting pale yellow soln was stirred for 15 min, and then CbzCl (5.8 mL, 40.6 mmol) was added in three portions over 15 min. The resulting slurry was vigorously stirred for 90 min and quenched by the addition of H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2–Et_2O, 95:5); this yielded the desired protected dipeptide **13** as a pale yellow solid.

Yield: 7.0 g (95%); mp 82 °C; $[\alpha]_D^{20}$ +52 (*c* 1.0, $CHCl_3$).

IR (film): 3370, 2950, 1747, 1711, 1532, 1383, 1219, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br d, *J* = 6.9 Hz, 1 H), 7.66–7.70 (m, 2 H), 7.57–7.60 (m, 2 H), 7.50 (app dd, *J* = 8.3, 1.6 Hz, 1 H), 7.29–7.38 (m, 6 H), 7.21 (app td, *J* = 6.0, 1.1 Hz, 1 H), 7.14 (app td, *J* = 7.5, 1.2 Hz, 1 H), 6.70 (br d, *J* = 7.1 Hz, 1 H), 5.28 (s, 2 H), 5.16 (dd, *J* = 9.0, 7.1 Hz, 1 H), 4.57 (app q, *J* = 7.2 Hz, 1 H), 3.60 (app d, *J* = 6.9 Hz, 2 H), 3.61 (s, 3 H), 1.30 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 173.1 (rotamers), 168.0, 167.9 (rotamers), 167.8, 167.7 (rotamers), 135.2, 134.4, 131.6, 130.0, 128.8, 128.7, 128.4, 125.1, 123.7, 123.2, 119.0, 117.1, 116.9 (rotamers), 115.4, 115.1 (rotamers), 68.7, 54.0, 53.9 (rotamers), 52.6, 52.5 (rotamers), 48.6, 25.0, 24.8 (rotamers), 18.5, 18.4 (rotamers).

ESI-MS (positive mode): *m*/*z* = 608.4, 576.3.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{27}N_3O_7Na$: 576.1747; found: 576.1750.

[Phthaloyl-(1-*p*-toluenesulfonyl-D-tryptophanyl)]-L-alanine Methyl Ester 14

n-Bu_4NHSO_4 (42 mg, 0.12 mmol) and freshly finely powdered NaOH (300 g, 7.5 mmol) were successively added to a soln of **2** (1.0 g, 2.5 mmol) in anhyd CH_2Cl_2 (25 mL). The resulting pale yellow soln was stirred for 15 min and TsCl (560 mg, 3.0 mmol) was added in three portions over 5 min. The resulting slurry was vigorously stirred for 90 min and quenched by the addition of H_2O (25 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2); this yielded the desired protected dipeptide **14** as a white solid.

Yield: 1.0 g (72%); mp 84 °C; $[\alpha]_D^{20}$ +67 (*c* 0.8, $CHCl_3$).

IR (KBr): 3355, 3052, 2945, 1777, 1690, 1537, 1199 cm^{-1}.

ESI-MS (positive mode): *m*/*z* = 596.6.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.2 Hz, 1 H), 7.65–7.71 (m, 2 H), 7.58–7.63 (m, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.16 (s, 1 H), 7.16 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.10 (td, *J* = 7.3, 1.1 Hz, 1 H), 6.94 (d, *J* = 8.1 Hz, 2 H), 6.64 (d, *J* = 7.1 Hz, 1 H), 5.10 (X of ABX, *J* = 10.0, 6.3 Hz, 1 H), 4.48 (app quint, *J* = 7.2 Hz, 1 H), 3.60 (s, 3 H), 3.57–3.65 (obs m, 2 H), 2.17 (s, 3 H), 1.28 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 167.9, 167.8, 144.8, 135.2, 134.5, 131.5, 130.2, 129.8, 126.8, 125.1, 124.5, 123.8, 123.4, 119.4, 117.7, 113.8, 53.9, 52.7, 48.6, 24.7, 21.6, 18.3.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{27}N_3O_7SNa$: 596.1467; found: 596.1472.

Methyl [2(2*R*),2*S*]-2-({4-[2-(Formylamino)phenyl]-4-oxo-2-phthalimidobutyryl}amino)propionate (15)

A soln of **2** (500 mg, 1.2 mmol) in anhyd CH_2Cl_2 (25 mL) was treated with MCPBA (70%, 1.2 g, 4.8 mmol) at –50 °C. The resulting mixture was warmed to r.t. over 2 h and quenched by the addition of a 10 wt% aq soln of $Na_2S_2O_3$ (20 mL) and sat. aq $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, EtOAc–PE, 50:50); this yielded the oxidized product **15** as a white solid.

Yield: 460 mg (85%); mp 85 °C; $[\alpha]_D^{20}$ +92 (*c* 0.5, $CHCl_3$).

IR (KBr): 3319, 2950, 1777, 1701, 1527, 1383, 989 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.31 (br s, 1 H), 8.70 (d, *J* = 8.5 Hz, 1 H), 8.42 (s, 1 H), 8.01 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.88 (dd, *J* = 5.6, 2.9 Hz, 2 H), 7.75 (dd, *J* = 5.5, 2.9 Hz, 2 H), 7.55 (t, *J* = 8.2 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 6.66 (d, *J* = 7.1 Hz, 1 H), 5.54 (X of ABX, *J* = 6.8, 6.8 Hz, 1 H), 4.57 (app quint, *J* = 7.2 Hz, 1 H), 4.27 (A of ABX, *J* = 18.3, 6.2 Hz, 1 H), 3.93 (B of ABX, *J* = 18.3, 7.4 Hz, 1 H), 3.67 (s, 3 H), 1.40 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9, 173.0, 167.8, 167.6, 139.8, 135.5, 134.5, 131.5, 130.9, 123.8, 123.3, 121.6, 121.3, 52.5, 49.3, 48.5, 38.7, 18.1.

ESI-MS (positive mode): *m*/*z* = 474.1.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}N_3O_7Na$: 474.1277; found: 474.1274.

[Phthaloyl-(2-bromo-D-tryptophanyl)]-L-alanine Methyl Ester (16)

NBS (42 mg, 0.24 mmol) and Et_3N (100 μL, 0.72 mmol) were added to a soln of **2** (100 mg, 0.24 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C. The resulting mixture was allowed to warm to r.t. and stirred overnight. The crude reaction mixture was concentrated and purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 95:5); this yielded the brominated dipeptide **16** as a pale yellow solid.

Yield: 59 mg (51%); mp 80 °C; $[\alpha]_D^{20}$ +57 (*c* 0.6, $CHCl_3$).

IR (KBr): 3324, 2925, 1716, 1511, 1383 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 7.68–7.75 (m, 2 H), 7.58–7.66 (m, 2 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.16 (d, *J* = 7.7 Hz, 1 H), 7.04 (td, *J* = 7.1, 1.2 Hz, 1 H), 6.97 (td, *J* = 7.1, 1.2 Hz, 1 H), 6.74 (d, *J* = 7.0 Hz, 1 H), 5.24 (X of ABX, *J* = 9.1, 7.1 Hz, 1 H), 4.59 (app quint, *J* = 7.1 Hz, 1 H), 3.67 (s, 3 H), 3.69 (A of ABX, *J* = 18.0, 7.1 Hz, 1 H), 3.54 (B of ABX, *J* = 14.7, 9.4 Hz, 1 H), 1.35 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 168.1, 167.9, 136.1, 134.2, 131.7, 127.3, 123.5, 122.5, 120.3, 117.9, 110.7, 110.3, 109.4, 53.7, 52.6, 48.6, 25.1, 18.3.

ESI-MS (positive mode): *m*/*z* = 522.1, 520.1.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}BrN_3O_5Na$: 520.0484; found: 520.0472.

(1*S*,3*R*)-1-[1-(Methoxycarbonyl)ethyl]-2-oxo-3-phthalimido-1,2,3,4-tetrahydropyrido[2,3-*b*]indole (17)

A 100-mL flask was charged with **2** (1.0 g, 2.38 mmol), evacuated under high vacuum and backfilled with argon. CH_2Cl_2 (50 mL) was added, the flask was cooled to 0 °C, and NCS (637 mg, 4.77 mmol) was added. The resulting mixture was stirred for 5 min and Et_3N (1.0 mL, 7.17 mmol) was added dropwise. The resulting mixture was allowed to warm to r.t., stirred overnight under argon, and concentrated. The crude residue was purified by flash chromatography (silica gel, EtOAc–PE, 40:60); this yielded the cyclized product **17** as a white solid.

Yield: 815 mg (82%); mp 191 °C; $[\alpha]_D^{20}$ +61 (*c* 1.5, $CHCl_3$).

IR (film): 3370, 2930, 1716, 1588, 1383 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 7.77 (dd, *J* = 5.3, 3.1 Hz, 2 H), 7.63 (dd, *J* = 5.5, 3.1 Hz, 2 H), 7.22–7.28 (m, 2 H), 7.02–7.04 (m, 2 H), 5.62 (q, *J* = 7.3 Hz, 1 H), 5.18 (X of ABX, *J* = 13.9, 7.5 Hz, 1 H), 3.68–3.80 (obs m, 1 H), 3.72 (s, 3 H), 3.00 (B of ABX, *J* = 14.5, 7.5 Hz, 1 H), 1.53 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 167.9, 166.4, 134.3, 133.7, 133.4, 132.0, 126.0, 123.6, 121.1, 120.7, 117.4, 111.5, 94.3, 53.2, 51.4, 50.9, 21.6, 15.8.

MS (CI, NH_3 gas): *m*/*z* = 418.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{19}N_3O_5Na$: 440.1222; found: 440.1227.

(1*S*,3*R*,4a*S*)-4a-Hydroxy-1-[1-(methoxycarbonyl)ethyl]-2-oxo-3-phthalimido-2,3,4,4a-tetrahydropyrido[2,3-*b*]indole (5)

A 250-mL flask was charged with **2** (630 mg, 1.5 mmol), evacuated under high vacuum and backfilled with O_2. CH_2Cl_2 (30 mL) was added, the flask was cooled to 0 °C, and NCS (400 mg, 3.0 mmol) was added. The resulting mixture was stirred for 5 min and Et_3N (630 μL, 4.5 mmol) was added dropwise. The resulting mixture was allowed to warm to r.t., vigorously stirred overnight under O_2 (balloon), and concentrated. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 92:8); this yielded **5** as a white solid.

Yield: 435 mg (64%); mp 156 °C; $[\alpha]_D^{20}$ +92 (*c* 0.6, $CHCl_3$).

IR (film): 3411, 2929, 1721, 1578, 1388 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.93 (br m, 4 H), 7.25–7.43 (m, 3 H), 7.18 (td, *J* = 5.3, 1.0 Hz, 1 H), 5.66 (X of ABX, *J* = 11.8, 6.0 Hz, 1 H), 5.52 (q, *J* = 7.1 Hz, 1 H), 3.73 (s, 3 H), 3.06 (br s, 1 H), 2.82 (A of ABX, *J* = 12.9, 6.0 Hz, 1 H), 2.62 (B of ABX, *J* = 12.9, 11.9 Hz, 1 H), 1.75 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.5, 167.2, 153.4, 136.1, 134.5, 131.1, 125.4, 123.9, 122.5, 120.4, 77.4, 52.7, 52.5, 46.7, 32.3, 14.9.

MS (CI, NH_3 gas): *m*/*z* = 434.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{19}N_3NaO_6$: 456.1172; found: 456.1171.

Photooxidation of 17 to 5

A 50-mL flask was charged with **17** (80 mg, 0.19 mmol) and CH_2Cl_2 (5 mL). The soln was purged with O_2, vigorously stirred under an atmosphere of O_2 (balloon) for 24 h and concentrated (MS analysis of the crude reaction mixture showed the presence of hydroperoxide **20** and hydroxy imine **5**). The crude mixture was purified by flash chromatography (silica gel, EtOAc–PE, 40:60); this yielded the photooxidized product **5**.

Yield: 71 mg (84%).

(2*S*,4*R*,5a*S*,9c*S*)-5a-Hydroxy-2-methyl-4-phthalimido-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione (6)

Glacial AcOH (385 μL, 6.7 mmol) was added dropwise to a soln of **5** (290 mg, 0.67 mmol) in MeOH (8 mL) at 0 °C. The resulting mixture was stirred for 30 min, treated with $NaBH_3CN$ (665 mg, 8.0

mmol) and slowly warmed to r.t. over 3 h. The resulting mixture was carefully quenched at 0 °C by the addition of a sat. aq soln of $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was dissolved in a mixture of CH_2Cl_2 (22.5 mL), acetone (2 mL), EtOH (0.5 mL), and 30 wt% aq NH_3 soln (0.25 mL), and treated with silica gel (3 g) for 105 min. The resulting slurry was concentrated and purified by flash chromatography (silica gel, CH_2Cl_2–acetone–EtOH–30 wt% aq NH_3, 93:5:1.9:0.1); this yielded the desired tetracyclic compound **6** as a white solid.

Yield: 243 mg (90%); mp 285 °C; $[\alpha]_D^{20}$ –21 (*c* 0.6, $CHCl_3$).

IR (film): 3411, 2919, 1711, 1388 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.75 (m, 2 H), 7.60–7.66 (m, 2 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 7.27 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.22 (d, *J* = 7.4 Hz, 1 H), 7.06 (td, *J* = 7.5, 0.7 Hz, 1 H), 5.30 (s, 1 H), 5.03 (X of ABX, *J* = 12.9, 3.2 Hz, 1 H), 4.33 (s, 1 H), 4.23 (q, *J* = 7.0 Hz, 1 H), 2.81 (A of ABX, *J* = 12.9, 12.9 Hz, 1 H), 2.34 (B of ABX, *J* = 12.9, 3.3 Hz, 1 H), 1.56 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 168.1, 167.8, 165.6, 138.9, 135.3, 134.4, 134.3, 132.0, 131.8, 130.8, 126.1, 124.4, 123.8, 123.7, 115.5, 83.2, 77.4, 60.4, 48.2, 37.4, 29.8, 14.4.

MS (CI, NH_3 gas): *m*/*z* = 404.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{17}N_3O_5Na$: 426.1066; found: 426.1073.

(2*S*,4*R*,5a*S*,9c*S*)-2-Methyl-4-phthalimido-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione

2,6-Lutidine (1.5 mL, 12.9 mmol) and TESOTf (2.1 mL, 9.3 mmol) were added dropwise to a soln of **6** (750 mg, 1.86 mmol) in CH_2Cl_2 (15 mL) at –20 °C. The resulting mixture was slowly warmed to r.t. over 1 h, stirred for 15 min, and quenched by the addition of a sat. aq soln of $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 95:5); this yielded the desired TES ether as a pale yellow solid.

Yield: 847 mg (88%); mp 93 °C; $[\alpha]_D^{20}$ –22 (*c* 0.6, $CHCl_3$).

IR (film): 2955, 2873, 1726, 1378, 1332, 748 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.83 (m, 1 H), 7.73–7.76 (m, 1 H), 7.64–7.67 (m, 2 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 7.14 (td, *J* = 7.7, 1.0 Hz, 1 H), 5.38 (s, 1 H), 5.14 (X of ABX, *J* = 12.9, 3.3 Hz, 1 H), 4.35 (q, *J* = 6.9 Hz, 1 H), 2.88 (A of ABX, *J* = 12.9, 12.9 Hz, 1 H), 2.44 (B of ABX, *J* = 12.9, 3.3 Hz, 1 H), 1.66 (d, *J* = 6.9 Hz, 3 H), 0.82 (t, *J* = 7.8 Hz, 9 H), 0.36–0.47 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 168.1, 167.6, 165.6, 140.1, 134.4, 134.3, 134.2, 132.1, 132.0, 131.0, 125.7, 125.0, 115.7, 83.9, 80.1, 59.9, 48.3, 39.8, 14.6, 6.9, 6.2.

MS (CI, NH_3 gas): *m*/*z* = 518.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{31}N_3O_5SiNa$: 540.1931; found: 540.1920.

(2*S*,4*R*,5a*S*,9c*S*)-4-Amino-2-methyl-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione

Hydrazine hydrate (5.5 μL, 0.11 mmol) was added to a soln of (2*S*,4*R*,5a*S*,9c*S*)-2-methyl-4-phthalimido-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione (51 mg, 0.098 mmol) in anhyd THF (0.5 mL) and absolute EtOH (0.5 mL). The resulting mixture was stirred at r.t. for 16 h and additional hydrazine hydrate (3.0 μL, 0.06 mmol) was added. The white soln was stirred for 8 h at r.t. and the solvents were removed under reduced pressure. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH–30 wt% aq NH_3, 96:3.5:0.5); this yielded the free amine as a white solid.

Yield: 25 mg (66%); mp 79 °C; $[\alpha]_D^{20}$ +31 (*c* 0.5, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.9 Hz, 1 H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.19 (td, *J* = 7.6, 1.0 Hz, 1 H), 5.30 (s, 1 H), 4.38 (q, *J* = 6.9 Hz, 1 H), 3.73 (X of ABX, *J* = 12.2, 3.2 Hz, 1 H), 2.64 (A of ABX, *J* = 13.0, 3.4 Hz, 1 H), 2.12 (br s, 2 H), 1.81 (B of ABX, *J* = 12.6, 12.6 Hz, 1 H), 1.71 (d, *J* = 6.9 Hz, 3 H), 0.83 (t, *J* = 8.0 Hz, 9 H), 0.35–0.44 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 172.0, 140.3, 134.6, 130.9, 125.7, 125.0, 115.6, 84.1, 79.9, 59.5, 50.0, 43.9, 15.0, 7.0, 6.1.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{29}N_3O_3SiNa$: 410.1876; found: 410.1873.

(2*S*,4*R*,5a*S*,9c*S*)-4-(2-Aminobenzamido)-2-methyl-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione (21)[5]

Isatoic anhydride (12.5 mg, 0.074 mmol) was added in one portion to a soln of (2*S*,4*R*,5a*S*,9c*S*)-4-amino-2-methyl-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione (19 mg, 0.049 mmol) in anhyd benzene (6.0 mL). The resulting suspension was refluxed for 16 h and the benzene was removed under reduced pressure. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 91:9); this yielded amino amide **21** as a sticky white solid.

Yield: 15.5 mg (63%); $[\alpha]_D^{20}$ –97 (*c* 0.66, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.8 Hz, 1 H), 7.46 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.38 (d, *J* = 7.4 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 5.2 Hz, 1 H), 6.76 (dd, *J* = 8.2, 0.9 Hz, 1 H), 6.70 (app td, *J* = 8.0, 1.1 Hz, 1 H), 5.41 (s, 1 H), 4.85–4.91 (m, 1 H), 4.44 (q, *J* = 6.9 Hz, 1 H), 3.12 (A of ABX, *J* = 12.7, 3.5 Hz, 1 H), 1.76 (B of ABX, *J* = 12.4, 12.4 Hz, 1 H), 1.75 (d, *J* = 7.0 Hz, 3 H), 0.90 (t, *J* = 8.1 Hz, 9 H), 0.49 (q, *J* = 7.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 169.0, 168.9, 147.8, 140.2, 134.4, 132.7, 130.9, 127.9, 125.8, 125.2, 118.0, 117.6, 116.3, 115.7, 83.9, 80.0, 59.7, 49.1, 41.5, 15.0, 6.2, 5.9.

ESI-MS (positive mode): *m*/*z* = 1035.8, 529.3, 507.3, 375.3, 120.0.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{34}N_4O_4SiNa$: 529.2247; found: 529.2241.

(2*S*,4*R*,5a*S*,9c*S*)-2-Methyl-4-(4-oxo-4*H*-quinazolin-3-yl)-5a-(triethylsiloxy)-4,5,5a,9c-tetrahydro-2a,9b-diazacyclopenta[*jk*]fluorene-1,3-dione (TES-Protected Chaetominine)[5]

Triethyl orthoformate (225 μL, 1.33 mmol) and PTSA·H_2O (5 mg, 0.025 mmol) were added to a soln of **21** (42 mg, 0.083 mmol) in anhyd benzene (11.5 mL). The resulting mixture was refluxed for 90 min and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O–30 wt% aq NH_3: 88:11.5:0.5); this yielded TES-protected-chaetominine as a white solid.

Yield: 39 mg (90%); mp 269 °C; $[\alpha]_D^{20}$ –23 (*c* 0.45, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.5 Hz, 1 H), 7.90 (s, 1 H), 7.71–7.80 (m, 2 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.51 (td, *J* = 7.3, 1.7 Hz, 1 H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1 H), 5.48 (s, 1 H), 4.45 (q, *J* = 6.9 Hz, 1 H), 2.64 (app br d, *J* = 10.3 Hz, 1 H), 2.31 (br m, 1 H), 1.75 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 8.0 Hz, 9 H), 0.43–0.52 (m, 6 H) (H14 was not observed due to slow rotation at the C14–N bond).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 160.7, 147.2, 140.2, 134.8, 133.9, 131.3, 127.7, 127.4, 127.3, 125.8, 125.0, 122.0, 115.8, 83.9, 80.0, 60.0, 48.3, 39.8, 14.6, 6.9, 6.2 (one amide carbonyl carbon was not observed due to slow rotation at the C14–N bond).

ESI-MS (positive mode): *m*/*z* = 555.0, 538.9, 517.0.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{32}N_4NaO_4Si$: 539.2091; found: 539.2086.

(–)-Chaetominine (1)[4,5]

A 49 wt% aq soln of HF (125 μL) was added dropwise to a soln of TES-protected chaetominine (34 mg, 0.066 mmol) in MeCN (2.3 mL). The resulting mixture was stirred at r.t. overnight, treated with additional 49 wt% aq HF (35 μL), and stirred at 30 °C for 6 h. The reaction mixture was next diluted with EtOAc (10 mL), successively washed with an aq sat. soln of $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O–MeOH–30 wt% aq NH_3, 60:33:6.5:0.5); this yielded synthetic chaetominine (**1**) as a white solid.

Yield: 25 mg (94%); mp 164 °C (Lit.[4] 161–163 °C, Lit.[5] 162–165 °C); $[\alpha]_D^{20}$ –48 (*c* 0.45, MeOH) {Lit.[4] $[\alpha]_D^{20}$ –70 (*c* 0.48, MeOH), –49.4 (*c* 0.26, MeOH)}.

IR (KBr): 3445, 1726, 1670, 1609, 1480, 1383 cm^{-1}.

ESI-MS (positive mode): *m*/*z* = 826.8, 441.0, 424.9, 403.0.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.29 (br s, 1 H), 8.18 (br d, *J* = 7.7 Hz, 1 H), 7.86 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.69 (d, *J* = 7.6 Hz, 1 H), 7.58 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.71 (br s, 1 H), 5.90 (br s, 1 H), 5.61 (br s, 1 H), 4.61 (q, *J* = 6.9 Hz, 1 H), 2.94 (A of ABX, *J* = 12.8, 12.8 Hz, 1 H), 2.53 (B of ABX, *J* = 12.8, 3.2 Hz, 1 H), 1.60 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.0, 165.5 (br), 160.0, 147.4, 147.0 (br), 138.7, 136.7, 134.7, 129.9, 127.27, 127.23, 126.4, 125.5, 124.9, 121.2 (br), 114.5, 82.5, 76.4, 59.6, 50.0, 38.1 (br), 14.0.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{18}N_4O_4Na$: 425.1226; found: 425.1215.

Acknowledgment

The authors thank the CNRS and the ANR (project ProteInh) for financial support. A. C. acknowledges the National Cancer Institute for a graduate fellowship and G. K. acknowledges the University of Versailles for a postdoctoral fellowship.

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